Office of New Drugs Biweekly Report

February 18, 2022

Reporting Period: February 7th to March 18th

Key Issues

NONRESPONSIVE

NONRESPONSIVE

[PAGE * MERGEFORMAT]

NONRESPONSIVE

[PAGE * MERGEFORMAT]


NONRESPONSIVE

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

[PAGE * MERGEFORMAT]

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

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Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information (Applicant/Sponsor name, indication) Planned Action
NONRESPONSIVE							

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

[PAGE * MERGEFORMAT]

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary

NONRESPONSIVE

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Medical Policy and Program Review Council

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

Safety Issues

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description

NONRESPONSIVE

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				

Drug Safety Communications				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
GnRH agonists	Multiple NDAs	DGE	4/26/2022	NISS 1004605: GnRH agonists indicated to treat central precocious puberty and idiopathic intracranial hypertension; SLC notification letter issued on 2/10/2022 (DSC not planned).

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
[redacted]	[redacted]	[redacted]	[redacted]	NONRESPONSIVE

[redacted]

[PAGE * MERGEFORMAT]

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
Nafarelin	NDA 019886	DUOG	4/1/2022	SLC notification letter sent 2/10/2022 regarding the risk of intracranial hypertension for the precocious puberty indication for this drug, which is administratively managed in DUOG. DGE sent SLC notification letters for the same issue for drugs in the same class that are administratively managed in their division. The action date of approval is expected to be in 4/2022.

NONRESPONSIVE

Publications and External Presentations

External Presentations					
Office/ Division	**FDA Presenters**	**Conference/Workshop/Mtg**	**Title/Topic**	**Location**	**Date and Time**

NONRESPONSIVE

Medical Countermeasures

Drug Name	**App. No.**	**Division**	**App. Information/Meeting Dates/Status**

NONRESPONSIVE

Leave and Coverage

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

In Clearance, OND-Authored			
Authoring Div. or Office	Title of Guidance/Document	Status	OND Clearance Due Date

NONRESPONSIVE

Regulatory Science Research Program Update

NONRESPONSIVE

Modernization Update

Workstream	Current Status	Upcoming Milestones

NONRESPONSIVE

Workstream	Current Status	Upcoming Milestones
	NONRESPONSIVE	

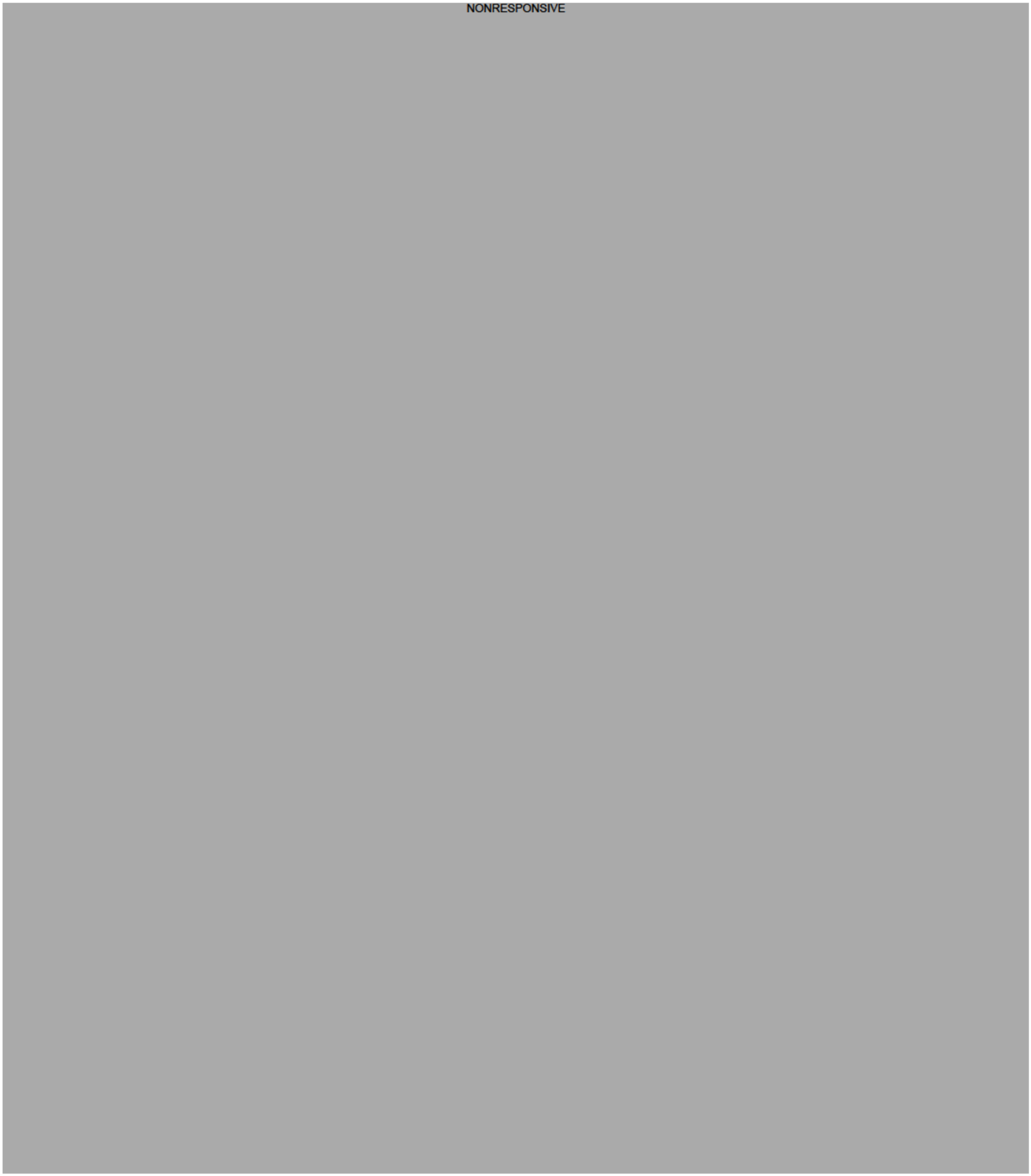
Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

Office of New Drugs Biweekly Report

March 4, 2022

Reporting Period: February 21st to April. 1st

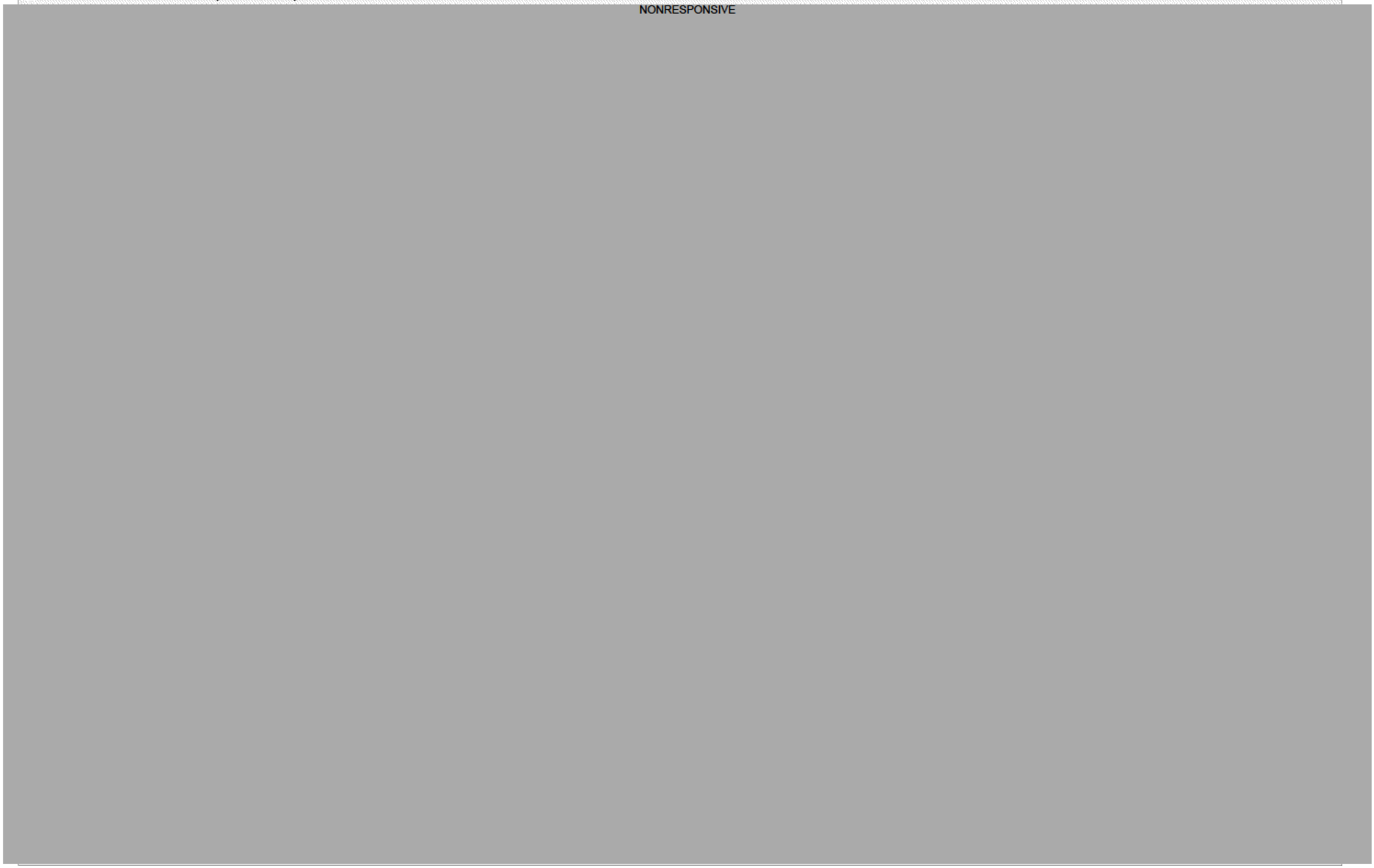
NONRESPONSIVE


NONRESPONSIVE

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)

NONRESPONSIVE


NONRESPONSIVE

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

[PAGE * MERGEFORMAT]

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

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Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

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Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information (Applicant/Sponsor name, indication) Planned Action
NONRESPONSIVE							

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Other Notable End-of-Phase Meetings					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Meeting Dates (Internal/Sponsor)**	**Application Information**
NONRESPONSIVE					

Clinical Holds					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Date Issued**	**Application Information**

NONRESPONSIVE

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Medical Policy and Program Review Council

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

Safety Issues

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**

NONRESPONSIVE

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Drug Safety Communications				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**

NONRESPONSIVE

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
Nafarelin	NDA 019886	DUOG	4/1/2022	SLC notification letter sent 2/10/2022 regarding the risk of intracranial hypertension for the precocious puberty indication for this drug, which is administratively managed in DUOG. DGE sent SLC notification letters for the same issue for drugs in the same class that are administratively managed in their division. The action date of approval is expected to be in 4/2022.

NONRESPONSIVE

Publications and External Presentations

Publications

NONRESPONSIVE

Medical Countermeasures

Drug Name	App. No.	Division	App. Information/Meeting Dates/Status
NONRESPONSIVE			

Leave and Coverage

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

NONRESPONSIVE

NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

NONRESPONSIVE

Working Groups and Standing Sub-Committees

NONRESPONSIVE

Citizen Petitions

Drug Name or Subject	Sponsor	Docket No.	Date Rec'd	Planned Action Date	Division	Brief Description of Issue
NONRESPONSIVE						

Regulatory Science Research Program Update

NONRESPONSIVE

NONRESPONSIVE

Modernization Update

Workstream	Current Status	Upcoming Milestones

NONRESPONSIVE

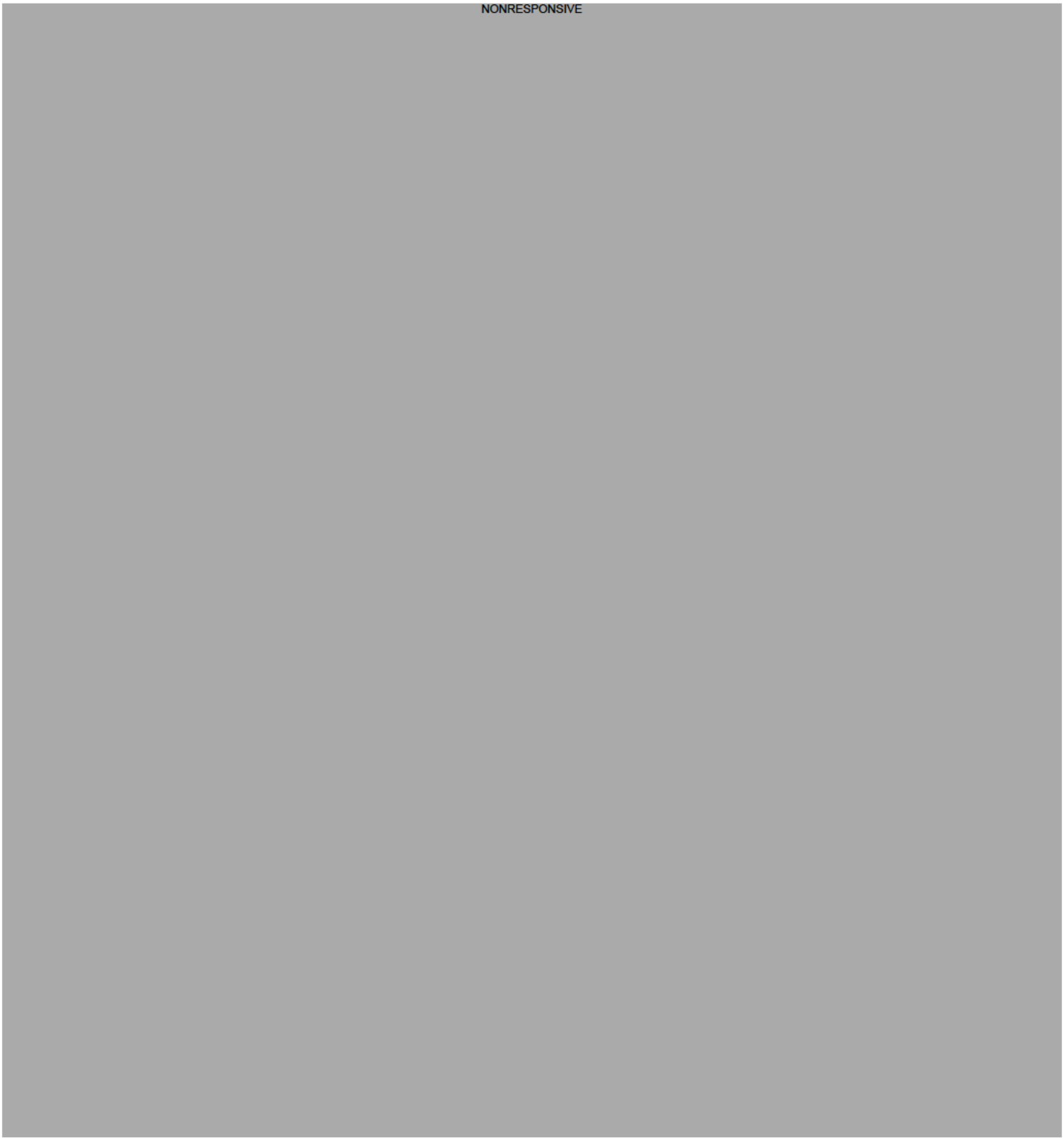
Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

Office of New Drugs Biweekly Report

March 18, 2022

Reporting Period: March 7th to April. 15th

NONRESPONSIVE


NONRESPONSIVE

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
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505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
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505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Biosimilar Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

[PAGE * MERGEFORMAT]

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Date Issued**	**Application Information**
NONRESPONSIVE					

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Medical Policy and Program Review Council

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
			NONRESPONSIVE

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

Safety Issues

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**

NONRESPONSIVE

Newly Identified Safety Signals

Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change

Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				
Nafarelin	NDA 019886	DUOG	4/1/2022	SLC notification letter sent 2/10/2022 regarding the risk of intracranial hypertension for the precocious puberty indication for this drug, which is administratively managed in DUOG. DGE sent SLC notification letters for the same issue for drugs in the same class that are administratively managed in their division. The action date of approval is expected to be in 4/2022.

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Publications and External Presentations

External Presentations					
Office/ Division	FDA Presenters	Conference/Workshop/Mtg	Title/Topic	Location	Date and Time
NONRESPONSIVE					

Medical Countermeasures

Drug Name	App. No.	Division	App. Information/Meeting Dates/Status
NONRESPONSIVE			

Leave and Coverage

NONRESPONSIVE

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

In Clearance, OND-Authored
NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

NONRESPONSIVE

Working Groups and Standing Sub-Committees

Project	Purpose	Risk/ Mitigation	Due Date
NONRESPONSIVE			

Project	Purpose	Risk/ Mitigation	Due Date
NONRESPONSIVE			

Citizen Petitions

Drug Name or Subject	Sponsor	Docket No.	Date Rec'd	Planned Action Date	Division	Brief Description of Issue
NONRESPONSIVE						

Regulatory Science Research Program Update

NONRESPONSIVE

Modernization Update

Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

[PAGE * MERGEFORMAT]

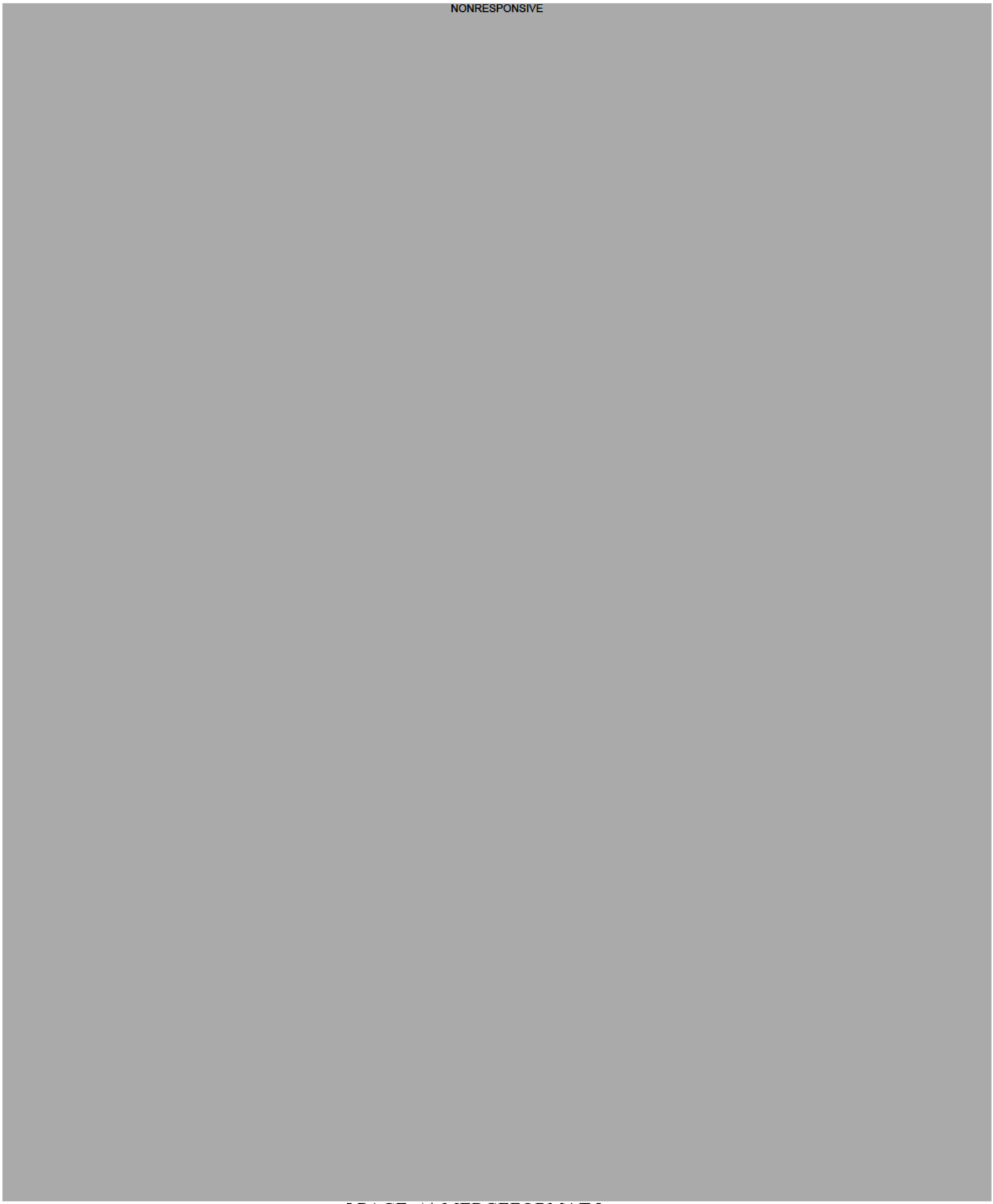
Office of New Drugs Biweekly Report

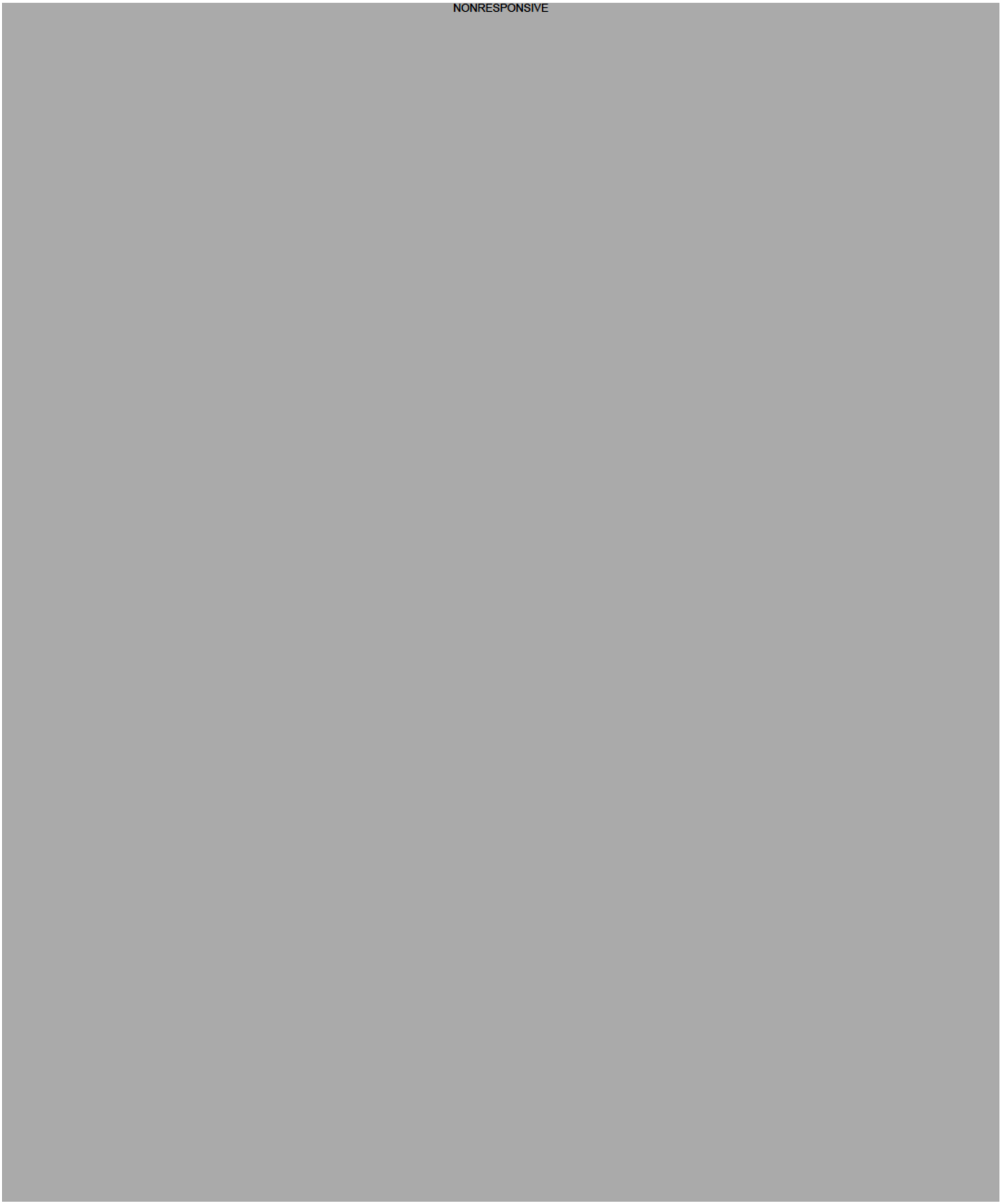
April 1, 2022

Reporting Period: March 21st to April. 29th

NONRESPONSIVE

[PAGE * MERGEFORMAT]

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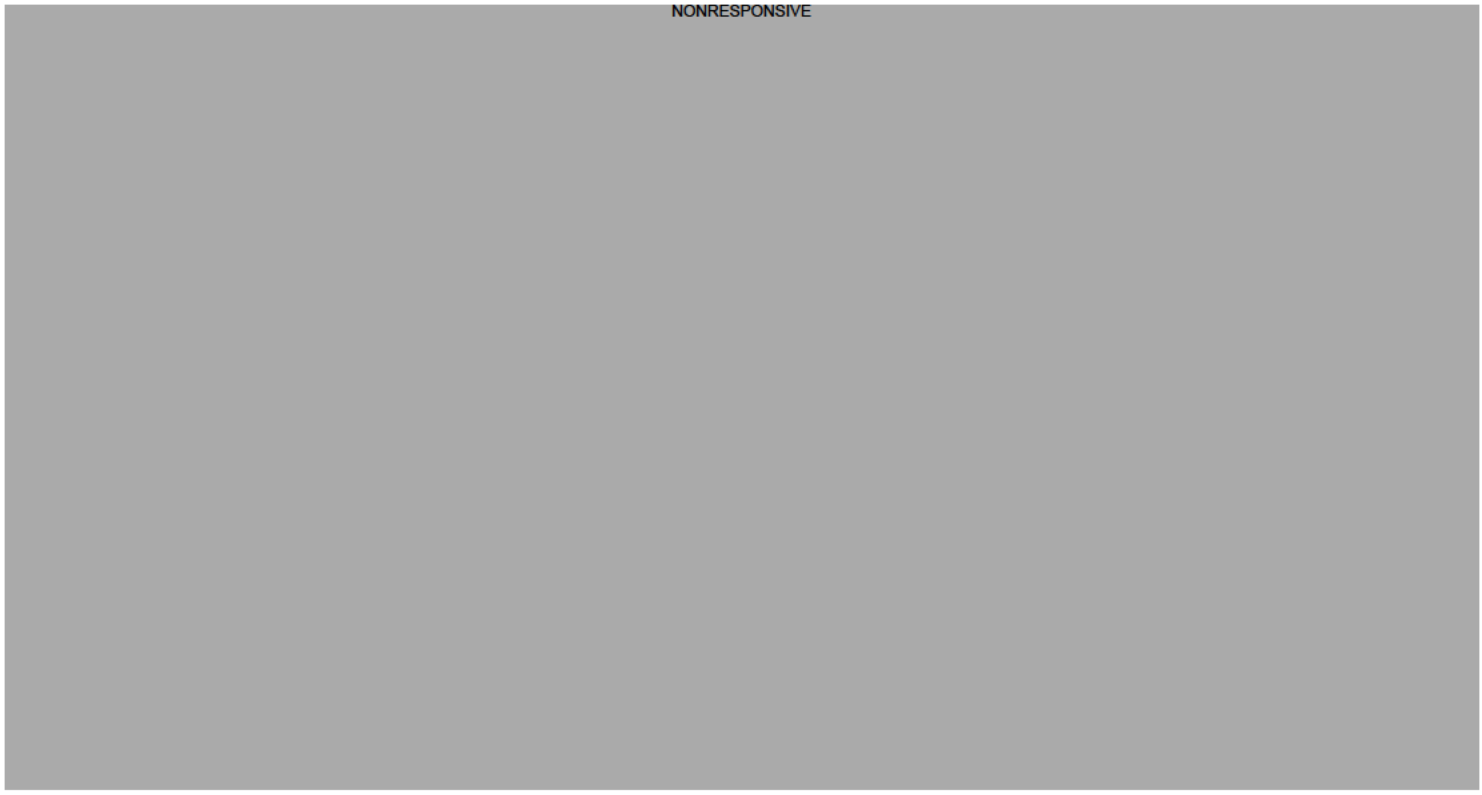
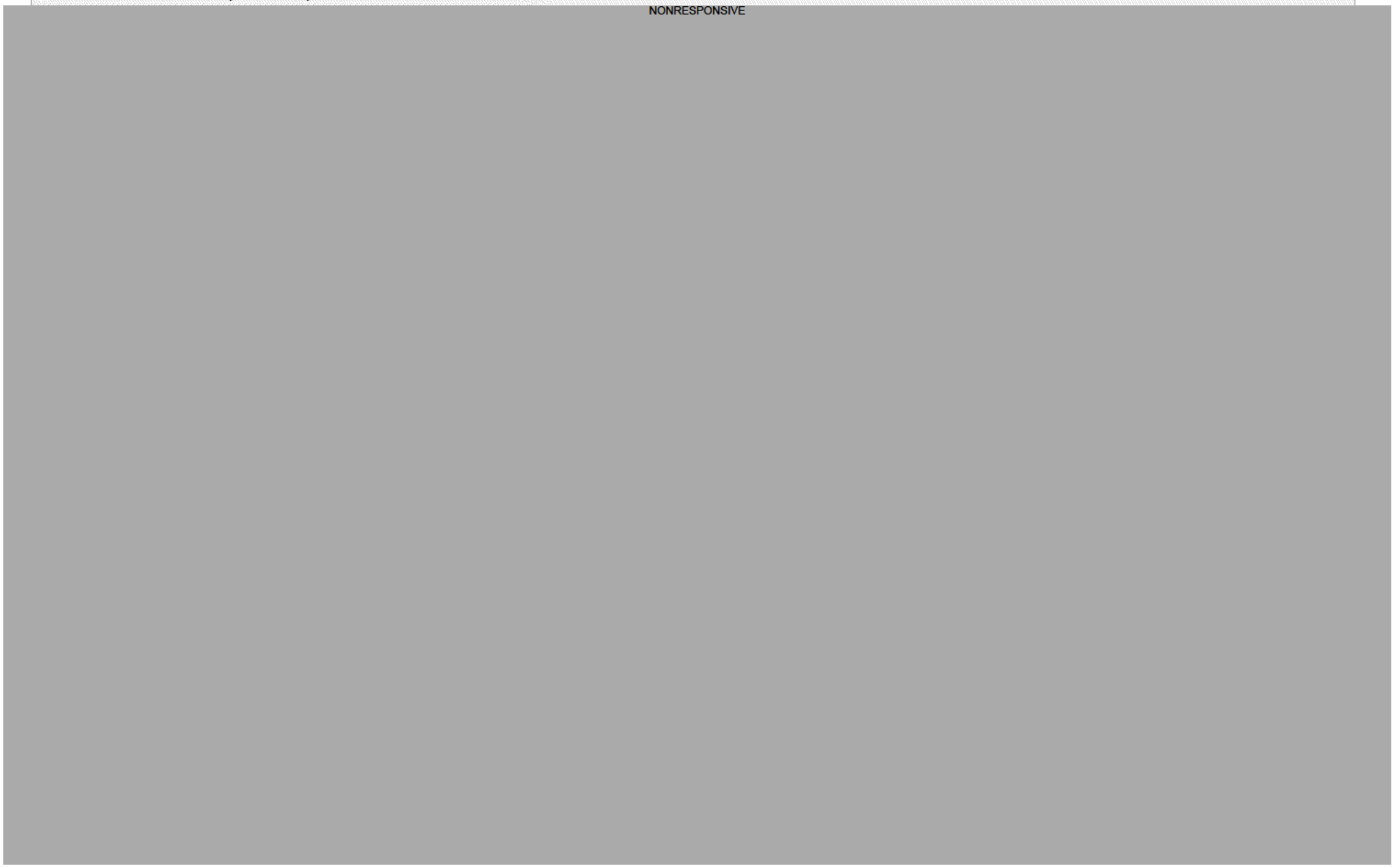

NONRESPONSIVE

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)
NONRESPONSIVE

[PAGE * MERGEFORMAT]


NONRESPONSIVE

505(b)(2) Applications

NONRESPONSIVE

[PAGE * MERGEFORMAT]

505(b)(2) Applications

NONRESPONSIVE

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

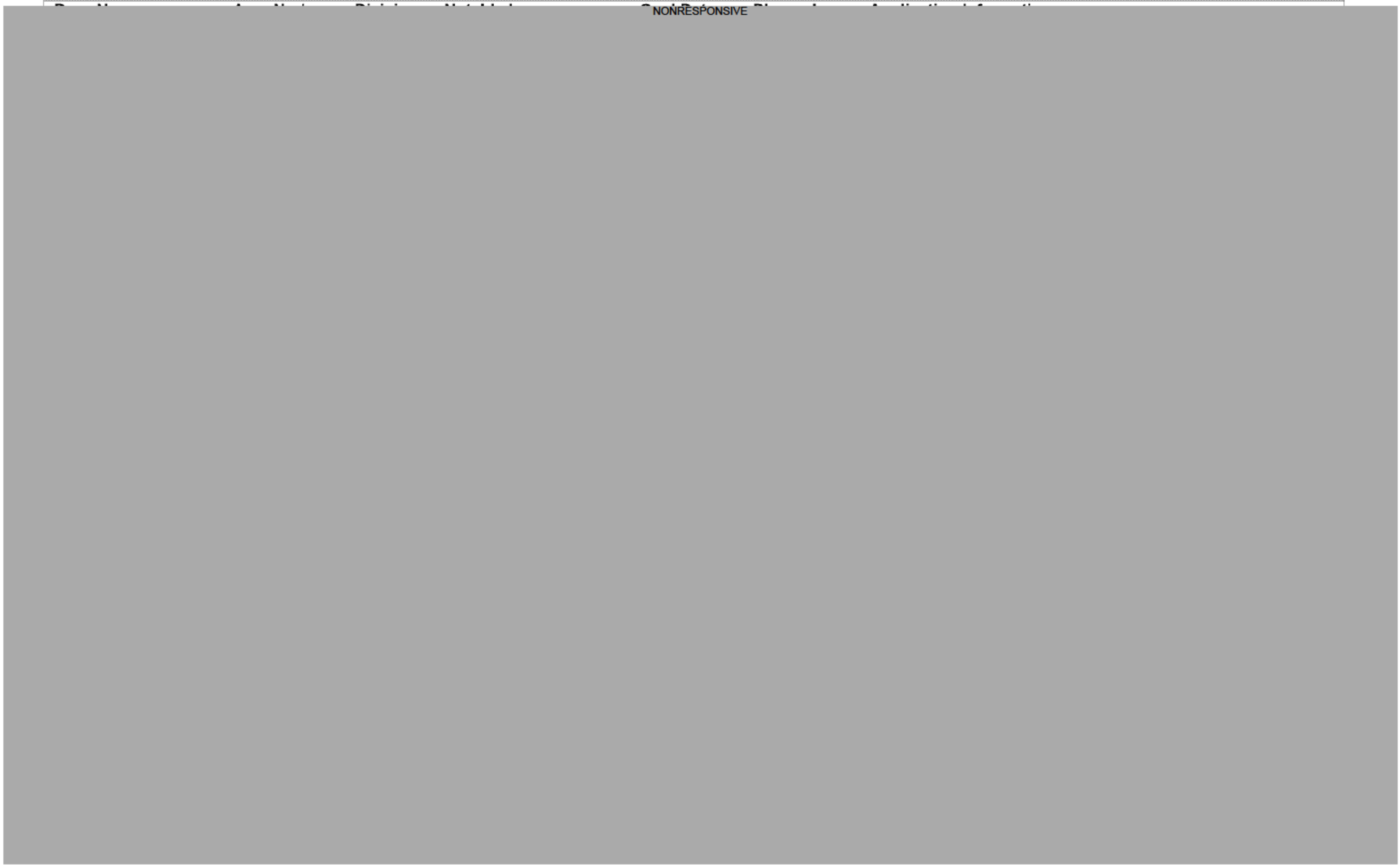
Biosimilar Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements

NONRESPONSIVE



Efficacy Supplements

NONRESPONSIVE

Other Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

[PAGE * MERGEFORMAT]

Notable Type A/Type B						
Meeting Type	**Drug Name**	**App. No.**	**Division**	**Notable Issue**	**Meeting Dates (Internal/Sponsor)**	**Application Information**

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Division	Date	Summary

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Medical Policy and Program Review Council

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

Safety Issues

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description

NONRESPONSIVE

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				
GnRH agonists	multiple	DGE	4/26/2022	NISS 1004605: GnRH agonists indicated to treat central precocious puberty and idiopathic intracranial hypertension; SLC notification issued on 2/10/2022 (DSC not planned).
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				
Nafarelin	NDA 019886	DUOG	4/2022	SLC notification letter sent 2/10/2022 regarding the risk of intracranial hypertension for the precocious puberty indication for this drug, which is administratively managed in DUOG. DGE sent SLC notification letters for the same issue for drugs in the same class that are administratively managed in their division. The action date of approval is expected to be in 4/2022.
NONRESPONSIVE				

Publications and External Presentations

External Presentations
NONRESPONSIVE

Leave and Coverage

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

NONRESPONSIVE

Working Groups and Standing Sub-Committees

NONRESPONSIVE

Regulatory Science Research Program Update

NONRESPONSIVE

project record are verified. SPARTA will remain open for approvals until Friday, April 15, 2022.

NONRESPONSIVE

Modernization Update

Workstream	Current Status	Upcoming Milestones

NONRESPONSIVE

Workstream	Current Status	Upcoming Milestones
	NONRESPONSIVE	

Office of New Drugs Biweekly Report

April 15, 2022

Reporting Period: April 4th to May. 13th

NONRESPONSIVE

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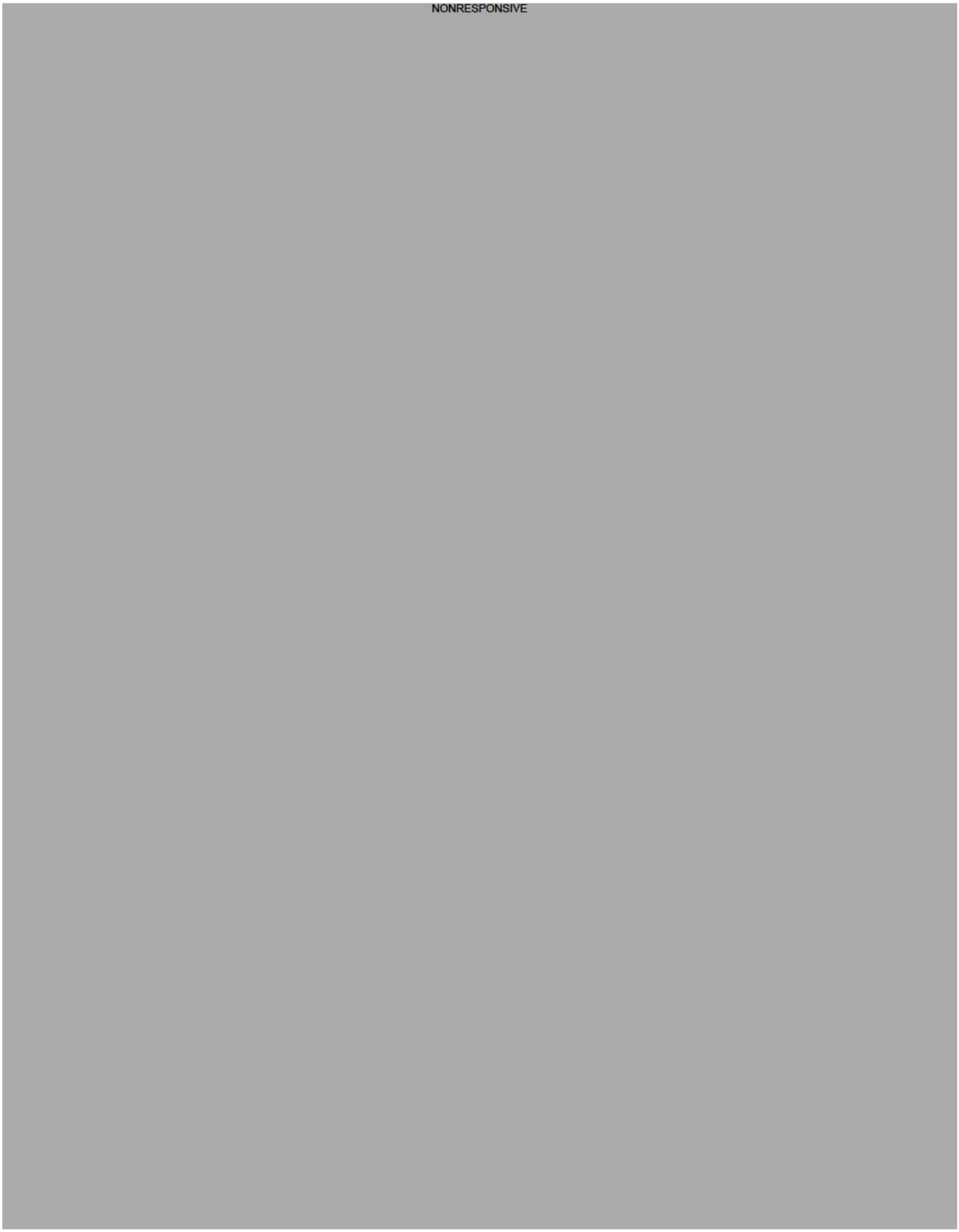

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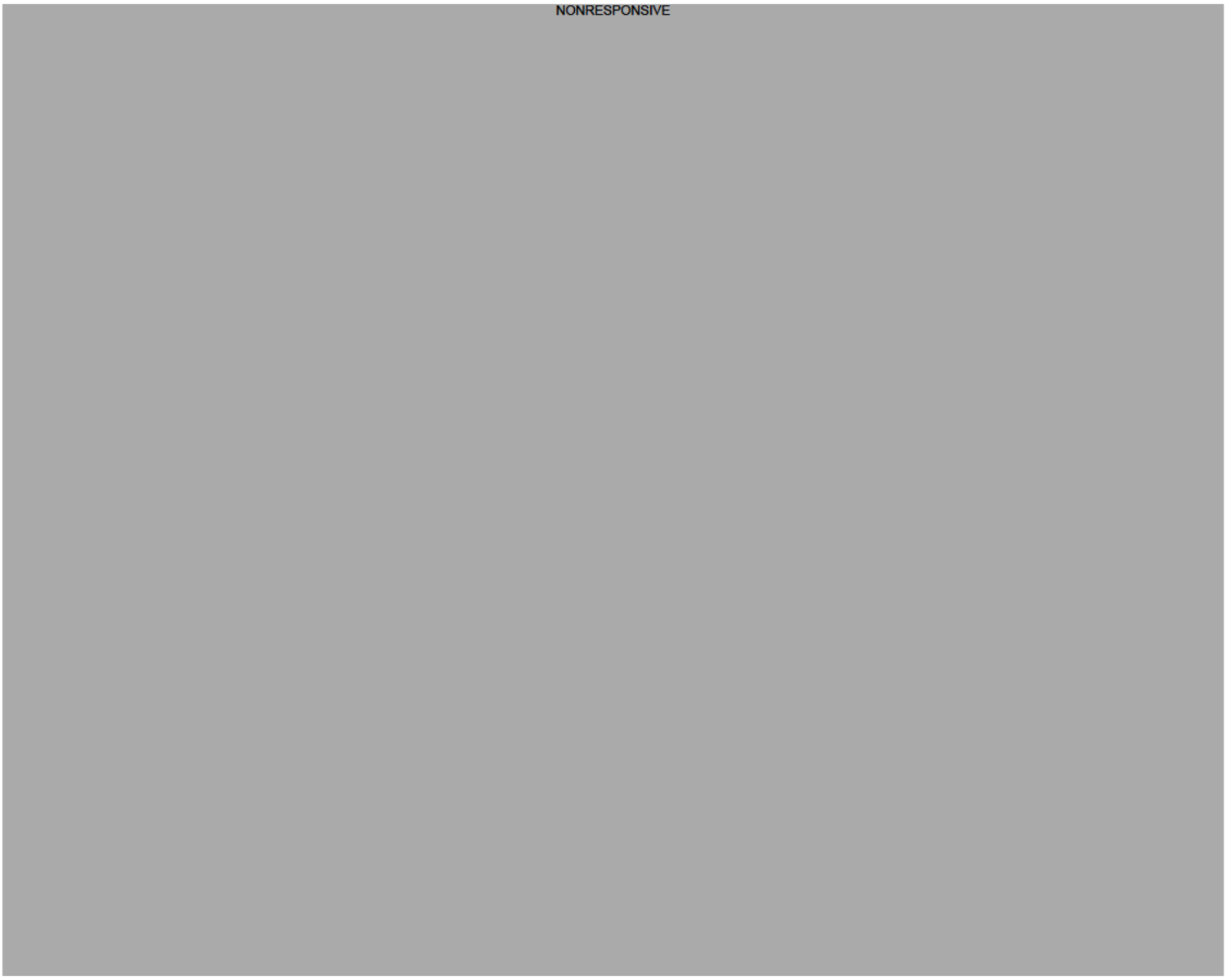

NONRESPONSIVE

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	**App. No./ Filing Status**	**Division**	**Notable Issue**	**Goal Date (PDUFA/ BsUFA)**	**Planned Action Date**	**Application Information Planned Action**
NONRESPONSIVE						
Lupron Depot 7.5 mg; 3M 22.5 mg, 4M 30 mg, and 6M 45 mg	NDA 019732/ S-045 NDA 020517/ S-043 Filed	DO 1		6/6/2022	5/6/2022	Abbvie; palliative treatment of advanced prostatic cancer; supplement is requesting to remove "palliative" from palliative treatment of advanced prostatic cancer. Filing date: 10/5/2021.
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Notable IND Applications

Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Biosimilar Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information

NONRESPONSIVE

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary

NONRESPONSIVE

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary

NONRESPONSIVE

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Drug Name or Meeting Title	Division	Date	Summary

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Medical Policy and Program Review Council

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

Safety Issues

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description

NONRESPONSIVE

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
GnRH agonists	multiple	DGE	4/21/2022	NISS 1004605: GnRH agonists indicated to treat central precocious puberty and idiopathic intracranial hypertension; SLC notification issued on 2/10/2022 (DSC not planned).
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	**App. No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				
Nafarelin	NDA 019886	DUOG	4/2022	SLC notification letter sent 2/10/2022 regarding the risk of intracranial hypertension for the precocious puberty indication for this drug, which is administratively managed in DUOG. DGE sent SLC notification letters for the same issue for drugs in the same class that are administratively managed in their division. The action date of approval is expected to be in 4/2022.

Publications and External Presentations

External Presentations					
Office/ Division	**FDA Presenters**	**Conference/Workshop/Mtg**	**Title/Topic**	**Location**	**Date and Time**
NONRESPONSIVE					

External Presentations

NONRESPONSIVE

Leave and Coverage

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

In Clearance, OND-Authored

NONRESPONSIVE

In Clearance, Authored Outside of OND
NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

In Clearance
NONRESPONSIVE

Working Groups and Standing Sub-Committees

Project	Purpose	Risk/ Mitigation	Due Date
NONRESPONSIVE			

Project	Purpose	Risk/ Mitigation	Due Date
NONRESPONSIVE			

Regulatory Science Research Program Update

NONRESPONSIVE

Modernization Update

Workstream	Current Status	Upcoming Milestones
	NONRESPONSIVE	

[PAGE * MERGEFORMAT]

Workstream	Current Status	Upcoming Milestones
	NONRESPONSIVE	

Office of New Drugs Biweekly Report

July 22, 2022

Reporting Period: July 11th to August 19th

Key:

Blue text indicates new information or new applications that were not on the previous report.

Red text indicates an application that did not receive action on the PDUFA/goal date.

NONRESPONSIVE

NONRESPONSIVE

[PAGE * MERGEFORMAT]

approval to regular approval. Received on February 24, 2022. Filing date: April 25, 2022. PDUFA date: August 24, 2022. Planned action date: August 4, 2022.

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)						
Drug Name	**App. No./ Filing Status**	**Division**	**Notable Issue**	**Goal Date (PDUFA)**	**Planned Action Date**	**Application Information Planned Action**
NONRESPONSIVE						

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications.							
Drug Name	App. No./	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Notable IND Applications.							
Drug Name	App. No./	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Biosimilar Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	**App. No./ Filing Status**	**Division**	**Notable Issue**	**Received Date**	**Goal Date (PDUFA/ BsUFA)**	**Planned Action Date**	**Application Information Planned Action**
NONRESPONSIVE							
Lupron Depot-PED (leuprolide acetate for depot suspension)	NDA 020263/ S-053 Unfiled	DGE		6/14/2022	4/14/2023	4/14/2023	AbbVie Endocrinology; additional 45 mg 6-month dosing regimen to the approved indication for the treatment of pediatric patients with central precocious puberty. Filing goal date: 8/13/2022.
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Notable Type A/Type B

Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Other Notable End-of-Phase Meetings

Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Other Notable End-of-Phase Meetings					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Meeting Dates (Internal/Sponsor)**	**Application Information**
NONRESPONSIVE					

[PAGE * MERGEFORMAT]

Clinical Holds					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Date Issued**	**Application Information**
NONRESPONSIVE					

[PAGE * MERGEFORMAT]

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

CDER Biosimilar Review Committee, CDER/CBER Biosimilar Policy Council, and CDER/CBER Biologicals Product Classification Subcommittee

Meeting Type	App. No.	Date	Office/ Division	Topic
NONRESPONSIVE				

Safety Issues

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**

NONRESPONSIVE

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description

NONRESPONSIVE

Publications and External Presentations

Publications			
Office/ Division	FDA Authors	Citation with Link	Publication Date

NONRESPONSIVE

Publications			
Office/ Division	FDA Authors	Citation with Link	Publication Date
NONRESPONSIVE			

External Presentations					
Office/ Division	FDA Presenters	Conference/Workshop/Mtg	Title/Topic	Location	Date and Time
NONRESPONSIVE					

Medical Countermeasures

Drug Name	App. No.	Division	App. Information/Meeting Dates/Status
NONRESPONSIVE			

Leave and Coverage

NONRESPONSIVE

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

In Clearance, OND-Authored			
Authoring Div. or Office	Title of Guidance/Document	Status (Draft, Final or Revision)	OND Clearance Due Date
NONRESPONSIVE			

In Clearance, Authored Outside of OND
NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

In Clearance
NONRESPONSIVE

Working Groups and Standing Sub-Committees

Project	Purpose	Risk/ Mitigation	Due Date
NONRESPONSIVE			

Modernization Update

Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

Office of New Drugs Biweekly Report

June 24, 2022

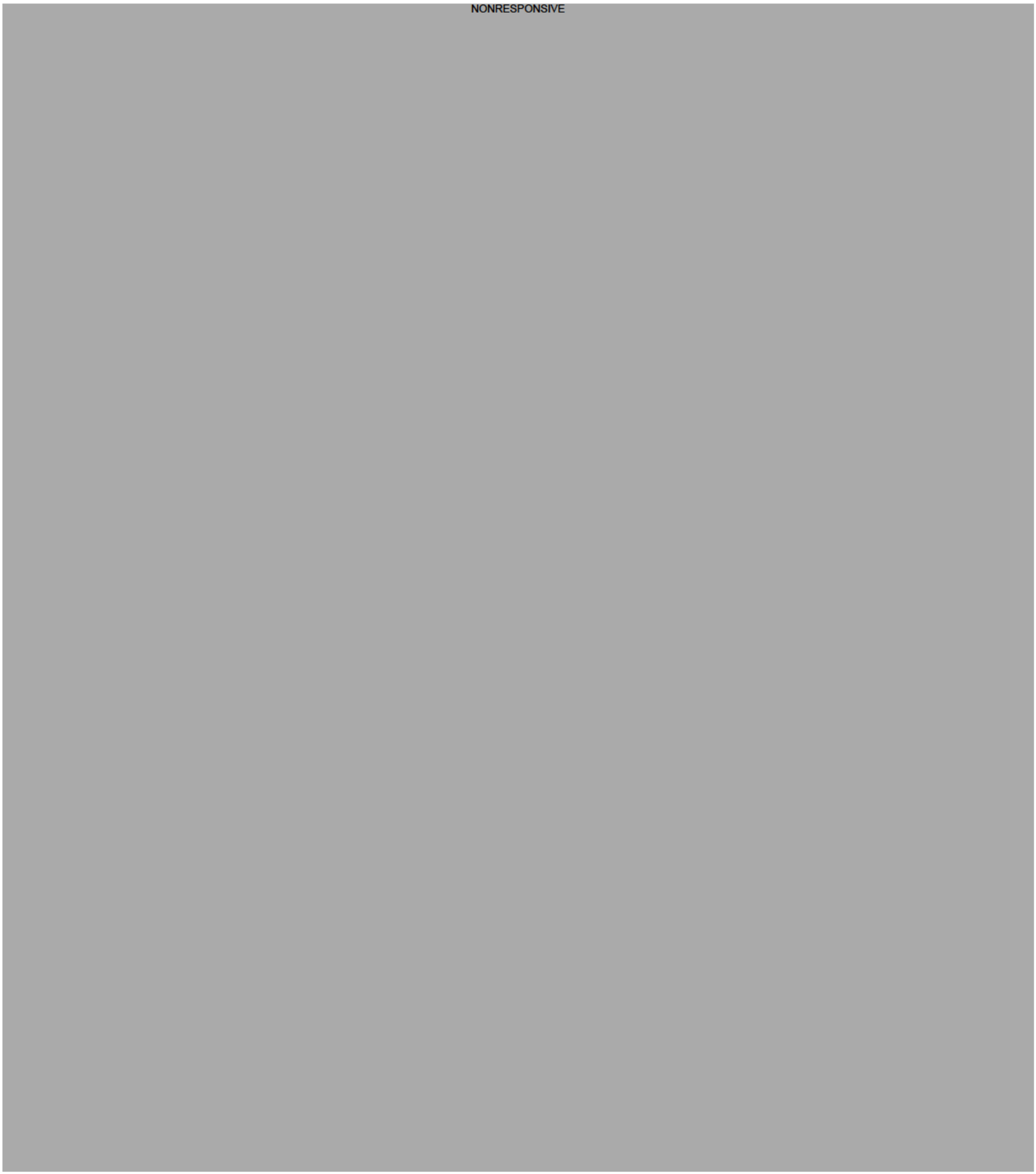
Reporting Period: June 13th to July 22nd

Key:

Blue text indicates new information or new applications that were not on the previous report.

Red text indicates an application that did not receive action on the PDUFA/goal date.

NONRESPONSIVE



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Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

[PAGE * MERGEFORMAT]

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications							
Drug Name	App. No./ Status	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
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NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Notable Type A/Type B						
Meeting Type	**Drug Name**	**App. No.**	**Division**	**Notable Issue**	**Meeting Dates (Internal/Sponsor)**	**Application Information**

NONRESPONSIVE

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Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Notable Type A/Type B

Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Other Notable End-of-Phase Meetings

Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Other Notable End-of-Phase Meetings					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Meeting Dates (Internal/Sponsor)**	**Application Information**
NONRESPONSIVE					

Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information
NONRESPONSIVE					

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

[PAGE * MERGEFORMAT]

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Medical Policy and Program Review Council

Office/ Division	Drug Name or Meeting Topic	Briefing Date	Summary of Recommendations (if available)
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

[PAGE * MERGEFORMAT]

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

Safety Issues

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**

NONRESPONSIVE

Newly Identified Safety Signals

Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Drug Safety Communications

Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change

Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description

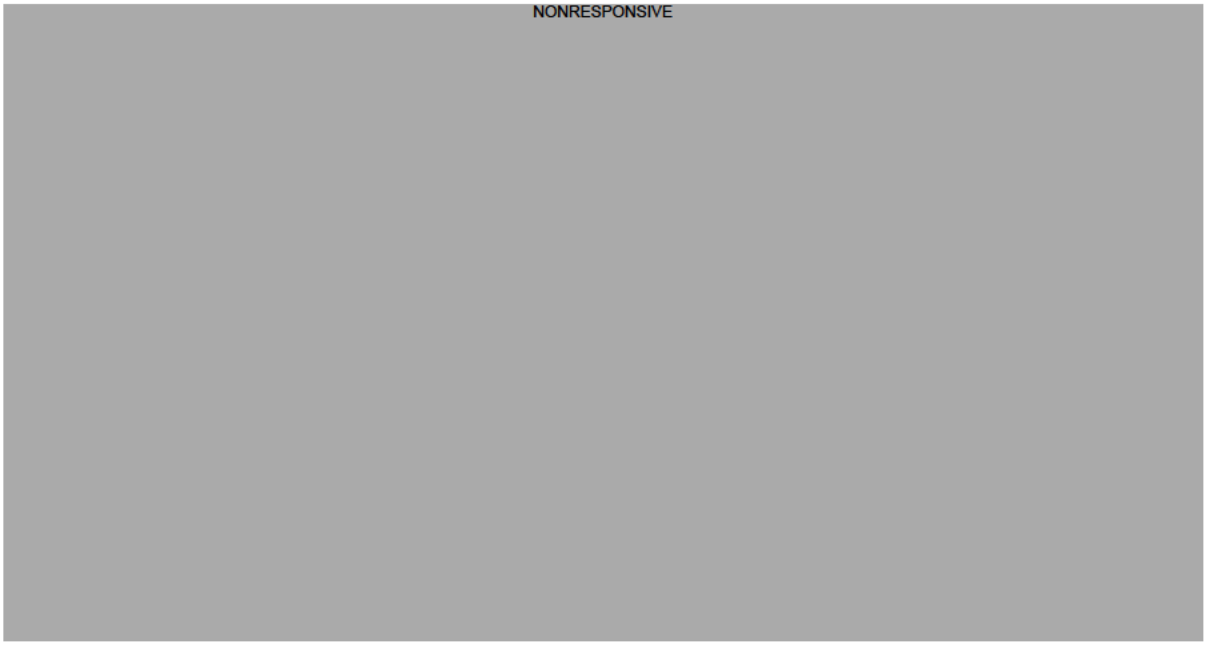
NONRESPONSIVE

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

External Presentations					
Office/ Division	FDA Presenters	Conference/Workshop/Mtg	Title/Topic	Location	Date and Time
NONRESPONSIVE					

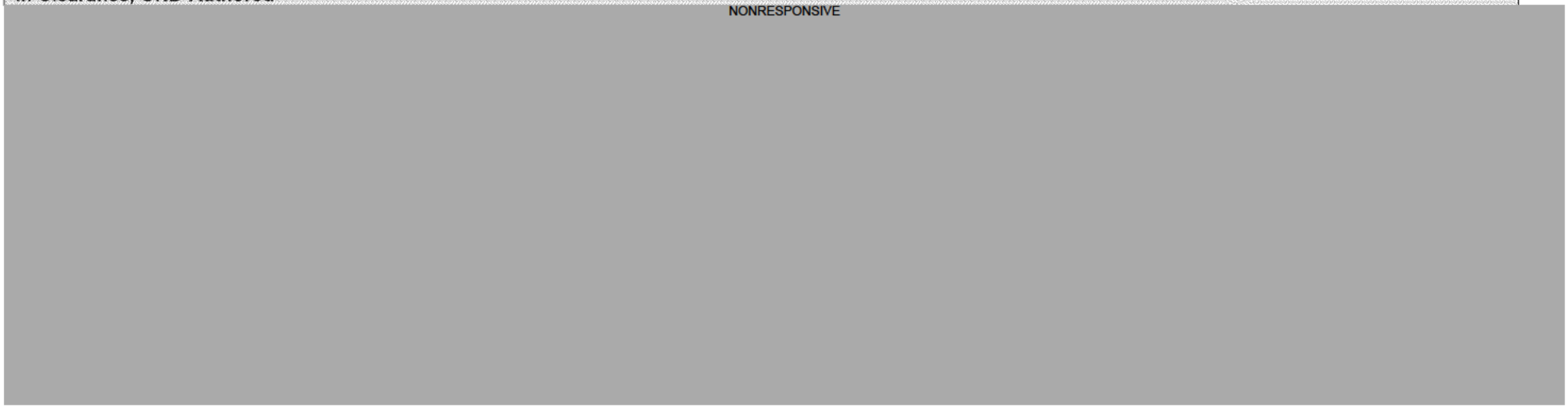
Leave and Coverage

NONRESPONSIVE



Guidances and Noteworthy Policy Documents Recently Published or In Clearance

In Clearance, OND-Authored
NONRESPONSIVE



In Clearance, Authored Outside of OND
NONRESPONSIVE

MAPPs and Noteworthy Process Documents In Clearance

In Clearance
NONRESPONSIVE

Working Groups and Standing Sub-Committees

Project	Purpose	Risk/ Mitigation	Due Date
NONRESPONSIVE			

Modernization Update

Workstream	Current Status	Upcoming Milestones
NONRESPONSIVE		

Workstream	Current Status	Upcoming Milestones
	NONRESPONSIVE	

Best Pharmaceuticals for Children Act
and
Pediatric Research Equity Act

Status Report to Congress
July 1, 2015 – June 30, 2020

TABLE OF CONTENTS

Executive Summary

Section 508 of the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, requires the Secretary of Health and Human Services to report on the implementation of sections 505A and 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which are commonly known as the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), respectively. This report was first required to be submitted to Congress by July 9, 2016, and then every 5 years thereafter. In addition to the FDASIA requirements, the FDA Reauthorization Act of 2017 (FDARA) added more reporting requirements for HHS, including requirements related to (1) pediatric research and labeling of certain drugs[1] for the treatment of cancer, and (2) the timing for submission of pediatric studies in accordance with BPCA and PREA.

This report, submitted pursuant to FDASIA and FDARA, (1) provides an assessment of implementation of BPCA and PREA, as well as the impact of those statutes, (2) highlights additional successes stemming from these two statutes, and (3) offers suggestions for advancing pediatric drug development by ensuring that the objectives underlying BPCA and PREA are effectively and efficiently implemented.

Background

This Executive Summary will provide a brief overview of the main points included in this report regarding (1) the impact of BPCA and PREA, including pediatric studies and labeling, timeliness of pediatric drug development, drug development for special populations, including children with cancer, children with rare diseases, and neonates, and the pediatric drug testing research program at the National Institutes of Health (NIH) and (2) the additional successes stemming from BPCA and PREA, including advances in regulatory science for pediatric drug development and global harmonization of pediatric research and drug development. In addition, this Executive Summary will briefly highlight FDA's work to help ensure COVID-19 therapeutics and vaccines are appropriately developed for children and will note the importance of post-marketing safety surveillance. Finally, this Executive Summary will conclude by listing the three potential program improvements described in this report.

Pediatric Studies and Labeling

The enactment of BPCA and PREA, each permanently authorized under FDASIA, has led to significant progress in the number, timeliness, and successful completion of studies

[1] In this report, references to *drugs* and *drug products* include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

of drugs in pediatric populations. Because of these legislative initiatives which require or incentivize pharmaceutical companies to develop medicines for children, labeling for over 900 drugs now contains new pediatric use information. Further, earlier integration of pediatric study planning has now become routine in drug development, a notable shift from the era before these laws were enacted.

Timeliness of Pediatric Drug Development

The successful implementation of BPCA and PREA is due, in part, to efforts by the U.S. Food and Drug Administration's (FDA's) Pediatric Review Committee (PeRC) which works across the Agency to consistently encourage timely pediatric drug development. During PeRC's weekly meetings, pediatricians and numerous other experts in disciplines such as chemistry, ethics, neonatology, pharmacology, statistics, and toxicology provide input and recommendations on pediatric submissions received by FDA from sponsors pursuant to BPCA and PREA (e.g., initial Pediatric Study Plans (iPSPs)). The PeRC has been working diligently to ensure that FDA provides timely responses and meaningful advice to pharmaceutical industry sponsors seeking to obtain a Written Request (WR) to conduct pediatric studies under BPCA. As such, FDA has met the requirement in section 505A(d)(3) of the FD&C Act, added by FDARA, to respond to a Proposed Pediatric Study Request (PPSR) within 120 days for nearly 90 percent of submissions. Additionally, the PeRC continues to provide consultation on all pediatric study plans submitted in accordance with PREA and to review all deferral extension requests for those studies to ensure the proposed pediatric study timelines are reasonable. FDA will continue these efforts to ensure timely pediatric studies are conducted by industry, thereby helping reduce the delay between the original approval of a drug and the incorporation of pediatric use information in labeling, which currently stands at approximately 6 years.

Development of Pediatric Cancer Drugs

An important shift in the regulatory landscape for pediatric cancer drug development has occurred with the implementation of FDARA. For example, early evidence suggests that the PREA amendments under section 504 of FDARA, commonly known as the Research to Accelerate Cures and Equity (RACE) for Children Act, have had a favorable impact on the timely consideration and initiation of studies of appropriate molecularly targeted cancer drugs that would previously have not been required and that would historically have gone unstudied in children.

FDA has engaged with stakeholders, including academia, the pharmaceutical industry, and patient advocacy groups, to implement the requirements under FDARA and to meet the needs of children with cancer. In accordance with FDARA, FDA issued "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology

Drugs: Amendments to Sec. 505B of the FD&C Act."[2] Further, to ensure the continued success of multi-disciplinary review through the PeRC, FDA created an Oncology Subcommittee of the PeRC to manage the increasing number of submissions related to pediatric cancer drug development. This subcommittee helps facilitate not only more timely and efficient pediatric development plans but also earlier discussions with sponsors regarding the issuance of WRs for oncology products, when appropriate.

Development of Drugs for Rare Pediatric Diseases

The Rare Pediatric Disease Priority Review Voucher incentive program, which was established under section 908 of FDASIA, has also impacted the paradigm for the development of drugs to treat certain rare childhood diseases. The program specifically targets diseases that have serious or life-threatening manifestations that primarily affect children. Since the incentive program began, FDA has granted over 480 rare pediatric disease designations for over 220 unique pediatric diseases and has awarded 32 rare pediatric disease priority review vouchers. However, drug development for rare pediatric diseases remains a challenge. As described in the 2019 report to Congress titled *Pediatric Labeling of Orphan Drugs*, which was required under FDARA, there is a public health need for additional pediatric information to be included in the labeling for over one-third of approved orphan indications that are relevant to the pediatric population.[3]

Development of Drugs for Neonates

Unique challenges persist regarding the conduct of studies in neonates, but FDA continues to encourage the conduct of these studies when appropriate. Considerable strides have been made since FDA's neonatology program was developed, with steady growth of the neonatal and perinatal consultation service for FDA's reviewers. FDA has been working to foster drug development for neonates and to overcome the obstacles to advancing neonatal regulatory science, particularly through its work with the International Neonatal Consortium. Guidance development to support the conduct of studies in neonates remains a focus for FDA. In 2019, in accordance with the requirements established in FDARA, FDA issued a draft guidance document to address the clinical pharmacology considerations for any planned studies in neonatal populations.[4] However, the current paradigm for drug development under BPCA and PREA has generally not resulted in a significant increase in research addressing neonatal-specific diseases and conditions. Since the first BPCA and PREA report to Congress in 2016, the labeling for 22 drugs has been updated to include essential information for

[2] https://www.fda.gov/media/133440/download.

[3] https://www.fda.gov/media/130060/download.

[4] https://www.fda.gov/media/129532/download. When final, this guidance will represent FDA's current thinking on this topic.

neonates, of which three labeling updates resulted from studies of off-patent drugs conducted through the pediatric drug testing research program at NIH.

The NIH Pediatric Drug Testing Research Program

The NIH program, established under section 409I of the Public Health Service Act in 2002 under the Best Pharmaceuticals for Children Act, has played a critical role in obtaining information about pediatric use of off-patent drugs. FDA and the National Institute of Child Health and Human Development (NICHD), which is part of NIH, collaborate on the study of off-patent drugs in pediatric clinical trials conducted under this program. The Pediatric Trials Network, established through an NICHD-awarded contract to the Duke Clinical Research Institute in 2010, has been vital to the continued growth and success of the NIH program. Between 2002 and 2016, FDA approved the labeling for three off-patent drugs as a result of this program. In the 5 years since the 2016 report to Congress, this number has more than tripled, with FDA approving the labeling for seven additional off-patent drugs.

Advances in Regulatory Science for Pediatric Drug Development

The legislative mandates in BPCA and PREA have stimulated scientific growth and innovation in the way drugs are developed for children. FDA has hosted numerous workshops to examine ways to optimize pediatric drug development and has published many peer-reviewed manuscripts describing scientific advances. The knowledge gained from these workshops and manuscripts has extended into tangible resources, as FDA has issued multiple guidance documents specifically related to scientific considerations in pediatric drug development. In addition, as described in this report, these workshops have been helpful to address specific challenges in pediatric drug development programs and may lead to opportunities for defining a feasible path forward, particularly for historically challenging drug development areas. Advancing the regulatory science to support timely and effective pediatric drug development remains a priority for FDA.

Global Harmonization of Pediatric Research and Drug Development

As FDA's work to enhance pediatric drug development continues, particularly for pediatric cancer, rare pediatric diseases, and neonates, the importance of international collaboration remains clear. FDA has continued to engage with stakeholders internationally to help assure children around the world participate in clinical trials that are well designed to meet international regulatory standards. FDA continues to host Pediatric Cluster conference calls with international regulators which, since their inception in 2007, have facilitated discussion of 570 products proposed for pediatric studies. In addition, as described in this report, FDA has collaborated with numerous international stakeholders through working groups seeking to advance pediatric drug development and foster consensus on regulatory approaches. International collaborative efforts have helped improve the development of therapeutics globally by (1) increasing

the efficiency of clinical trial enrollment for small populations, (2) expanding information and knowledge-sharing with global experts, and (3) harmonizing clinical trial designs to meet requirements across regulatory authorities.

COVID-19 Therapeutics and Vaccines for Children

The increasing connectivity of our world and the benefits of aligning on global activities have been highlighted by the coronavirus disease 2019 (COVID-19) pandemic. FDA has been working diligently to help ensure COVID-19 therapeutics and vaccines are appropriately developed for children. For example, between January 2020 and October 2021, FDA facilitated an international discussion of COVID-19 products at 17 Pediatric Cluster conference calls and issued five Common Commentaries, which are documents that convey non-binding high-level comments from regulators to pharmaceutical industry sponsors, to align and expedite international development for COVID-19 pediatric therapeutics. Also, PeRC discussions related to COVID-19 product development have highlighted the need for the ethical inclusion of children, including neonates, in clinical trials when appropriate. Between January 2020 and October 2021, the PeRC reviewed 49 iPSPs for products relevant to COVID-19 that are subject to PREA.

Pediatric Advisory Committee and Post-Marketing Pediatric Safety Surveillance

Product development during the pandemic has underscored the importance of an efficient and effective post-marketing surveillance of the safety of products in the pediatric population. FDA continues to implement the congressionally mandated[5] post-marketing pediatric safety review process with reporting to the Pediatric Advisory Committee. Several important labeling changes, which will be highlighted in this report, have stemmed from this process and from discussions with the committee.

Program Improvements for Continued Advancement of Product Development in Children

As this report will demonstrate, BPCA and PREA have been instrumental in improving pediatric drug development and labeling. To continue advancing product development for children, FDA will conclude this report with the following three potential program improvements that may help ensure the objectives underlying the statutes are effectively and efficiently implemented: (1) removal of the orphan exemption under PREA, (2) modernize pediatric pharmacovigilance, and (3) establish a periodic review of Humanitarian Device Exemptions.

[5] See sections 505A(l) and 505B(i) of the FD&C Act.

Introduction

Pediatric drug studies and labeling are governed largely by two sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act): section 505A and section 505B. First, to incentivize sponsors to conduct pediatric studies of drugs when the U.S. Food and Drug Administration (FDA or Agency) determines the studies may produce benefits in pediatric populations, section 505A of the FD&C Act (commonly referred to as the Best Pharmaceuticals for Children Act (BPCA)), allows FDA to issue Written Requests (WRs) to pharmaceutical industry sponsors to conduct those studies. Upon completion of these studies, sponsors can qualify for 6 months of marketing exclusivity as an incentive to do so. BPCA allows FDA to request pediatric studies of drugs that cannot be required under section 505B of the FD&C Act (commonly referred to as the Pediatric Research Equity Act (PREA)) when the applications or supplements for those drugs are not subject to the requirements of PREA. Second, PREA requires that sponsors of certain new drug applications (NDAs), biologics license applications (BLAs), or supplements thereto submit, as applicable (1) assessments regarding the drug's safety, effectiveness, dosing, and administration in pediatric populations or (2) reports on the molecularly targeted pediatric cancer investigation that is designed to yield clinically meaningful pediatric study data regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.[6] Together, these statutes encourage more effective labeling of drug and biological products for use in neonates, infants, children, and adolescents.[7]

In the 2016 BPCA and PREA report to Congress,[8] FDA provided a detailed overview of the history of pediatric laws, rules, and regulations. That report highlighted FDA's efforts as early as 1994 to add pediatric use information in labeling and described the first pediatric drug development incentive legislation that was enacted as part of the Food and Drug Administration Modernization Act (FDAMA) in 1997. These early efforts paved the way for the subsequent enactment, in 2002 and 2003, of the BPCA and PREA, respectively, both of which became permanent in 2012, with modifications, under the Food and Drug Administration Safety and Innovation Act (FDASIA).[9]

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[6] Sponsors must submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation with any application (or supplement to an application) for which such assessments or reports are required by PREA, unless FDA defers or waives the requirement. See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act.

[7] There are other laws that impact pediatric studies of drugs and biologics, such as section 529 of the FD&C Act (i.e., the rare pediatric disease priority review voucher program) and sections 526 and 527 of the FD&C Act (which authorize orphan drug designation and orphan exclusivity). A further discussion of these laws is included, when relevant, in this report.

[8] See "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress" at https://www.fda.gov/media/99184/download.

[9] FDASIA (Pub. L. 112-144). 126 Stat. 993 (July 9, 2012).

BPCA and PREA have been amended several times over the years,[10] most recently in 2017 under the Food and Drug Administration Reauthorization Act of 2017 (FDARA). FDARA amended sections 505A of the FD&C Act and 505B of the FD&C Act as follows:

- Amended section 505A to require FDA (1) to review and act on a Proposed Pediatric Study Request (PPSR) or proposed amendment to a WR within 120 days of submission and (2) to submit to the Pediatric Review Committee (PeRC) any response to a PPSR.

- Amended section 505B(e)(2)(C) to require FDA, upon request, to meet with the sponsor of an application for a drug intended to treat a serious or life-threatening disease or condition to discuss preparation of the initial Pediatric Study Plan (iPSP) no later than the end-of-Phase 1 meeting or within 30 calendar days of request receipt, whichever is later.[11]

- Amended section 505B to require the sponsor of an original application for a new active ingredient, including a drug for an indication for which orphan designation has been granted, to submit with the application reports on the molecularly targeted pediatric cancer investigation if the drug or biological product that is the subject of the application is intended to treat an adult cancer and is directed at a molecular target that FDA determines is "substantially relevant to the growth or progression of a pediatric cancer."

- Amended section 505B(d) to require FDA to inform the Pediatric Advisory Committee (PAC) of correspondence about noncompliance with certain PREA requirements.

Section 508 of FDASIA requires the Secretary of Health and Human Services to report by July 9, 2016, and every 5 years thereafter, on various activities resulting from the implementation of sections 505A (BPCA) and 505B (PREA) of the FD&C Act. The 2016 BPCA and PREA status report to Congress, which was the initial such report, highlighted the progress made in the study of drugs in the pediatric population with a focus on the impact of the pediatric-specific provisions under FDASIA.[12] The current report provides an assessment of the implementation and impact of the pediatric statutes

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[10] Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85). 121 Stat. 823 (September 27, 2007); Patient Protection and Affordable Care Act (Pub. L. 111-148). 124 Stat. 119 (March 23, 2010); FDASIA(July 9, 2012); FDARA (Pub. L. 115-52). 131 Stat. 1005 (August 18, 2017).

[11] The law continues the requirement for applications for other drugs that FDA meet as soon as practicable, but within 90 calendar days of the receipt of the iPSP, unless FDA determines that a written response to the iPSP is sufficient to communicate comments on the iPSP and that no meeting is necessary. See section 505B(e)(2)(C) of the FD&C Act. FDA is also required to meet with applicants to discuss the bases for deferrals or waivers in accordance with section 505B(e)(2)(C)(i)(III) of the FD&C Act.

[12] See "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress" at https://www.fda.gov/media/99184/download.

on specific measures in accordance with requirements established under FDASIA, as well as the additional reporting requirements created under FDARA.[13] The report also highlights additional successes stemming from BPCA and PREA and offers suggestions for advancing pediatric drug development by ensuring that the objectives underlying the statutes are effectively and efficiently implemented.

Implementation and Impact of Pediatric Statutes: Mandated Reporting Elements and Other Requirements Under the Law

In accordance with the reporting requirements specified under FDASIA and FDARA, this section provides an assessment of the implementation and impact of BPCA and PREA in improving pediatric use information in labeling; describes FDA's implementation of the requirements under FDARA not only to achieve earlier submissions by sponsors of pediatric studies under BPCA but also to improve pediatric research and the labeling of drugs for pediatric cancer; describes successes and limitations to studying drugs for rare pediatric diseases; provides an overview of the progress and challenges in developing drugs for neonates; and describes achievements of the program under section 409I of the Public Health Service Act (409I program) at the National Institutes of Health (NIH). This section also highlights FDA's continued progress in the congressionally mandated[14] post-marketing pediatric safety review process with reporting to the PAC.

1.1 Pediatric Labeling and Timeliness of Pediatric Drug Development

1.1.1 Progress in Improving Pediatric Use Information in Labeling

Enactment of BPCA and PREA has led to significant progress in the number, timeliness, and successful completion of studies of drugs in pediatric populations. Over 900 drugs now contain new pediatric labeling information, largely resulting from the successful implementation of both BPCA and PREA.

Since the 2016 BPCA and PREA report to Congress, labeling for 281 products (211 drugs and 70 biologics) has been updated with pediatric use information. The labeling

[13] Unless otherwise noted, the data provided in this report extend 5 years from the end of the reporting period for the 2016 report to Congress (i.e., from July 1, 2015, through June 30, 2020). The additional reporting requirements under FDARA are reported from July 1, 2017, through June 30, 2020. However, to facilitate an assessment of the early impact of FDARA on pediatric cancer research, the report includes information for pediatric oncology through early 2021. Finally, given that the COVID-19 pandemic is an ongoing public health emergency, data for matters related to COVID-19 are provided from January 1, 2020, through October 31, 2021.

[14] See section 505A(l) and 505B(i) of the FD&C Act.

changes have provided important information to support pediatric use for a variety of diseases or conditions, including but not limited to allergies, viral infections, asthma, cancer, neurological disorders, and rare diseases. These labeling changes support the health of children by ensuring that pediatric healthcare providers can make evidence-based decisions about treating children with these conditions. The following list provides selected examples of pediatric approvals since the 2016 report to Congress:

- **Allergenics:** Palforzia (peanut (Arachis hypogaea) allergen powder-dnfp), an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut, for patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy.

- **Antivirals:** Harvoni (ledipasvir/sofosbuvir) for the treatment of hepatitis C in patients aged 3 years to 11 years; Tybost (cobicistat) for the treatment of HIV-1 infection in patients weighing at least 35 kilograms; Viread (tenofovir disoproxil fumarate) for the treatment of chronic hepatitis B in patients aged 2 years and older; and Intelence (etravirine) for the treatment of HIV-1 in patients aged 2 years to 6 years.

- **Asthma:** Nucala (mepolizumab), an add-on maintenance treatment of patients with severe asthma aged 6 years to 11 years; Dulera (mometasone furoate and formoterol fumarate dihydrate) for the treatment of asthma in patients 5 years to 11 years; Dupixent (dupilumab) as an add-on treatment in moderate to severe asthma in patients aged 12 years and older; and Arnuity Ellipta (fluticasone furoate) for the maintenance of asthma in patients aged 5 years to 11 years.

- **Cancer:** Blincyto (blinatumomab) for Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia in pediatric patients; Kymriah (tisaegenlecleucel; CAR T cell) for the treatment of acute lymphoblastic leukemia in patients aged 3 years and older; Opdivo (nivolumab) for treatment of microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer in patients aged 12 years and older; Rozlytrek (entrectinib) for treatment of solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy, in patients aged 12 years and older; and Sprycel (dasatinib) for Philadelphia chromosome-positive acute lymphoblastic leukemia in patients aged 1 year and older.

- **Neurological Disorders:** Gilenya (fingolimod) for the treatment of pediatric patients aged 10 years and older with relapsing-remitting multiple sclerosis; Lyrica (pregabalin) for treatment of partial-onset seizures in patients aged 1 month to 4 years; and Fycompa (perampanel) for the treatment of partial onset seizures in patients aged 4 years and older.

- **Rare Diseases:** Koselugo (selumetinib) for the treatment of patients aged 2 years and older with neurofibromatosis type 1; Lampit (nifurtimox) for the treatment of Chagas disease in patients aged birth to less than 18 years; and Luxturna (voretigene neparvovec-rzyl) for biallelic RPE65 mutation-associated retinal dystrophy in pediatric patients.

See Appendix 1 for a complete list of labeling changes under BPCA and PREA.

1.1.2 Timeliness of Pediatric Study Planning and Conduct Under BPCA and PREA

Earlier integration of pediatric study planning has now become routine in drug development, a notable shift from the era before BPCA and PREA were enacted. Successful implementation of these laws is due, in part, to FDA's efforts to consistently encourage, across the Agency through weekly meetings of the PeRC, the timely development of pediatric drugs. Although it remains difficult to assess the impact of earlier study planning under these laws on the timeliness of completing pediatric studies, FDA has implemented the strategies described below that have improved this timeliness. See section 1.1.2.5 of this report for more information.

1.1.2.1 *Encouraging Earlier Submission of Studies Under BPCA and PREA*

Section 505(c) of FDARA required FDA, acting through the PeRC, to develop and implement a plan no later than 1 year after enactment to achieve, when appropriate, a sponsor's earlier submission of pediatric studies under BPCA. This plan was to include recommendations to achieve (1) an earlier discussion of PPSRs and WRs between FDA and sponsors and, if appropriate, a discussion of such requests at the meetings required under section 505B(e)(2)(C) of the FD&C Act; (2) an earlier issuance of WRs for pediatric studies under BPCA, including for investigational new drugs prior to the submission of an application; and (3) shorter timelines, when appropriate, for completion of studies pursuant to a WR.

FDA's efforts to date have primarily focused on the pediatric oncology program and meetings of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC), but FDA has also taken steps in non-oncology programs, recognizing that a single approach may not fit all areas of pediatric drug product development. The PeRC has successfully implemented the following:

- Established an Oncology Subcommittee of the PeRC to specifically address FDA's implementation of the pediatric oncology-related provisions of FDARA. This subcommittee works to assure a consistent clinical and scientific expertise in FDA's review of proposed studies under these FDARA provisions. The review of these studies may allow for earlier and more efficient discussions of PPSRs to accelerate pediatric drug development through the earlier issuance of WRs for oncology products.

- Increased the duration of the weekly PeRC meetings not only to provide more time to address WRs, amended WRs, and inadequate PPSR letters but also to allow for more discussion on the feasibility, timing, and types of studies to request in a WR, with the goal of helping FDA provide improved advice to sponsors that could lead to the earlier issuance of WRs for non-oncology products.

In addition, FDA created Early Advice (Type F) meetings in accordance with FDARA to allow for discussions with sponsors, early in the drug development process, regarding the sponsors' development plans for pediatric patients. These meetings are intended to provide an opportunity to discuss the Agency's current thinking about a product development program and FDA's expectations for early assessment in the pediatric population unless the sponsor can provide a justification for a waiver or deferral. The availability of such early advice meetings may also allow for discussions of the appropriateness and timing of a submission of a PPSR.

The plan that was implemented under section 505(c) of FDARA to achieve an earlier submission of studies requested under BPCA appears to have been effective to the extent that there has been an increase in the combined number of WRs and amended WRs[15] issued by FDA for both oncology and non-oncology products in recent years. An analysis of the last 8 years was conducted to evaluate any effect from the 2017 changes in BPCA and PREA on FDA's issuance of WRs and amended WRs. The data were divided into two roughly equal 4-year cohorts for comparison: (1) WRs and amended WRs issued August 2012 to June 2016 and (2) those issued between August 2016 and June 2020. Between August 2012 and June 2016, FDA issued 37 original or amended WRs for oncology products. Between August 2016 and June 2020, FDA issued 56 original or amended WRs, which was a 51 percent increase. For non-oncology drugs, a similar but less dramatic trend was observed. Between August 2012 and June 2016, FDA issued 112 original or amended WRs. During the current review period (between August 2016 and June 2020), FDA issued 125 original or amended WRs, which was a 12 percent increase.

Whether the increase in the number of original and amended WRs will lead to an earlier completion of studies by industry is not yet clear. Importantly, in certain cases, delaying the issuance of an original or amended WR is not only reasonable but appropriate. For example, when studies are considered to be infeasible because of a need to identify appropriate endpoints, populations, or study designs, the issuance of a WR earlier would likely not lead to an earlier completion of studies. Similarly, the need to further evaluate safety concerns in adults that may be relevant to the pediatric population may appropriately lead to delays in the issuance of a WR. Additionally, the earlier issuance of WRs would not in all cases lead to an earlier completion of studies because the completion of pediatric studies under a WR remains voluntary. The obligation to complete studies pertains only to pediatric studies conducted under PREA. Finally,

[15] FDA believes that there is often a need to amend a WR in order to incorporate important changes in drug development approaches over time.

whether shorter timelines can be achieved is dependent on things other than just the earlier establishment of a WR or the mandatory requirements under PREA.

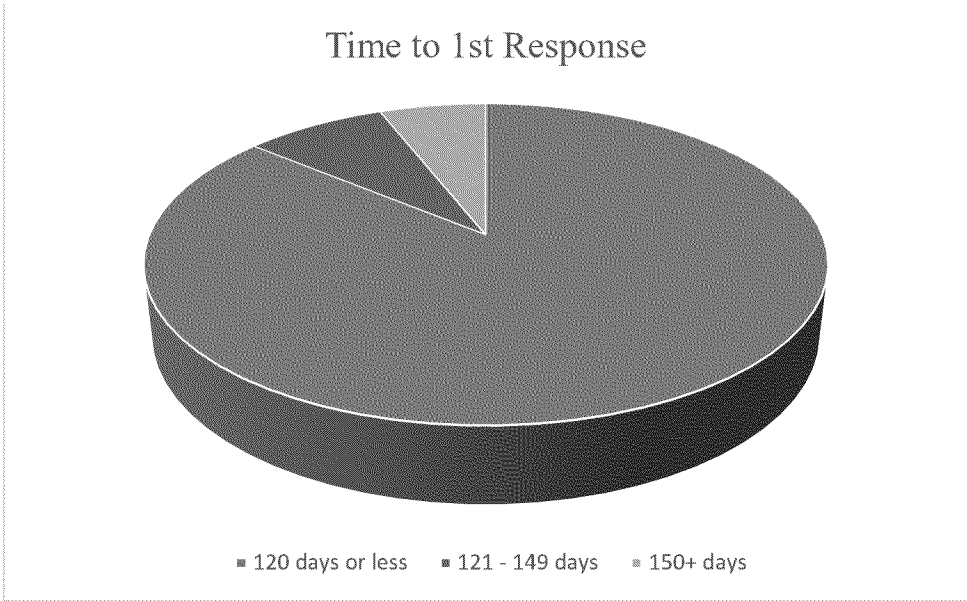
In addition to encouraging earlier discussions, shorter timelines for FDA to receive pediatric submissions for many pediatric drug development programs will likely involve an improvement in the efficiency of clinical trial operations, the availability of efficient clinical trial networks, and the use of innovative trial designs. Such discussions have been ongoing in many areas of pediatric therapeutics development. See section 1.6 of this report for more information.

1.1.2.2 *FDA's Responses to PPSRs*

FDARA amended section 505A of the FD&C Act by, among other things, adding section 505A(d)(3), which requires FDA to respond to all PPSRs within 120 days of receipt, and by adding section 505A(f)(7), which requires FDA to provide to the PeRC any response issued to a PPSR, including all letters informing sponsors that a PPSR was inadequate to receive a WR.

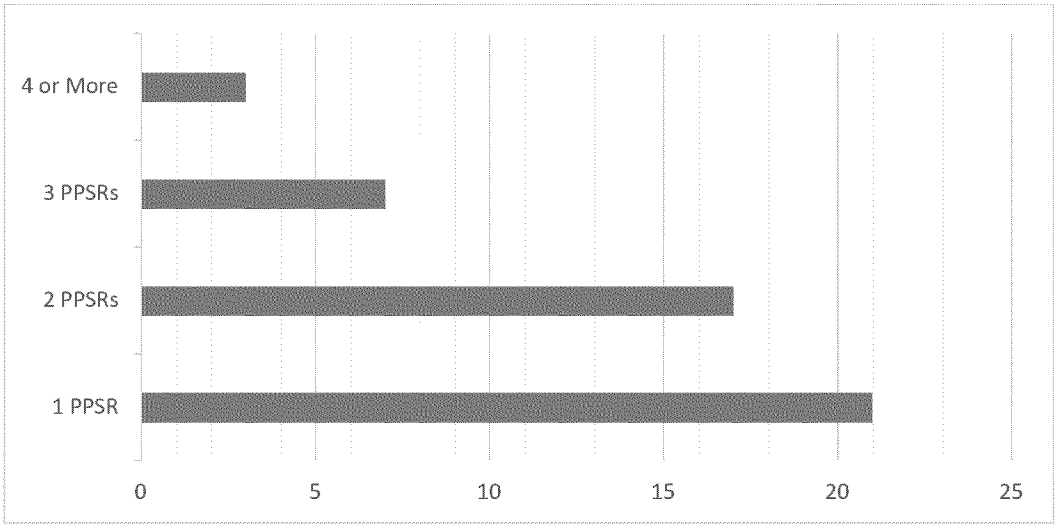
Since the implementation of FDARA, FDA has received 170 PPSRs. The mean time from receipt of a PPSR to an initial response (either a WR or an inadequate PPSR letter) was 110 days (range 17-375 days). FDA responded to 86 percent (147/170) of the PPSRs within 120 days as required under FDARA. See Figure 1. FDA's response was delayed by more than 30 days in only 6 percent (10/170) of the PPSRs. During the same time frame (i.e., from July 1, 2017, to June 30, 2020), FDA issued 48 WRs. Of the WRs issued, 44 percent (21/48) were issued in response to the first PPSR. These data demonstrate that FDA is responding to PPSRs in a timely manner and that submission of a single PPSR often leads to FDA's issuance of a WR.

Figure 1: Time (Days) From Submission of a PPSR to FDA's Response (n=170)



Additionally, there is often a need for the sponsor to negotiate with FDA the details of a WR (including the appropriate conditions/indications and types of studies needed) prior to FDA's issuance of a WR. When this need arises, sponsors may receive an inadequate PPSR letter. If a sponsor intends to pursue a WR after receipt of an inadequate PPSR letter, then the sponsor may respond by submitting another PPSR. Seventeen sponsors submitted two PPSRs before receiving a WR; seven sponsors submitted three PPSRs before receiving a WR; and three sponsors submitted four or more PPSRs before receiving a WR. See Figure 2. The mean time from submission of the first PPSR to issuance of a WR was 261 days (median 137 days; range 17-851 days).

Figure 2: Number of PPSRs Submitted Before Issuance of a WR (n=48)



These data demonstrate that often, there is a need for a sponsor to negotiate with FDA the details of a WR prior to FDA's issuance of a WR. Notably, there is a difference in the number of PPSRs reviewed (170) compared to the number of WR issued (48) during this reporting period (i.e., from July 1, 2017, to June 30, 2020); this difference, in part, is explained because some sponsors choose not to pursue a WR after FDA has issued an inadequate letter.

Of the 48 WRs issued, 16 (33 percent) have been amended at least one time (range 1-3 amendments). (The average time from the sponsor's request for an amendment to an amended WR was 98 days (range 39-132 days).) Ten (21 percent) of the 48 WRs were issued prior to FDA's approval of an original NDA or BLA for an adult indication. Together, these data demonstrate that FDA is willing to amend WRs when appropriate, and in some cases, multiple amendments have been agreed upon by FDA and sponsors.

Finally, these data confirm that, in the vast majority of cases, FDA is meeting timelines established for the review of PPSRs as required under FDARA. In addition, these data suggest that many PPSRs do not lead to the issuance of a WR. Although the specific reasons for this finding were not evaluated, sponsors often choose not to pursue a WR

after receiving FDA's feedback because the conduct of studies under a WR is voluntary. A WR may include requests for studies for one or more indications that may benefit children and may include indications that are not being pursued in adult populations. These data also suggest, however, that when a WR is issued, only a single PPSR was needed nearly 50 percent of the time.

1.1.2.3 *WRs Issued Under BPCA and Sponsor Responses*

Section 508 of FDASIA requires that FDA report on the number of WRs issued, accepted, and declined and provide a listing of any important gaps in pediatric information as a result of such declined requests.[16] From July 1, 2015, through June 30, 2020, FDA issued 96 WRs under BPCA. For the 96 WRs, 92 sponsors agreed to conduct the studies and four sponsors declined. These data demonstrate that sponsors rarely decline WRs after they are issued and suggest that FDA issues WRs for studies that sponsors are willing to conduct.

The sponsors who declined the WR cited the following reasons: (1) non-agreement with the types and designs of the studies in the WR; (2) non-agreement with the additional studies requested in the WR that were not required under PREA; (3) there was an insufficient amount of time remaining for the studies to be completed before the remaining exclusivity expired; and (4) an inability to conclude that the studies requested in the WR were feasible.

1.1.2.4 *Pediatric Study Planning Under PREA*

Section 508 of FDASIA requires that FDA provide an assessment of the timeliness and effectiveness of pediatric study planning under PREA. This provision requires that FDA report on the number of required studies that have not met the initial deadline, including the number of deferrals and deferral extensions[17] granted and the reasons such extensions were granted; the number of waivers granted;[18] and the number of noncompliance letters issued.[19]

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[16] For the current reporting period (i.e., from July 1, 2015, to June 30, 2020), FDA has not referred any pediatric studies pursuant to section 505A(n) of the FD&C Act.

[17] Section 505 of FDASIA amended PREA to ensure the completion of pediatric studies and authorized FDA to grant an extension of assessments deferred under PREA.

[18] See https://www.fda.gov/science-research/pediatrics/pediatric-tracking-requirements-under-fdaaa.

[19] Section 505 of FDASIA requires FDA to issue, and publicly post, noncompliance letters for failure to comply with certain PREA requirements, including the failure to submit required pediatric assessments under PREA.

iPSPs

The total number of iPSPs reviewed by FDA and agreed[20] by calendar year from January 1, 2015, to June 30, 2020) is presented in Table 1.

Table 1: iPSPs Submitted to FDA*

Calendar Year	*iPSPs*	*Agreed iPSPs*	*Amended Agreed iPSPs*	*Non-Agreed iPSPs*
2015	256	229	0	14
2016	265	226	6	18
2017	250	190	8	15
2018	280	199	13	8
2019	359	245	8	19
2020	167	153	18	11
Totals	**1577**	**1242**	**53**	**85**

* The data collected are by calendar year. The numbers provided for 2015 include the entire calendar year; in the last BPCA and PREA report to Congress, only the first 6 months of 2015 were reported. Similarly, because the numbers in the table reflect FDA's reviews through June 2020, the 2020 numbers reflect only the first 6 months of the year. Due to the timeline described in section 505B(e) of the FD&C Act, the number of agreed and non-agreed iPSPs may not equal the number of iPSPs each year because iPSPs submitted later in the calendar year may be acted upon in the following year.

The data on the number of iPSPs submitted to FDA clearly demonstrate an increase since 2018, which is largely due to the implementation of the pediatric oncology-related provisions of FDARA. See section 1.2.1 of this report. Despite the increase in the number of iPSP submissions, there has not been an apparent increase in the number of non-agreed iPSPs issued by FDA, suggesting that FDA and sponsors are agreeing on iPSPs in the vast majority of cases, including iPSPs submitted for oncology products.

Deferral Extensions

The total number of deferral extension (DE) requests that were received, granted, and denied by FDA from January 1, 2015, to June 30, 2020 by calendar year and by FDA's Centers is presented in Table 2.

[20] After a sponsor submits an iPSP, the FDA has 90 days to review the iPSP and provide a written response to the iPSP, or meet with the sponsor to discuss the iPSP, as appropriate. This review process includes consultation with the PeRC. The sponsor then has a second 90-day period during which it may review FDA's comments and initiate any needed negotiations to discuss the iPSP. By the end of this second 90-day review period, the sponsor must submit an agreed iPSP. FDA then has 30 days after receipt of the agreed iPSP to review and issue correspondence confirming agreement or issue correspondence stating disagreement. If the FDA does not agree, the iPSP is considered a non-agreed iPSP. See section 505B(e) of the FD&C Act.

Table 2: DE Requests Received, Granted, and Denied by CDER (CBER)^ by Calendar Year*

Calendar Year	*DE Requests Granted*	*DE Requests Denied*	*DE Requests Received*
2015	37 (2)	19 (0)	71 (3)
2016	41(4)	19 (0)	76 (4)
2017	67 (2)	34 (1)	101 (1)
2018	53 (2)	19 (1)	87 (3)
2019	55 (4)	34 (0)	104 (4)
2020	31 (1)	10 (0)	60 (1)
Totals	**299**	**137**	**515**

^ CDER – Center for Drug Evaluation and Research; CBER – Center for Biologics Evaluation and Research
* The data collected are by calendar year. The numbers provided for 2015 include the entire calendar year; in the last BPCA and PREA report to Congress, only the first 6 months of 2015 were reported. Similarly, because the numbers reflect DE requests through June 2020, the 2020 numbers reflect only the first 6 months of the year. The Agency has 45 days to respond to a DE request. Therefore, the number of DE requests granted and denied may not equal the number of DE requests in a given year because a DE request that is submitted in the last 45 calendar days of a year may be acted upon in the following year.

The number of DE requests received, granted, and denied between 2015 and the first half of 2020 has remained relatively constant. Overall, approximately 70 percent of the DE request decisions resulted in FDA granting a deferral extension. However, it should be noted that the number of DE requests denied has increased since the 2016 BPCA and PREA report to Congress. Thirty-one percent (137/436) of DE requests were denied over the last 5 years compared to 14 percent in the last report. FDA reviewed the potential reasons for this increase (i.e., from 14 percent in the 2016 report to 31 percent in the current report) and has concluded that the change occurred because the 2016 report included data only from July 2012 through June 2015, which represented only the first 3 years of implementation of the DE program. During the initial phase of implementation, FDA granted a greater percentage of DE requests to allow for studies that were already delayed to be given additional time to complete these studies. Thus, there is a lower percentage of DE request denials during the first 3 years of the implementation. Since then, the percentage of denials per year has ranged from 27 percent (2018) to 37 percent (2019).

The reasons cited for sponsors requesting a DE in the current reporting period were similar to those described in the 2016 report.[21] It should be noted that the data for 2020 reflect some DE requests due to impacts of the COVID-19 pandemic on clinical trial operations. FDA granted a relatively high percentage of these DE requests in recognition of the need for sponsors to adjust study timelines due to disruptions caused by the pandemic.

[21] See "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress" at https://www.fda.gov/media/99184/download.

The first noncompliance letters were publicly posted on August 26, 2013, on FDA's website.[22] Between April 5, 2013, and June 30, 2020, FDA issued a total of 106 noncompliance letters to 72 sponsors. Of these 106 letters, FDA issued 63 letters (59 percent) to 52 sponsors since the 2016 BPCA and PREA report to Congress.

Under section 508(b)(13) of FDASIA, as amended by FDARA, FDA is required to report the number of sponsors who received pediatric exclusivity for studies completed and submitted after they had received a non-compliance letter. Table 3 lists the sponsors who received pediatric exclusivity for studies completed and submitted after they had received a non-compliance letter that was issued between July 1, 2017, and June 30, 2020.

Table 3: Sponsors Qualifying for Pediatric Exclusivity After Receiving a Non-Compliance Letter

Sponsor	*Product*	*Date of Non-Compliance Letter*	*Date of Submission*	*Date Qualified for Pediatric Exclusivity*
Rhodes Pharmaceuticals	Aptensio XR (methylphenidate hydrochloride extended release) capsules	7/12/2017	9/14/2018	3/15/2019
Allergan Sales, LLC	Viibryd (vilazodone hydrochloride) tablets	7/6/2018	8/1/2019	1/21/2020
Teva Pharmaceuticals	ArmonAir Respiclick (fluticasone propionate/salmeterol xinafoate inhalation powder)	1/30/20	12/21/20	6/10/2021
Teva Pharmaceuticals	AirDuo Digihaler/AirDuo Respiclick (fluticasone propionate/salmeterol xinafoate inhalation powder)	1/30/20	12/21/20	6/10/2021

Overall, these data demonstrate that qualifying for pediatric exclusivity after receiving a noncompliance letter for the completion of these studies under PREA is an uncommon occurrence. Only 11 percent (4/37) of products that qualified for pediatric exclusivity

[22] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm and https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/prea-non-compliance-letters.

between July 1, 2017, and June 30, 2020, received a non-compliance letter. FDA reviewed the circumstances under which these four products qualified for pediatric exclusivity after having received a noncompliance letter. FDA's review suggests that these rare occurrences have not identified a gap or loophole in the statutory requirements such that sponsors are qualifying for pediatric exclusivity for studies that were not conducted with due diligence.

1.1.2.5 *Time From the Application's Approval to Inclusion of Pediatric Information in the Approved Product's Labeling*

Section 504(d) of FDARA amended the reporting requirements under section 508 of FDASIA to require that FDA report on the average length of time after the approval of an application under section 505(b)(1) of the FD&C Act or section 351(a) of the Public Health Service Act (PHS Act) before studies conducted pursuant to either section 505A or 505B of the FD&C Act or section 351(m) of the PHS Act are completed, submitted, and incorporated into the labeling.

From July 1, 2017, to June 30, 2020, the average length of time between approval of an application under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act and the inclusion of any pediatric use information in the approved product's labeling was approximately 6 years. For products regulated by CDER, the average time between original approval and the inclusion of any pediatric use information was 6.25 years (range 0.6-17.1 years). Notably, of the 96 CDER pediatric approvals identified in this analysis, only six products included any pediatric use information as part of the original approval. In addition, four products (not included in this analysis) had studies waived because the drug was considered to be either unsafe or ineffective in pediatric patients, and this information was included in labeling at the time of the original approval. For products regulated by CBER, the average time between original approval and the inclusion of any pediatric use information was 4.8 years (range 1-10.1 years). Notably, 86 percent (12/14) of original CBER applications approved during this period included pediatric-specific use information for all or part of the intended pediatric age range.

These data suggest that there remains a substantial lag between the original approval of a drug and the inclusion of specific pediatric-use information in the drug's labeling. FDA believes that measures to decrease this lag, such as the requirement in section 505B(e)(2) of the FD&C Act to submit iPSPs no later than 60 days after an end-of-Phase 2 meeting, unless another time is agreed upon between FDA and the applicant, will have a positive effect, but this effect is difficult to assess at this time because many of the sponsors for drugs with pediatric labeling changes identified for this analysis had an end-of-Phase 2 meeting that pre-dated the requirement. Notably, there appears to be some improvement in the inclusion of pediatric use information at the time of original approval for CBER-regulated products.

1.1.2.6 *Summary of the Timeliness of Pediatric Study Planning and Conduct Under BPCA and PREA*

Overall, FDA believes that the programs directed toward the timely completion of pediatric assessments under BPCA and PREA have been successful. FDA's review of iPSPs, DE requests, PPSRs, and WRs have met required timelines in the vast majority of cases. For example, FDA has met the requirement enacted under FDARA to respond to a PPSR within 120 days for nearly 90 percent of PPSR submissions. Additionally, the PeRC continues to provide consultation on all pediatric study plans submitted in accordance with PREA and to review all DE requests for PREA studies, with both actions aimed at ensuring the proposed pediatric study timelines are reasonable. Additionally, the issuance of noncompliance letters has called attention to sponsors who have not completed studies according to agreed-upon timelines required under PREA.

The consistency in the data over the last 5 years has been due, in large part, to the work of the PeRC and the Oncology Subcommittee of the PeRC. In addition to reviewing iPSPs, DE requests, PPSRs, and WRs, the experts on the PeRC provide important scientific and regulatory advice to aid FDA's review divisions in achieving efficient and feasible pediatric product development plans across CDER and CBER. FDA will continue these efforts to encourage the submission of timely pediatric studies by sponsors to help reduce the delay between the original approval of a drug and the incorporation of pediatric use information in the drug's labeling, which currently stands at approximately 6 years.

1.2 Special Populations: Children with Cancer, Children with Rare Diseases, and Neonates

1.2.1 Pediatric Cancer: Advances in Research and Labeling of Cancer Drugs

Section 504 of FDARA, commonly known as the Research to Accelerate Cures and Equity (RACE) for Children Act, amended PREA by requiring sponsors to submit reports to FDA on pediatric investigations for certain new drugs directed at a molecular target determined to be substantially relevant to the growth or progression of one or more pediatric cancers regardless of whether that drug is for an indication for which orphan designation has been granted.

FDA, with the National Cancer Institute (NCI), has engaged with stakeholders, including the American Society of Clinical Oncology, the American Association for Cancer Research, Biotechnology Innovation Organization (BIO), Pharmaceutical Research and Manufacturers of America (PhRMA), Drug Information Association (DIA), Friends of Cancer Research, the American Academy of Pediatrics (AAP), the American Society of Pediatric Hematology-Oncology, the International Society of Pediatric Oncology, and numerous patient advocacy organizations, as part of its implementation of the

amendments to the FD&C Act under section 504 of FDARA to meet the needs of children with cancer.

FDA convened a public meeting of the Pediatric Oncology Subcommittee of the ODAC in collaboration with NCI on April 20, 2018, for numerous reasons, including (1) to solicit feedback from physicians and researchers on FDA's development of a guidance document and the molecular target lists and (2) to discuss additional scientific and operational challenges related to pediatric cancer drug development in accordance with the requirements added by FDARA. In May 2021, FDA issued a final guidance document titled "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act."[23] This guidance document finalized the draft guidance document entitled "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs" that was issued in December 2019 and finalized certain recommendations related to FDA's implementation of FDARA that were included in the January 2020 draft guidance document entitled "Pediatric Study Plans for Oncology Drugs: Questions and Answers." Additionally, the "Relevant Molecular Target List" and the "Non-Relevant Molecular Target Leading to Waiver List" are available on FDA's website and updated quarterly.[24]

As mentioned earlier, Type F meetings provide an opportunity for sponsors to discuss their pediatric development plans early in their drug development process. Specifically, Type F meetings related to oncology have provided an opportunity for sponsors to discuss the Agency's current thinking about the relevance of a specific molecular target and FDA's expectations for early investigation in the pediatric population unless the sponsor can provide justification for a waiver or deferral. Between August 2019 and June 2020, 16 Type F meetings were requested to discuss 16 distinct new drugs directed at a molecular target. All meetings were conducted by the Pediatric Oncology Program in FDA's Oncology Center of Excellence, in collaboration with the appropriate oncology review division or office in CDER or CBER and members of the Oncology Subcommittee of the PeRC, within the 30-day timeline.

1.2.1.1 *Impact of FDARA on Sponsors' Conduct of Pediatric Cancer Research*

Early evidence suggests that the RACE for Children Act has had a favorable impact on sponsors' timely consideration and initiation of studies of appropriate molecularly targeted cancer drugs that would historically have gone unstudied in children. The requirement for sponsors to comply with the amended PREA provisions requiring them to submit reports on the molecularly targeted pediatric cancer investigation for certain molecularly targeted cancer drugs became effective on August 18, 2020 (which was 3 years after enactment of the legislation). Since that date, sponsors now subject to this

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdara-implementation-guidance-pediatric-studies-molecularly-targeted-oncology-drugs-amendments-sec.

[24] See https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology.

requirement must include in the agreed iPSP a description of the molecularly targeted pediatric cancer investigation.

FDA analyzed the iPSPs submitted from August 18, 2019, through March 30, 2021, in advance of the related original NDA or BLA submissions. This analysis demonstrated that pediatric investigations of molecularly targeted cancer drugs were proposed by sponsors and agreed to by FDA in approximately 45 percent of cases and justifications for planned full waivers were provided by sponsors in 55 percent of agreed iPSPs. This analysis also demonstrated that justifications for age-dependent partial waivers and deferrals to obtain additional adult efficacy and safety data, as well as planned deferrals for the submission of results of pediatric studies, have been submitted to and agreed upon by FDA.

Thirty-eight agreed iPSPs associated with original NDAs or BLAs were reviewed by the Oncology Subcommittee of the PeRC during the review period cited above (i.e., between August 18, 2019, to March 30, 2021). Twenty-one of the agreed iPSPs included plans for pediatric studies, and 17 of the agreed iPSPs included justifications for a waiver of pediatric studies based on the molecular mechanism of action of the drug.

Of those 21 agreed iPSPs that included plans for pediatric studies, fourteen included age-appropriate partial waivers and planned deferrals for the sponsor's submission of the results of its pediatric studies because the associated original NDA or BLA for the adult indication of the proposed product was anticipated to occur before the completion of the pediatric studies. All approvals of products with such planned deferrals will, if the deferrals are granted, include post-marketing requirements for the sponsor's submission of data from the pediatric studies. Based on the adult indications for these products, such studies would likely have been waived under PREA if not for the revisions to PREA made by section 504 of FDARA.

For drugs approved prior to August 18, 2020, that have molecular targets that are determined to be substantially relevant to the growth or progression of a pediatric cancer and that would have been subject to PREA requirements under section 505B(a)(1)(B) of the FD&C Act if the application had been filed later, FDA has issued 10 WRs.

1.2.1.2 *Advances in Labeling Drugs for Pediatric Cancer*

Since the 2016 report to Congress, the following 16 oncology drugs have been approved and labeled for use in the pediatric population: blinatumomab, tisagenlecleucel, avelumab, ipilimumab, dasatinib, gemtuzumab ozogamicin, calaspargase pegol, tagraxofusp, larotrectinib, emapalumab, entrectinib, pembrolizumab, nivolumab, selumetinib, selpercatinib, and tazemetostat. Four of the 16 oncology drug approvals resulted from studies conducted pursuant to BPCA: blinatumomab, tisagenlecleucel, dasatinib, entrectinib. One of the 16 oncology drug approvals resulted from studies conducted pursuant to PREA: nivolumab.

Of note, tisagenlecleucel, a genetically engineered (chimeric antigen T cell (CAR-T cell)) product was initially approved for the treatment of relapsed/refractory acute lymphoblastic leukemia in the pediatric population based on the results of a clinical trial conducted as part of a WR issued under BPCA. Also of note are the simultaneous adult and pediatric approvals for tissue/histology agnostic indications of the targeted agents larotrectinib, entrectinib, and selpercatinib based on the known molecular drivers of several diverse and histologically distinct tumors that occur in adults and children.

1.2.2 Rare Pediatric Diseases: Successes and Limitations in Drug Development

Section 508 of FDASIA requires that FDA provide an assessment of the successes of and limitations to studying drugs for rare diseases under BPCA and PREA. In addition to BPCA and PREA, other laws impact the study of drugs intended to treat rare pediatric diseases, such as sections 526 and 527 of the FD&C Act (which authorize orphan drug designation and orphan exclusivity per the Orphan Drug Act[25]) and section 529 of the FD&C Act (which authorizes the rare pediatric disease (RPD) priority review voucher (PRV) program).

The Orphan Drug Act, enacted in 1983, was established to encourage the development of drugs for rare diseases. However, the provisions of the Orphan Drug Act do not require pharmaceutical industry sponsors to evaluate drugs with orphan designation in any specific populations affected by a rare disease. Section 505 of FDARA required FDA to report on the lack of pediatric use information in the labeling of drugs for indications that have received an orphan designation. As described in the 2019 report to Congress on the pediatric labeling of orphan drugs, there is a public health need for additional pediatric information in the labeling for over one-third of approved orphan indications that are relevant to the pediatric population. In some cases, there is no pediatric information at all in the labeling, and in other cases, the labeling does not address the full age range of the affected pediatric patients. As noted in that report, FDA found that studies were ongoing or that FDA had issued a WR for pediatric studies to address labeling for 29 of 127 (23 percent) of those indications not fully labeled for pediatric use.[26]

PREA does not apply to drugs for an indication for which orphan designation has been granted under section 526 of the FD&C Act, except for certain molecularly targeted cancer drugs.[27] As such, PREA does not serve to ensure the evaluation in the pediatric population of such drugs subject to this "orphan exemption." Notably, the impact of the RACE for Children Act, which requires pediatric studies of certain oncology drugs regardless of orphan drug designation, appears promising. As described above, early evidence suggests that the RACE for Children Act has had a favorable impact on the timely consideration and initiation of studies of appropriate molecularly targeted cancer

[25] Public Law 97-414, as amended, codified at sections 525-528 of the FD&C Act (21 U.S.C. 360aa-360dd).

[26] See https://www.fda.gov/media/130060/download.

[27] See section 505B(k) of the FD&C Act.

drugs that would previously have not been required and that would historically have gone unstudied in children.

1.2.2.1 *Rare Pediatric Disease Priority Review Voucher Program*

The RPD PRV program, established in 2012 under FDASIA, is an additional program to encourage treatments for rare pediatric diseases.[28] Products may be designated as a "drug for a rare pediatric disease" under this program. To be a "rare pediatric disease," a disease must be (1) a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years and (2) a rare disease or condition within the meaning of section 526 of the FD&C Act.[29]

As of September 2021, FDA has granted over 480 rare pediatric disease designations for over 220 unique pediatric diseases and has awarded 32 RPD PRVs. Nearly 80 percent (25/32) of products approved under the RPD PRV program were the first approved therapy for the disease. Most products receiving RPD PRVs treat the underlying disease rather than a specific disease symptom, representing significant progress in developing disease-modifying therapies for diseases for which such therapies had not been available. Approved products receiving an RPD PRV include (1) the first ever FDA-approved gene therapy (Kymriah (tisagenlecleucel) for a form of acute lymphoblastic leukemia) and (2) the first directly administered gene therapy approved in the United States that targets a disease caused by a gene mutation (Luxturna (voretigene neparvovec-rzyl) for biallelic RPE65 mutation-associated retinal dystrophy, an eye disease that causes blindness in early childhood). Other RPD PRV products include targeted therapies for the treatment of spinal muscular atrophy and Duchenne muscular dystrophy.

1.2.3 Progress and Challenges in Developing Drugs for Neonates

Section 508 of FDASIA requires that FDA report on efforts made by the Agency to increase the number of studies conducted in the neonatal population and the results of these efforts. FDA continues to encourage and support the conduct of studies in neonates by (1) providing reviewers across the Agency with expert neonatal-perinatal consultation services, (2) encouraging inclusion of neonates, when appropriate, in drug development programs, and (3) developing guidance documents to facilitate neonatal studies. In addition, FDA has been working to overcome the obstacles to advancing neonatal regulatory science, recognizing the importance of establishing a strong scientific foundation to support drug development for neonates.

Considerable strides have been made since FDA's neonatology program was developed within the Office of Pediatric Therapeutics. This program has seen steady growth of its

[28] FDASIA, Pub. L. 112-144. 126 Stat 993 (July 9, 2012).

[29] The Consolidated Appropriations Act, 2021, extended the RPD PRV program's two-part sunset period. Under the current provisions, after September 30, 2024, FDA may award an RPD PRV only if the drug has rare pediatric disease designation and if that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any RPD PRVs.

neonatal-perinatal medicine consultation service, which provides expertise to reviewers across the Agency in the development and use of FDA-regulated products that benefit neonates. FDA's neonatology staff also remain active on the PeRC, consistent with section 505C of the FD&C Act, and are integral in fostering drug development in neonates and addressing the unique challenges of evaluating products in this population during PeRC discussions.

Guidance development to support the conduct of studies in neonates remains a focus for FDA's neonatology program. In August 2019, in accordance with FDARA, FDA issued the draft guidance document titled "General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products" to address the clinical pharmacology considerations for any planned studies in neonatal populations.[30] When final, this guidance document will represent the Agency's current thinking on this topic.

Since the 2016 report to Congress, under BPCA and PREA, the labeling for 22 drugs has been updated to include the drug's dosing, safety, and/or efficacy for neonates.[31] The labeling changes have provided important information to support neonatal use for a selection of drug products, particularly antivirals and other anti-infectives, that would historically have gone unlabeled in the neonatal population. However, the current paradigm for drug development under BPCA and PREA generally has not resulted in a significant increase in research addressing neonatal-specific diseases/conditions. Of the 22 labeling updates, only one product is indicated for a condition that solely affects the neonatal population (i.e., Cafcit (caffeine citrate) for the treatment of apnea of prematurity).

FDA considers the inclusion of neonates, when appropriate, when issuing WRs under BPCA.[32] Also, the 409I program has fostered improvements in neonatal drug labeling. However, drugs under development for adult conditions may not be relevant for addressing the unique pathophysiology of neonatal conditions, in which case studies in accordance with PREA may not be appropriate. To ensure therapeutics are available for conditions that are unique to the neonatal population, it is important that the pharmaceutical industry develop products specifically to address neonatal conditions. Currently, there are no FDA-approved drugs indicated to treat or prevent some of the major morbidities that result from preterm birth, including chronic lung disease, preterm brain injury, and necrotizing enterocolitis.

1.2.3.1 *Advancing Regulatory Science in the Conduct of Studies in Neonates*

FDA recognizes that advancing the science to support regulatory decision-making in the development of drugs to treat conditions affecting neonates is of utmost importance and

[30] https://www.fda.gov/media/129532/download.

[31] Labeling updates resulted from the 409I program (3 drugs), PREA (11 drugs), BPCA (6 drugs), and BPCA plus PREA (2 drugs).

[32] See section 505A(a) of the FD&C Act.

involves collaboration with internal and external stakeholders. FDA's neonatology program continues to support and contribute to efforts to further the science and to develop tools to streamline drug development programs. For example:

- In collaboration with CDER, FDA's neonatology program recently completed the first phase of a project re-evaluating gestational age endpoints for clinical trials of products intended to reduce preterm birth. This project involves using existing datasets to model alternative approaches to endpoint selection for these clinical trials.

- FDA collaborated in a consensus process with the International Neonatal Consortium (INC) that led to the development of a standard severity grading scale for neonatal adverse events called the neonatal adverse event severity scale. Although severity scales have been developed in other research fields, the existing scales are not applicable to neonates. Use of the neonatal severity scale will improve the quality and consistency of safety evaluations during the conduct of neonatal clinical trials.

- FDA awarded a multi-year grant to INC and the Critical Path Institute (C-Path) to advance standards and methodologies to generate real-world evidence from existing real-world data within neonatal datasets and electronic health records through a neonatal data pilot project. The INC/C-Path team has obtained electronic health records data and clinical trial data that will be used to create a disease progression model of preterm chronic lung disease to improve trial design and the development of therapies for neonates. This pilot project will also generate real-world evidence to support normal and abnormal laboratory values to guide assessments in clinical trials.

- FDA awarded a multi-year grant to Columbia University to evaluate the long-term neurodevelopmental outcomes of children with intrauterine opioid exposure. The project will use electronic health records that incorporate maternal, neonatal, and pediatric data to assess whether abnormal neurodevelopment may be associated with (1) a pharmacologic treatment for neonatal withdrawal, (2) the infant's sex, and (3) maternal/demographic characteristics. These data will help provide a better understanding of the outcomes of children with intrauterine opioid exposure and the impact of treatment during the neonatal period.

- FDA used the Broad Agency Announcement process[33] (1) to study actigraphy as a potential endpoint in clinical trials involving patients with pulmonary arterial

[33] This process is a specialized contract mechanism that makes it possible for the Agency to solicit innovative ideas and approaches to developing and evaluating FDA-regulated products by tapping into external knowledge and infrastructure in areas where FDA has limited expertise or capacities. The proposals solicited from industry, academia, and other government agencies enable FDA to better understand the breath of innovative scientific and technical solutions available to solve difficult regulatory science problems.

hypertension beginning from birth and (2) to evaluate the comparative safety of feeding device types among graduates of the neonatal intensive care unit who required tube feeding.

1.3 Achievements of the 409I Program

Section 409I of the PHS Act, which was created by the Best Pharmaceuticals for Children Act in 2002, requires NIH, in consultation with FDA and experts in pediatric research, to develop and publish a priority list of needs in pediatric therapeutics. Among other things, section 409I specifically mandates NIH to (1) identify and prioritize drugs and therapeutics that need further study in pediatric populations and (2) sponsor clinical trials of prioritized drugs. Data from these trials are to be submitted to FDA, which will determine if labeling changes are appropriate.

1.3.1 Prioritizing Drugs and Therapeutics for Further Study

One of the primary responsibilities of the 409I program involves prioritizing needs in pediatric therapeutics. Based on the prioritization process, more than 220 drugs/therapeutics and 50 conditions/indications have been prioritized for further study. Due to limitations in fit and feasibility, all prioritized drugs cannot be studied under the 409I program; however, the BPCA priority list serves as a catalog of needs that remain in the pediatric population.[34]

1.3.2 Clinical Trials of Prioritized Drugs

The initial years of the program included gathering data (e.g., through systematic literature reviews); convening expert panels; and conducting or co-funding single molecule safety, efficacy, and pharmacokinetic clinical trials based on WRs that NIH received from FDA. From 2004 to 2012, NIH received approximately 22 WRs and conducted and/or co-funded 14 clinical trials in the following areas:

- Lithium for the treatment of pediatric bipolar disease (2 trials)
- Lorazepam for the treatment of status epilepticus (2 trials)
- Lorazepam for sedation
- Sodium Nitroprusside for the treatment of blood pressure (2 trials)
- Baclofen for the treatment of spasticity in cerebral palsy (2 trials)
- Meropenem for the treatment of intra-abdominal infections in neonates
- Oncology trials with the Children's Oncology Group (4 trials)

The 409I program's current success can be attributed largely to work done by the Pediatric Trials Network (PTN) at the Duke Clinical Research Institute and by the Data Coordinating Center at the Emmes Corporation. The PTN, originally funded in 2010 and

[34] See https://www.nichd.nih.gov/research/supported/bpca/prioritizing-pediatric-therapies .

funded again in 2017, has developed and implemented 40 pediatric clinical trials across more than 100 clinical sites to improve the knowledge of medicines used in children, with 21 clinical study reports submitted to FDA for label change considerations.

1.3.3 Labeling Changes Under the 409I Program

The collaborative activities of NIH and FDA that have stemmed from this program have led to 15 labeling changes, which are listed below.[35] Notably, two of these labeling changes are for devices. Of the 15 changes, 10 occurred through the process established for the 409I program.[36] Between 2002 and 2016, FDA approved labeling for three drugs through this program. Since the 2016 report to Congress, the number of drugs with approved labeling changes has more than tripled, with FDA approving the labeling for seven additional drugs. FDA approved a change to the labeling of the following products to provide details related to the product's use in pediatric patients:

- Acyclovir for the treatment of neonatal herpes simplex virus
- Ampicillin for the treatment of sepsis and/or meningitis
- Bactrim for the treatment of infections per Standard of Care
- Caffeine Citrate for the short-term treatment of apnea of prematurity
- Clindamycin for the treatment of serious infections
- Doxycycline for the treatment of life-threatening infectious diseases
- Lithium for the treatment of bipolar disorder
- Lisinopril for the treatment of hypertension in kidney transplant recipients
- Lorazepam for the treatment of status epilepticus
- Meropenem for injection for the treatment of intra-abdominal infections
- Propylthiouracil for the treatment of hyperthyroidism (the labeling was changed for safety and dosing)
- Pralidoxime for use in organophosphate poisoning
- Sodium Nitroprusside for the treatment of blood pressure in the perioperative environment
- Mercy TAPE to estimate body weight based on measurements of arm length and upper arm circumference
- Mercy BabyTAPE to estimate body weight of infants from birth to 90 days of age

1.3.4 Dissemination of Information Obtained from 409I Research

Data from NIH-funded studies pursuant to the 409I program are published in an FDA public docket for all labeling changes, in peer-reviewed journals for scientific advancements, and on the National Institute of Child Health and Human Development's (NICHD's) Data and Specimen Hub (DASH) for investigators to access the datasets publicly. To date, the 409I program and the PTN have contributed more than 100 peer-

[35] See https://www.nichd.nih.gov/research/supported/bpca/accomplishments.

[36] See https://www.fda.gov/drugs/development-resources/nih-funded-pediatric-labeling-changes-drugs-studied-under-409i-process.

reviewed publications to the scientific literature. Until recently, NIH-funded 409I findings had been accessible to pediatricians only through the FDA-issued drug labeling changes. Now, one-page study summaries are available both on the 409I website and on the DASH; in addition, the PTN website provides lay summaries geared towards families and patients and provides an overview of 409I-supported studies.[37] The summaries on the 409I website also link to FDA's drug labeling, PubMed, and NICHD's DASH.

1.3.5 NIH-Sponsored Training Programs

NIH has sponsored several programs aimed at training pediatric investigators, including the T32 Pediatric Clinical and Developmental Pharmacology Network and the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub. These two programs will be discussed in turn below.

First, the T32 Pediatric Clinical and Developmental Pharmacology Training Network was formed as a result of the requirements in section 409I of the PHS Act for NIH to consider the adequacy of the infrastructure necessary to conduct pediatric pharmacological research, including research networks and trained pediatric investigators. The training goals of the program continue to expand to foster more entry points for aspiring clinicians-scientists, cultivating their intellectual curiosity and maintain continuity promoting and sustaining their career development.

Second, the MPRINT Hub is a new initiative that is partially funded by the 409I program.[38] The goal of MPRINT will be not only to provide a bridge between translational research and clinical research but also to be a platform for improved dissemination and training in the respective pharmacology fields. The MPRINT Hub is prepared to serve as a scientific service center and science catalyst that will

- Provide a hub of knowledge and expertise in maternal and pediatric therapeutics to the scientific community
- Serve as a platform for innovative multidisciplinary research
- Synergize with other resources and networks across NIH and among various stakeholders
- Catalyze and accelerate maternal and pediatric therapeutics towards precision medicine

[37] These summaries are available at https://www.nichd.nih.gov/research/supported/bpca/resources/study-summaries, https://dash.nichd.nih.gov/, and https://pediatrictrials.org/.
[38] https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint.

1.4 PAC Activities: Evaluation of FDA's Post-Marketing Pediatric Safety Reviews and Other Matters in Pediatric Product Development and Use

FDA continues to implement the congressionally mandated pediatric-focused post-marketing safety review of drugs and biologics for the 18-month period after a pediatric labeling change pursuant to BPCA and PREA and to facilitate the sharing of these reviews with the PAC.

Since the 2016 report to Congress, FDA has reviewed 189 products (164 drugs and 25 biologics) for post-marketing pediatric safety and shared information with the PAC either through a formal presentation or posting on the web. FDA's post-market pediatric safety reviews and evaluation by the PAC have led to important labeling changes, such as the following:

- In completing the pediatric-focused safety reviews for mesalamine utilizing the FDA Adverse Event Reporting System (FAERS), FDA identified four non-fatal, serious, unlabeled adverse events. FDA presented this information to the PAC, which concurred with FDA's recommendation to add nephrogenic diabetes insipidus to the Adverse Reactions section of the labeling for all mesalamine products.

- In completing the pediatric-focused safety reviews for three stimulants indicated for the treatment of attention-deficit hyperactivity disorder (ADHD), FDA identified a potential drug-drug interaction between an ADHD stimulant and an antipsychotic agent. Upon further review, FDA identified 36 cases of acute hyperkinetic movement disorder, most involving acute dystonic reactions, in FAERS and the medical literature. FDA presented this information to the PAC, which concurred with FDA's risk mitigation plan to add this information to the Drug Interaction section of the labeling for methylphenidate products and risperidone.

As indicated above, these reviews have provided an opportunity for the detection of safety concerns in children that may not have been identified in prelicensure clinical trials. However, the legislatively mandated 18-month pediatric-focused safety reviews overlap substantially with the Agency's routine post-marketing safety surveillance. FDA previously has shown that scheduled safety assessments provide only a small, incremental benefit over ongoing FDA pharmacovigilance activities.[39] FDA is currently conducting a similar analysis for the 18-month pediatric-focused safety review process and anticipates the same trends may be observed. Using a standardized time-based approach and schedule to review the safety of drugs with new pediatric use information

[39] Sekine S, Pinnow EE, Wu E, et al. 2016. Assessment of the Impact of Scheduled Post-marketing Safety Summary Analyses on Regulatory Actions. Clinical Pharmacology & Therapeutics. 100(1): 102-108

may not be the most effective and efficient approach for safety signal detection. For example, some products may undergo multiple pediatric labeling changes, thus prompting completion of multiple 18-month pediatric safety reviews for the same product. To ensure this process is optimized to identify new or serious pediatric safety concerns, FDA is evaluating strategies to develop a more modernized approach that involves a risk-based framework for pediatric pharmacovigilance. A modernized approach that considers each product's pharmacological characteristics and clinical use to inform the time, nature, and extent of safety review strategies could result in a more efficient safety signal detection. This approach would be similar to FDA's risk-based approach to pediatric medical device surveillance for PAC review and would allow for an aligned pediatric safety surveillance approach across all medical products.

1.4.1 Strategies for Optimal Utilization of PAC Expertise

FDA has considered approaches to ensure new or serious pediatric safety concerns are prioritized for discussion during PAC meetings because of the vast and ever-expanding pediatric-focused post-marketing safety surveillance and pharmacovigilance process. In addition, FDA has sought to more effectively access valuable PAC expertise for discussion of other scientific and clinical matters surrounding pediatric product development and use.

FDA implemented a new approach in 2016 for sharing information for PAC review that involves a risk-based process in which the post-marketing safety reviews for drugs and for medical devices approved under a Humanitarian Device Exemption (HDE) with labeling for pediatric use, that have a low safety risk are posted on FDA's website for review by the PAC. The reviews for drugs and HDE devices that are not low safety risk are presented at a PAC meeting in a standard or abbreviated format. By implementing this risk-based process, FDA has been able to discuss, during PAC meetings, additional topics surrounding pediatric product development and use. For example, FDA convened a PAC meeting to discuss serious behavior and mood-related changes in children with use of montelukast, a prescription drug for asthma and allergy management. Montelukast prescribing information already included warnings about mental health side effects, including suicidal thoughts or actions; however, review of additional information and discussion at the PAC meeting led to a re-evaluation of the benefits and risks of montelukast use. This re-evaluation prompted FDA (1) to require a Boxed Warning in the prescribing information of montelukast to describe serious mental health side effects and to recommend that montelukast should be reserved to treat allergic rhinitis in patients who are not treated effectively with or cannot tolerate other allergy medicines and (2) to require that a new Medication Guide be given to patients with each montelukast prescription.

FDA has brought additional topics to the PAC for discussion as well, including drug development considerations for testosterone replacement therapy in male adolescents for conditions associated with a deficiency or absence of endogenous testosterone resulting from structural or genetic etiologies; the role of pharmacogenomics in pediatric product development; the use of prescription opioid products containing hydrocodone or codeine

for the treatment of cough in pediatric patients; and an overview of the Center for Devices and Radiological Health's perspective on the current state of pediatric medical device development and potential strategies for supporting innovators and innovation to optimize health equity and safety for pediatric populations. In addition, FDA convened a meeting of the PAC and the Pediatric Ethics Subcommittee of the PAC to discuss a referral by an Institutional Review Board under 21 CFR 50.54 for a clinical investigation involving pediatric patients with Duchenne muscular dystrophy. At the meeting, the ethical considerations regarding the placement of a totally implantable central venous access device in patients receiving placebo during the 2-year study were discussed.

1.5 Guidance Documents

FDA has issued many guidance documents since the 2016 report to Congress related to implementation of the pediatric statutes and conduct of pediatric research, including the following draft and final guidance documents that are relevant to this report:

- *Final Guidance Document — FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act (May 2021)* [40]

  This guidance document addresses early planning for the pediatric evaluation of certain molecularly targeted cancer drugs. This guidance document finalized the draft guidance entitled "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs" that was issued in December 2019 and finalized certain recommendations related to FDA's implementation of FDARA that were included in the January 2020 draft guidance document entitled "Pediatric Study Plans for Oncology Drugs: Questions and Answers."

- *Final Guidance Document — Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (July 2020)* [41]

  This guidance document provides recommendations regarding the submission of iPSPs and amendments to an iPSP. This guidance document was required under section 505B(e)(7) of the FD&C Act, added by section 506 of FDASIA. After issuing two draft guidance documents, in July 2013 and March 2016, FDA finalized this guidance document in July 2020 after incorporating comments received on those drafts. FDA continues the process of developing a proposed rule regarding iPSPs in accordance with section 505B(e)(7) of the FD&C Act.

[40] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdara-implementation-guidance-pediatric-studies-molecularly-targeted-oncology-drugs-amendments-sec.

[41] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended.

- *Draft Guidance Document — General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products (August 2019)*[42]

  This guidance document was required under section 505(d)(2) of FDARA and addresses the clinical pharmacology considerations for any planned studies in neonatal populations. When final, this guidance document will represent the Agency's current thinking on this topic.

- *Revised Draft Guidance Document — Rare Pediatric Disease Priority Review Vouchers (July 2019)*[43]

  This revised draft guidance document provides information on the implementation of the rare pediatric disease priority review voucher program. When final, this guidance document will represent the Agency's current thinking on this topic.

- *Final Guidance Document — Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling (March 2019)* [44]

  This guidance document provides recommendations to help ensure that information on the use of prescription drugs in pediatric patients (whether positive, negative, or inconclusive) is consistently placed in the proper sections and subsections within labeling so the information is clear and accessible to healthcare providers.

- *Final Guidance Document — E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (April 2018)*[45]

  Pediatric drug development has evolved since the publication of the original guidance document titled "E11 Clinical Investigation of Medicinal Products in the Pediatric Population" in 2000, requiring a renewed look at regulatory and scientific advances relevant to pediatric populations. The purpose of the addendum is to complement and provide clarification and current regulatory perspectives on topics in pediatric drug development.

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[42] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance.

[43] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf.

[44] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good.

[45] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population.

Impact of Pediatric Statutes: Beyond the Mandates

The pediatric statutes have stimulated scientific growth and innovation in the way drugs are developed for children and have spurred robust international collaboration to ensure pediatric studies are well designed to meet global regulatory standards so pediatric trials are not needlessly repeated.

1.6 Advancing Regulatory Science for Pediatric Drug Development

FDA recognizes that encouraging the timely completion of pediatric studies involves not only the earlier review of pediatric study plans but also, increasingly, cooperation of all pediatric stakeholders involved in the drug development process. In certain areas of pediatric therapeutics development, there are difficulties in identifying a feasible path forward. FDA has created opportunities for stakeholders to meet to discuss feasible development approaches in areas of unmet need and in areas in which development has been historically difficult. Since 2015, FDA has hosted numerous workshops to examine ways to optimize pediatric drug development and has published many peer-reviewed manuscripts describing scientific advances. Workshops and publications have focused on essential areas in modern pediatric drug development programs, including the use of complex innovative trial designs, new techniques in predicting and analyzing clinical pharmacology information in children, pediatric extrapolation of adult effectiveness data, consistent data collection and sharing, and application of biomarkers and surrogate endpoints to help better understand the drug's clinical benefit in children. Table 4 provides a listing of select pediatric-focused workshops convened by FDA.

These workshops have been extremely well received by external stakeholders and have led to specific meaningful changes that have created pathways to drug approval in pediatric populations. For example, after FDA and the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) convened, in 2017, the workshop "Drug Development in Pediatric Heart Failure: Extrapolation, Clinical Trial Design, and Endpoints," FDA reviewed the data necessary to support pediatric extrapolation based on a bridging biomarker for certain drugs that may be useful in the treatment of pediatric heart failure. Based on this review, FDA agreed that a bridging biomarker could be used to support the approval of Entresto (sacubitril/valsartan). In 2019, FDA approved Entresto for the "treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older"; Entresto is only the second drug approved for the treatment of pediatric heart failure.

Table 4: Select Pediatric Workshops and Meetings Hosted by FDA (2015-2020)

Workshop Title	Date
FDA's Advancing the Development of Pediatric Therapeutics (ADEPT) Workshops	
Pediatric Clinical Trial Endpoints for Rare Diseases With a Focus on Pediatric Patient Perspectives (ADEPT 6)	November 12, 2019
Advancing Pediatric Pharmacovigilance (ADEPT 5)	September 14, 2018
Application of "Big Data" to Pediatric Safety Studies (ADEPT 4)	September 18-19, 2017
Successes and Challenges of Performing Long-Term Pediatric Safety Studies (ADEPT 3)	April 13-14, 2016
FDA and M-CERSI Co-Hosted Workshops	
Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)	October 2, 2019
Pediatric Formulations	June 18-19, 2019
Pediatric Clinical Investigator Training	February 28, 2019
Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?	May 16, 2019
Pediatric Inflammatory Bowel Disease	November 16, 2018
Drug Development in Pediatric Heart Failure: Extrapolation, Clinical Trial Design, and Endpoints	October 27, 2017
Pediatric Master Protocols	September 23, 2016
Quantitative Assessment of Assumptions to Support Extrapolation of Efficacy in Pediatrics	June 1, 2016
Use of Exposure Matching and Exposure-Response for Extrapolation of Efficacy in Pediatric Product Development	January 22, 2015
FDA and Duke-Margolis Center for Health Policy Co-Hosted Meetings	
Prospect of Direct Benefit in Pediatric Clinical Trials	March 29, 2019
Advancing Endpoint Development for Preterm Neonates With Pulmonary Morbidities	October 2, 2018
Additional Workshops Co-Organized by FDA	
Institute for Advanced Clinical Trials (I-ACT) for Children Workshops	
Remote Patient Monitoring and Children in the COVID-19 Pandemic: What's the Opportunity and What's the Impact	October 16, 2020
Developing Pediatric Treatments for COVID-19	May 28, 2020
Pediatric Research Innovation Forum: Inclusion of Adolescents in Adult Clinical Trials	October 15-16, 2019

I-ACT for Children and Duke Clinical Research Institute Workshops	
Youth Tobacco Cessation: Science and Treatment Strategies	May 15, 2019
DIA Workshops	
DIA Pediatric Drug Development Workshop	October 28-29, 2019

FDA also continues to engage in various outreach activities with external stakeholders to facilitate an understanding of regulatory issues and to share updates on FDA's pediatric-focused efforts. FDA gives numerous pediatric-related presentations each year to external stakeholders and collaborates in several consortia and working groups focused on advancing pediatric research and drug development. For example, FDA participates annually in a "Pediatric Liaison" meeting with BIO. Additionally, FDA has awarded several grants to support pediatric research and development. These grants help fund activities ranging from bench research to pediatric clinical trials, including efforts toward establishing a sustainable infrastructure to support timely and efficient pediatric clinical trials.

FDA also engages in regulatory science research to address challenges in pediatric drug development, especially the development of drugs targeting rare pediatric diseases. Over the past 5 years, FDA has published numerous papers in scientific journals that have advanced the development of pediatric therapeutics. A primary focus of FDA's regulatory science research in pediatrics has involved research questions to address specific challenges encountered in the development of drugs for pediatric patients, including extrapolating efficacy, designing innovative trials, developing clinical trial endpoints, assessing safety, and selecting appropriate doses. Additionally, FDA has created a large database of clinical trial data from over 1,600 pediatric clinical trials; this database has been used to address these challenges.

In addition, pediatric research collaborations have been developed using many effective mechanisms, including research collaboration agreements, memoranda of understanding, and Broad Agency Announcements. These pediatric-focused research efforts have helped advance the development of pediatric therapies in many areas.

1.7 Global Harmonization of Pediatric Research and Drug Development

FDA continues to engage with international stakeholders to help ensure children around the world participate in clinical trials that are well designed to meet international regulatory standards. FDA's international collaborative efforts have helped improve therapeutics development globally by increasing the efficiency of clinical trial enrollment for small populations, by expanding information and knowledge-sharing with global experts, and by harmonizing clinical trial designs to help ensure pediatric clinical trials are not needlessly repeated. These efforts have helped (1) improve what is known about

therapies for pediatric populations and (2) convey this knowledge in prescribing information.

1.7.1 International Pediatric Cluster Conference Calls

FDA's Office of Pediatric Therapeutics continues to coordinate monthly Pediatric Cluster conference calls with global regulators in Europe, Japan, Canada, and Australia. From the Pediatric Cluster's inception in 2007 to June 2020, the Pediatric Cluster has discussed 570 products proposed for pediatric study. The most common clinical trial issues discussed have included the scope of pediatric drug development, safety, dosing, types of clinical trials, and trial design. In 2012, FDA and the European Medicines Agency (EMA) developed a process for sharing brief Common Commentary documents for certain topics discussed at the Pediatric Cluster. These documents convey non-binding high-level comments from regulators to pharmaceutical industry sponsors. From July 2012 to June 2020, FDA issued 45 Common Commentaries spanning most therapeutic areas.

The Pediatric Cluster has been an important forum for collaboration with international regulatory agencies regarding pediatric cancer drug development, including attempting to align decision-making and advice to sponsors, particularly since implementation of the RACE for Children Act. From August 2019 through June 2020, 14 new oncology products have been the subject of high-level scientific discussions during 16 Pediatric Cluster calls, which have attempted to provide coordinated advice to sponsors to facilitate global drug development. During this time frame, three Common Commentaries regarding three cancer drugs have been issued. In addition, in a publicly posted general topic Common Commentary, FDA and EMA jointly discussed the simultaneous submission of oncology iPSPs and Paediatric Investigation Plans (PIPs) to FDA and EMA, respectively, to further facilitate this global coordination.[46]

1.7.2 Important Efforts to Encourage International Collaboration

Highlighted below are several activities and initiatives FDA has undertaken to encourage international collaboration in pediatric drug development:

- FDA participates with EMA in the ACCELERATE Platform, an international, multi-stakeholder group focused on accelerating the development of new therapies for children with cancer. Given the rarity of cancer in children generally; in, more importantly, specific histologic types; and now in, even more significantly, genomically categorized subtypes of rare cancers, international studies and coordinated global development programs are particularly important.

- FDA serves on EMA's initiative for the European Network of Paediatric Research's working group on international cooperation, which is tasked with

[46] https://www.fda.gov/media/147197/download.

comparing the pre-market regulatory and ethical requirements for the conduct of pediatric clinical trials and for participation as a clinical trial site across the following five jurisdictions: United States, European Union, Canada, Japan, and Australia.

- FDA participates on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's E11A Expert Working Group, which is currently drafting a guideline on pediatric extrapolation.

- FDA collaborates with Japan's Pharmaceuticals and Medical Devices Agency Asia Training Center to host an annual international pediatric review workshop designed to further disseminate information on advances in scientific and technical knowledge for pediatric drug development. Over the 3 years since the joint workshop began, 81 international regulators from 21 countries have participated, as well as the World Health Organization (WHO).

- FDA is a member of the WHO Paediatric Regulatory Network, which serves as a forum for enabling dialogue and fostering development of international consensus on effective regulatory approaches for increasing the availability of pediatric medical products around the world.

- FDA serves on a working group with the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard which seeks to recommend harmonized approaches and tools to regulate and facilitate pediatric research worldwide.

Stakeholder Input

In accordance with section 508 of FDASIA, FDA held a public pediatric stakeholder meeting on November 21, 2019, to obtain input from patient groups, consumer groups, regulated industry, academia, and other interested parties on any recommendations or information relevant to this BPCA and PREA report to Congress. The meeting information, materials, and webcast are available on FDA's website.[47] In response to FDA's October 2019 *Federal Register* request for comments and announcement of a November 2019 meeting,[48] stakeholders from the pharmaceutical industry and advocacy organizations provided input on BPCA and PREA. Stakeholders generally supported the continued implementation of BPCA and PREA in the development and labeling of drugs for pediatric populations. In this section, several key themes that emerged from the stakeholder input for this meeting are described.

[47] https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/pediatric-stakeholder-meeting-public-meeting-11212019-11212019#event-information.

[48] 84 FR 57451 (Oct. 25, 2019).

1.8 Need for Issuing or Updating FDA's Guidance Documents

Stakeholders generally agreed that FDA needs to issue guidance documents on key pediatric issues as well as update and/or finalize existing guidances. One organization, BIO, noted that the draft guidance document titled "How to Comply with the Pediatric Research Equity Act," which published in 2005, had not yet been finalized.[49] BIO also asserted that the 1999 revised draft guidance document on complying with BPCA was never finalized and has since been withdrawn and replaced with a Frequently Asked Questions document, on which stakeholders never had an opportunity to comment.[50]

PhRMA expressed concern with "the delay" in publishing a final guidance document on FDA's implementation of the FDARA amendments to PREA regarding molecularly targeted cancer drugs.[51] PhRMA recommended that FDA provide "appropriate regulatory flexibility" for applications that will be submitted shortly after the FDARA implementation date.[52]

In addition, stakeholders recommended modernizing the guidance documents on BPCA and PREA to maintain a balance between the two statutes, and to provide guidance on the use of innovative approaches in pediatric drug development, the use of external data (historical clinical trial data or natural history real-world data) in single arm trials, and the use of extrapolation in pediatric programs. An early alignment on comprehensive pediatric drug development plans that encompasses studies under both PREA and BPCA was encouraged by stakeholders to allow them to initiate studies as soon as possible.

1.9 Suggestions on Policy Implementation

FDA's approach to WRs was noted, by stakeholders, as a concern. Specifically, PhRMA expressed concern with WRs for "lengthy clinical trials that cannot be completed in time to receive meaningful pediatric exclusivity"; with "overly broad" WRs, including "studies that may not be feasible or that are exploratory in nature"; and with perceived "inconsistent FDA input over time."[53] Similarly, BIO noted that "requesting numerous broad, exploratory pediatric studies in Written Requests lessens the effectiveness of

[49] BIO's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[50] Id.

[51] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[52] Id.

[53] Id.

BPCA as an incentive, because a Sponsor may be unable to complete the studies in time to earn the pediatric exclusivity incentive."[54]

PhRMA also expressed concern over the potential abandonment of the orphan-drug exemption in PREA. PhRMA stated that doing so "would undermine the incentives for innovators to pursue orphan-drug development and introduce feasibility challenges for satisfying the resulting pediatric study obligations."[55] PhRMA commented that removing the orphan-drug exemption would "disturb the balance between PREA and BPCA," suggesting that FDA can utilize the BPCA process for obtaining studies of orphan drugs.[56] PhRMA also mentioned (1) the recent changes under FDARA that narrowed the exemption in section 505B(k) so that it does not apply for certain cancer drugs and (2) FDA's issuance of a guidance document that clarified its policy on orphan designation for pediatric subpopulations.[57] PhRMA suggested that

> no new changes to PREA should be considered before the impact of the latest changes is assessed and before the Government Accountability Office (GAO) conducts a study and publishes a report on the effectiveness of requiring assessments and investigations under section 505B for the development of drugs for pediatric cancer indications.[58]

Conversely, in a presentation on behalf of the AAP, Bridgette Jones, MD, highlighted that "orphan drug approvals are increasing, and therefore, so are the number of new drugs that are exempt from pediatric study requirements" and recommended that FDA "act quickly to remove the PREA orphan exemption."[59] In addition, Katie Coester, MPP, from the Elizabeth Glaser Pediatric AIDS Foundation noted that "lack of PREA application to orphan drugs impacts numerous pediatric diseases and conditions, including common comorbidities affecting children living with HIV" and asserted that "PREA should be applied to orphan drugs."[60]

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[54] BIO's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[55] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[56] Id.

[57] See https://www.fda.gov/media/109496/download.

[58] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[59] See https://www.fda.gov/media/132831/download.

[60] See https://www.fda.gov/media/132827/download.

1.10 Importance of International Alignment on Pediatric Studies

Stakeholders urged FDA to continue to work with EMA and its international counterparts to harmonize pediatric testing requirements and provide sponsors with greater transparency on the coordination between international bodies. PhRMA, in particular, noted the significant challenges of pediatric drug development when different regulators provide inconsistent advice, which PhRMA suggests is "further complicated by the fact that discussions with EMA and FDA about pediatric drug development plans occur at different development stages."[61]

Stakeholders noted that additional discussions that are not currently addressed via the Pediatric Cluster and associated Common Commentary process are needed to better support timely pediatric access to medicines through aligned scientific advice from global health authorities. They suggested that a forum for timely and aligned pediatric testing advice from FDA and EMA would significantly facilitate efficient pediatric drug development.

1.11 Necessary Advances in Pediatric Product Development and Use

Stakeholders raised concerns regarding the challenges associated with pediatric drug development for neonates, including the lack of scientific understanding regarding endpoints and biomarkers and the lack of natural history information for diseases in the neonatal population. These stakeholders suggested that (1) FDA hold stakeholder meetings to discuss mechanisms for addressing these challenges, ensure that (2) FDA's neonatologists engage in discussion with FDA's review divisions and sponsors, and (3) FDA seek additional external expertise on the development of drugs for neonates as needed.

One stakeholder commented on the struggles with treating a range of conditions, including rare disorders, using medication and devices that lack a pediatric label or indication. This stakeholder suggested creating a National Pediatric Safety Registry and requested FDA's assistance in the collection of data that could serve to facilitate pediatric labeling while also providing patients, parents, and providers with more helpful safety data.[62]

In addition, this stakeholder expressed the need for conducting pharmacokinetic/pharmacodynamic evaluations, developing pediatric friendly drug formulations, limiting placebo control study designs, and allowing the extrapolation of

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[61] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[62] North American Society for Pediatric Gastroenterology, Hepatology and Nutrition's (NASPGHAN's) response to FDA's *Federal Register* notice (FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

efficacy from adult studies. This stakeholder also encouraged the enrollment of late adolescents in adult designed studies, the creation of pediatric-focused clinical outcome measures, and a requirement for a pediatric needs assessment early in development.[63]

Finally, another stakeholder suggested that FDA "maximize the use of biomarkers, including biomarkers for accelerated approval based on reasonable links between the proposed biomarker and the underlying condition to be treated."[64] This stakeholder suggested that "to the extent that biomarkers can be used as reasonable bases for expectation of improved clinical and welfare outcomes, they should be incorporated in the FDA structured benefit risk approach."[65]

Coronavirus Disease 2019 (COVID-19) Pandemic

FDA has been working tirelessly to address the need for therapeutic and vaccine development to address the COVID-19 pandemic, including the needs of children. A rapid global alignment on the development of pediatric therapeutics and vaccines that address the needs of children while not slowing access to adult populations has been supported by frequent and productive activities both internal and external to FDA. For example, of the 32 Pediatric Cluster conference calls hosted by FDA between January 2020 and October 2021, 17 calls included discussions related to pediatric development programs for COVID-19 therapies. These discussions resulted in the issuance of four Common Commentaries for COVID-19 products and one general Common Commentary for the submission of iPSPs and PIPs for products for the prevention and treatment of COVID-19. Early in the pandemic (May 2020), FDA co-moderated a virtual workshop held by I-ACT for Children to share information and discuss therapeutic research and innovative approaches to obtain data necessary to advance COVID-19 therapeutics for children. In June 2020, NIH announced funding for a study to evaluate drugs prescribed to children with COVID-19 through the NICHD-funded PTN.[66]

Internally at FDA, the CDER and CBER review divisions have worked with the PeRC to achieve agreed-upon iPSPs for COVID-19 therapies and vaccines. Between January 2020 and October 2021, the PeRC reviewed 49 iPSPs relevant to COVID-19 products that are subject to PREA. Importantly, Veklury (remdesivir), the first drug approved by FDA to treat COVID-19, included, as part of the original approval, pediatric patients 12 years and older who weigh at least 40 kilograms. Further, Comirnaty (an mRNA

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[63] Id.

[64] Kermit Kubitz's response to FDA's *Federal Register* notice (FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[65] Id.

[66] See https://www.nichd.nih.gov/newsroom/news/061020-COVID-19-BPCA.

COVID-19 vaccine), the first FDA-approved COVID-19 vaccine, also included pediatric patients 16 years and older as part of the original approval.

In addition to moving rapidly to address the COVID-19 pandemic in children, FDA has continued work with drug developers who have experienced delays in non-COVID-19 drug development due to the pandemic. During the time period covered by this report, in recognition of the need for sponsors to adjust study timelines due to disruptions caused by the pandemic, FDA has granted a relatively high percentage of PREA deferral extension requests associated with the impacts of the COVID-19 pandemic on clinical trial operations (see Table 2).

Program Improvements for Continued Advancement of Product Development in Children

While BPCA and PREA have been instrumental in improving pediatric research, product development, and labeling, FDA continues to evaluate strategies for further improvements, which are discussed in this section.

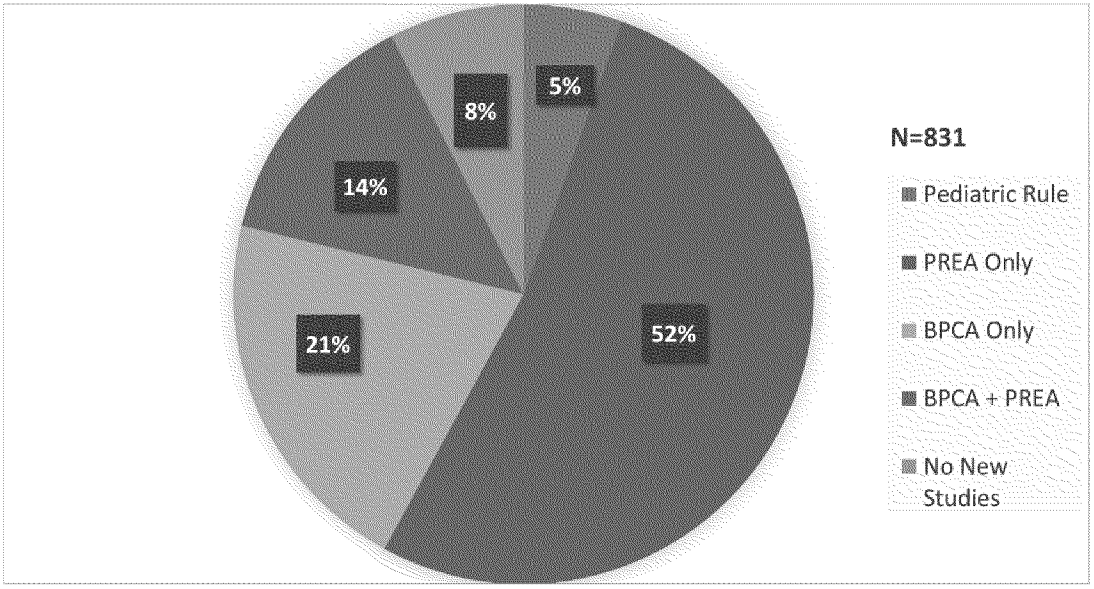
1.12 Removal of the Orphan Exemption Under PREA

As discussed in section 1.2.1, there has been some progress in the development of therapeutics to treat pediatric cancers. Some of this success can be attributed to the passage of section 504 of FDARA which, among other things, includes the removal of the orphan exemption under PREA for certain drugs that are directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer. Furthermore, as described in section 1.2.2, there is a public health need for additional pediatric information in labeling for over one-third of approved orphan indications that are relevant to the pediatric population.[67]

FDA strongly believes that requirements under PREA have driven, not impeded, the development of therapies for children. The majority of pediatric labeling changes have resulted from studies conducted under PREA, not BPCA (see Figure 3). These data suggest that removal of the orphan exemption under PREA would improve the availability of approved therapies for pediatric patients with rare diseases.

[67] See https://www.fda.gov/media/130060/download.

Figure 3: Pediatric Labeling Changes From 1998-2019



One concern expressed by industry is that the removal of the orphan exemption may change the financial calculus for the development of rare pediatric disease treatments. FDA acknowledges this concern but notes that other incentive programs are available to encourage the development of therapies to treat rare pediatric diseases that are not precluded by the elimination of the orphan exemption under PREA. Furthermore, FDA has granted waivers under PREA, as appropriate, when a rare disease that is the subject of an application does not affect children. Additionally, pediatric experts on the PeRC are able to consistently review development programs for pediatric rare diseases as presented in iPSPs and provide advice that would potentially improve the speed and efficiency of drug development in rare pediatric diseases.

FDA is concerned that the orphan exemption under PREA may be limiting the availability of evidence-based data for drugs for all relevant pediatric age groups with rare diseases and is evaluating potential strategies to address this concern.

1.13 Optimization of Post-Marketing Surveillance of Pediatric Medical Products

1.13.1 Modernize Pediatric Pharmacovigilance

Using a standardized time-based approach to review the safety of drugs with new pediatric use information may not be the most effective or efficient approach for safety signal detection. The 18-month pediatric-focused safety reviews required by sections 505A(*l*) and 505B(i) of the FD&C Act overlap substantially with the Agency's established post-marketing safety surveillance through FAERS. Risk-based approaches,

as opposed to time-based approaches, are now being implemented by FDA as part of its overall pharmacovigilance strategies.

FDA is evaluating ways to advance pediatric pharmacovigilance using similar modern risk-based approaches to help ensure pediatric pharmacovigilance is optimized to identify new or serious pediatric safety concerns.

1.13.2 Establish Periodic Review of HDEs

The Pediatric Medical Device Safety and Improvement Act of 2007 added, at section 520(m)(6)(A) of the FD&C Act, an exemption from the restriction on profit-making for certain HDE devices that are approved and labeled for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or a pediatric subpopulation. Section 520(m)(8) of the FD&C Act requires these devices to undergo an annual review by the PAC of the appropriateness of the HDE for the pediatric population for which the device was approved. This legislative requirement for an annual review by the PAC overlaps with FDA's review of annual reports required in approval orders for HDEs under 21 CFR 814.126(b).

To ensure that post-marketing HDE surveillance for these devices is optimized to focus the PAC's review on new or serious pediatric safety concerns, as well as on scientific and clinical matters surrounding pediatric product development and use, FDA is evaluating ways to align the PAC's annual review to ensure the appropriateness of the HDE for the pediatric population for which the device was approved with the currently required periodic review for adverse event reports.

Conclusion

Prior to passage of the first incentive provisions for the completion of pediatric studies under FDAMA in 1997, more than 80 percent of approved drugs had no pediatric-specific labeling information. Since then, over 900 drugs have been labeled with pediatric information because of legislative initiatives that have required or incentivized pharmaceutical industry sponsors to conduct pediatric studies. FDA now has more than 2 decades of experience implementing these legislative initiatives and reviewing data obtained from pediatric studies. The knowledge gained has affirmed the importance of obtaining information to support pediatric use. The safety, effectiveness, and dosing of drugs may differ between adults and children, and understanding these differences is essential for healthcare providers to make evidence-based decisions about treating pediatric patients.

An important shift in the regulatory landscape for pediatric cancer drug development has occurred with implementation of FDARA. Early evidence suggests that the RACE for Children Act has had a favorable impact on the timely consideration and initiation of studies of appropriate molecularly targeted cancer drugs that would previously have not

been required and that would historically have gone unstudied in children. While the pediatric statutes have led to important progress in labeling products for pediatric use, unique challenges persist regarding the conduct of studies and labeling of products for rare pediatric diseases and for neonates.

In addition to ensuring therapeutics are developed for all relevant pediatric populations, achieving shorter timelines from FDA's initial drug approval to the incorporation of pediatric use information into labeling remains a key objective for FDA. The Agency has been working diligently to ensure proposed pediatric study timelines are reasonable and to provide timely responses and meaningful advice to pharmaceutical industry sponsors regarding pediatric drug development plans. As described in this report, a delay of approximately 6 years remains between the original approval of a drug and incorporation of pediatric use information in labeling. Whether the earlier issuance of WRs and an earlier discussion of pediatric study plans will have a positive impact remains to be seen. In addition to earlier pediatric study planning, achieving shorter timelines will involve more efficient clinical trial operations and improvements in pediatric clinical trial infrastructure. Importantly, greater efficiency in pediatric drug development also involves continued progress in the regulatory science to support pediatric drug development programs. Addressing pediatric-specific study design issues, including endpoints, biomarkers, and exposure-response relationships, and incorporating into adult drug development programs assessments that help to tackle these issues is essential.

Since the last BPCA and PREA report to Congress, FDA has made substantial efforts to address scientific and regulatory issues unique to the development of therapeutics for children by hosting workshops to address pediatric drug development needs, conducting important regulatory research, issuing guidance documents related to pediatric therapeutics development, and collaborating with numerous national and international consortia and organizations to gain a consensus on approaches for pediatric therapeutics development. The Agency also continues to collaborate with international regulatory authorities to help assure pediatric trials are well designed to meet international regulatory standards.

The 409I program has played a critical role in obtaining information about pediatric use for off-patent drugs. Since the last report to Congress, the number of approved labeling changes that have occurred under this program has more than tripled. Importantly, three of the 22 drugs updated to include dosing, safety, and/or efficacy information in labeling for neonates resulted from studies conducted under the 409I program. Further, under this program, NIH continues to identify and prioritize drugs that need additional study in pediatric patients, disseminate information to researchers and the public, and serve as a source of knowledge and training for the scientific community.

FDA believes that these efforts over the past 5 years have continued to advance the important progress that has been made in increasing the availability of approved drugs for children. FDA is committed to continuing its work with all stakeholders over the next 5 years and beyond.

Appendix 1: Pediatric Labeling Changes Under BPCA and PREA Since the 2016 Report to Congress (Covering July 1, 2015, Through June 30, 2020)

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
6/26/2020	Lialda delayed-release tablets	Mesalamine	Mildly to moderately active ulcerative colitis	PREA Only
6/19/2020	Sivextro tablet	tedizolid phosphate	Acute bacterial skin and skin structure infections (ABSSSI)	PREA Only
6/12/2020	Gardasil 9	Human Papillomavirus 9-valent Vaccine, Recombinant	Prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine	PREA Only
6/12/2020	Tivicay tablets	dolutegravir	Human Immunodeficiency Virus-1 (HIV-1) infection	PREA + BPCA
6/12/2020	Tivicay PD tablets for oral suspension	dolutegravir	HIV-1 infection	PREA + BPCA
5/26/2020	Dupixent injection	dupilumab	Moderate-to-severe atopic dermatitis (AD)	PREA Only
5/26/2020	VESIcare LS oral suspension	solifenacin succinate	Neurogenic detrusor overactivity (NDO)	PREA + BPCA
5/26/2020	Zosyn injection	piperacillin/tazobactam	Nosocomial pneumonia	PREA Only
5/22/2020	Phexxi vaginal gel	lactic acid/citric acid/potassium bitartrate	Prevention of pregnancy	PREA Only
5/1/2020	Fensolvi injectable	leuprolide acetate	Central precocious puberty (CPP)	PREA Only
4/26/2020	Jublia topical solution	efinaconazole	Onychomycosis of the toenail	PREA Only
4/23/2020	MenQuadfi	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine	Prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y	PREA Only
4/20/2020	Cymbalta	duloxetine	Fibromyalgia	PREA Only
4/1/2020	Sevenfact	Coagulation factor VIIa (recombinant)-jncw	Bleeding episodes occurring in patients with hemophilia A or B with inhibitors	PREA Only
3/26/2020	Taltz injection	ixekizumab	Moderate-to-severe plaque psoriasis	PREA Only
3/23/2020	Eucrisa ointment	crisaborole	Mild to moderate atopic dermatitis	PREA + BPCA
3/19/2020	Epclusa	sofosbuvir/velpatasvir	Chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
3/4/2020	Cleocin Phosphate	clindamycin injection; clindamycin injection in dextrose	Clindamycin dosing and body weight	409I(BPCA)
3/4/2020	Acticlate; Acticlate Cap	doxycycline hyclate	Doxycycline pharmacokinetics	409I(BPCA)
3/2/2020	Cafcit Injection	caffeine citrate	Apnea of prematurity	409I(BPCA)
2/12/2020	Doryx; Doryx MPC	doxycycline hyclate	Doxycycline pharmacokinetics	409I(BPCA)
1/31/2020	Audenz	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted	Active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine	PREA Only
1/31/2020	Palforzia	Peanut (Arachis hypogaea) Allergen Powder-dnfp	Mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut	PREA Only
1/31/2020	Viibryd	vilazodone hydrochloride	Major depressive disorder (MDD)	PREA + BPCA
1/28/2020	Agriflu	Influenza Virus Vaccine	Active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine	PREA Only
1/24/2020	Dificid	fidaxomicin	Clostridioides difficile-associated diarrhea (CDAD)	BPCA Only
12/20/2019	Vibramycin; Vibra-Tabs	doxycycline monohydrate; doxycycline hyclate; doxycycline calcium; doxycycline hyclate	Doxycycline pharmacokinetics	409I(BPCA)
12/20/2019	Mycamine	micafungin	Candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses without meningoencephalitis and/or ocular dissemination	PREA Only
12/19/2019	Conjupri	levamlodipine	Hypertension	PREA Only
12/19/2019	Fiasp	insulin aspart	Diabetes mellitus	PREA Only
12/18/2019	Aralzo	tazarotene	Acne vulgaris	PREA Only
12/6/2019	Abraxane	paclitaxel	Recurrent or refractory pediatric solid tumors	BPCA Only
12/4/2019	Latuda	lurasidone hydrochloride	Growth	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
11/15/2019	Harvoni	ledipasvir/sofosbuvir	Chronic hepatitis C virus infection in patients with severe renal impairment including patients with end stage renal disease on dialysis	PREA Only
11/13/2019	Lumason	Sulfur Hexafluoride Lipid-Type A Microspheres	Use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult and pediatric patients with suboptimal echocardiograms	PREA Only
11/5/2019	Sorilux	calcipotriene	Plaque psoriasis of the scalp and body	PREA Only
10/25/2019	Opana	oxymorphone HCl	Postoperative pain	PREA Only
10/18/2019	Amzeeq	minocycline	Inflammatory lesions of non-nodular moderate to severe acne vulgaris	PREA Only
10/18/2019	Botox	onabotulinumtoxinA	Lower limb spasticity	PREA Only
10/18/2019	Ultomiris	ravulizumab-cwvz	Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA)	PREA Only
10/10/2019	Wilate	von Willebrand Factor/Coagulation Factor VIII Complex (Human)	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
10/4/2019	Aklief	trifarotene	Acne vulgaris	PREA Only
10/4/2019	Quzyttir	cetirizine hydrochloride	Acute urticaria	PREA Only
10/3/2019	Tybost	cobicistat	HIV-1 infection	PREA + BPCA
10/3/2019	Descovy	emtricitabine/tenofovir alafenamide	Pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection	PREA Only
10/1/2019	Entresto	sacubitril/valsartan	Symptomatic heart failure with systemic left ventricular systolic dysfunction	PREA + BPCA
9/26/2019	Mavyret	glecaprevir/pibrentasvir	Chronic hepatitis C virus infection (HCV)	PREA Only
9/25/2019	Dysport	abobotulinumtoxinA	Upper limb spasticity	PREA Only
9/13/2019	Teflaro Injection	ceftaroline fosamil	Acute Bacterial Skin and Skin Structure Infections (ABSSSI)	PREA Only
9/13/2019	Mydayis	mixed salts of a single-entity amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA + BPCA
9/12/2019	Nucala	mepolizumab	Severe asthma with an eosinophilic phenotype	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
9/10/2019	Gvoke	glucagon	Severe hypoglycemia in patients with diabetes	PREA Only
9/10/2019	Aczone Gel	dapsone	Acne vulgaris	PREA Only
8/29/2019	Riomet ER	metformin hydrochloride	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus	PREA Only
8/28/2019	Harvoni Oral Pellets	ledipasvir/sofosbuvir	Chronic hepatitis C virus	PREA + BPCA
8/28/2019	Harvoni	ledipasvir/sofosbuvir	Chronic hepatitis C virus (HCV)	PREA + BPCA
8/28/2019	Sovaldi	sofosbuvir	Chronic hepatitis C virus	PREA + BPCA
8/22/2019	Tybost	cobicistat	HIV-1 infection	PREA + BPCA
8/15/2019	Rozlytrek	entrectinib	Solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation that are metastatic or where surgical resection is likely to result in severe morbidity and have progressed following treatment or have no satisfactory alternative therapy	BPCA Only
8/12/2019	Dulera Inhalation Aerosol	formoterol fumarate/mometasone furoate	Asthma	PREA + BPCA
8/12/2019	Asmanex HFA	mometasone furoate	Asthma	PREA Only
8/8/2019	Clenpiq	sodium picosulfate/magnesium oxide/anhydrous citric acid	Cleansing of the colon as a preparation for colonoscopy	PREA Only
7/30/2019	Enstilar Foam	calcipotriene/betamethasone dipropionate	Plaque psoriasis of the scalp and body	PREA + BPCA
7/25/2019	Taclonex	calcipotriene/betamethasone dipropionate	Plaque psoriasis of the scalp and body	PREA Only
7/24/2019	Baqsimi nasal powder	glucagon	Severe hypoglycemia in patients with diabetes	PREA Only
7/8/2019	Katerzia oral suspension	amlodipine benzoate	Hypertension	PREA Only
6/20/2019	Botox	onabotulinumtoxinA	Upper limb spasticity	PREA Only
6/18/2019	Biktarvy	bictegravir/emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
6/17/2019	Victoza	liraglutide	Type 2 diabetes mellitus	PREA + BPCA
6/14/2019	Aptensio XR	methylphenidate hydrochloride	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
6/6/2019	Nucala	mepolizumab	Severe asthma	PREA Only
5/23/2019	Lyrica	pregabalin	Partial-onset seizures (POS)	PREA + BPCA
5/23/2019	Slynd	drospirenone	Prevention of pregnancy	PREA Only
5/16/2019	Gattex	teduglutide	Short Bowel Syndrome (SBS)	PREA Only
5/16/2019	Fragmin	dalteparin sodium	Symptomatic venous thromboembolism (VTE) to reduce recurrence	PREA Only
5/16/2019	Livalo	pitavastatin	Heterozygous familial hypercholesterolemia (HeFH)	PREA Only
5/7/2019	Sutent	sunitinib malate	Refractory solid tumors	BPCA Only
5/6/2019	Sorilux	calcipotriene	Plaque psoriasis of the scalp and body	PREA Only
5/1/2019	Dengvaxia	Dengue Tetravalent Vaccine, Live	Prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4	PREA Only
4/30/2019	Mavyret	glecaprevir/pibrentasvir	Chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)	PREA + BPCA
4/26/2019	Benlysta	belimumab	Active, antibody systemic lupus erythematosus (SLE)	PREA Only
4/22/2019	Corlanor Oral Solution	ivabradine	Symptomatic heart failure due to dilated cardiomyopathy (DCM)	BPCA Only
4/18/2019	Opdivo	nivolumab	Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC)	PREA Only
4/3/2019	Welchol Chewable Bar	colesevelam HCl	Heterozygous familial hypercholesterolemia	PREA Only
3/29/2019	Octaplas	Pooled Plasma (Human), Solvent/Detergent Treated	Indicated (1) as replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease or undergoing cardiac surgery and liver transplantation and (2) plasma exchange in patients with thrombotic thrombocytopenic purpura	PREA Only
3/21/2019	Doptelet	avatrombopag	Juvenile animal toxicity	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
3/14/2019	Avycaz	ceftazidime/avibactam	Complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI)	PREA Only
3/11/2019	Dupixent	dupilumab	Moderate-to-severe atopic dermatitis	PREA Only
3/1/2019	Flector Topical System	diclofenac epolamine	Acute pain due to minor strains, sprains, and contusions	PREA Only
2/27/2019	Adhansia XR	methylphenidate hydrochloride	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
2/22/2019	Chantix	varenicline	Aid to smoking cessation	PREA + BPCA
2/19/2019	Esperoct	Antihemophilic Factor (Recombinant), GlycoPEGylated-exei	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
1/29/2019	Vfend	voriconazole	(1) Invasive aspergillosis (2) Candidemia and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds (3) Esophageal candidiasis (4) Serious infections caused by Scedosporium apiospermum and Fusarium species	PREA + BPCA
1/25/2019	Zovirax	acyclovir	Neonatal herpes virus infection (HSV)	409I(BPCA)
12/21/2018	Vaxelis	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of hepatitis B virus	PREA Only
12/21/2018	Sprycel	dasatinib	Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL)	BPCA Only
12/12/2018	Exjade; Jadenu	deferasirox	Transfusion-dependent anemia requiring chelation therapy due to iron overload	BPCA Only
12/11/2018	Viread	tenofovir disoproxil fumarate	Chronic hepatitis B (CHB)	PREA + BPCA
11/29/2018	Astagraf XL	tacrolimus	Prophylaxis of organ rejection in kidney transplant patients, in combination with other immunosuppressants	PREA Only
11/21/2018	Spy Agent Green	Indocyanine green	Visualization of vessels, blood flow and tissue perfusion before, during, and after various surgical procedures, including	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
			minimally invasive surgeries and visualization of extrahepatic biliary ducts	
11/9/2018	Oralair	Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product	PREA Only
11/7/2018	Primatene Mist	epinephrine	Mild symptoms of intermittent asthma	PREA Only
10/26/2018	Xyrem	sodium oxybate	Cataplexy or excessive daytime sleepiness in patients with narcolepsy	BPCA Only
10/24/2018	Xofluza	baloxavir marboxil	Acute uncomplicated influenza	PREA Only
10/19/2018	Dupixent	dupilumab	Moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	PREA Only
10/4/2018	Lithium	lithium	Acute manic or mixed episodes of bipolar I disorder and maintenance monotherapy of bipolar I disorder	409I(BPCA)
10/4/2018	Afluria; Afluria Quadrivalent	Influenza Vaccine	Active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	PREA Only
10/1/2018	Seysara	sarecycline	Inflammatory lesions of non-nodular moderate to severe acne vulgaris	PREA Only
9/28/2018	Xolair	omalizumab	Moderate to severe persistent asthma	PREA Only
9/27/2018	Promacta	eltrombopag	Chronic immune (idiopathic) thrombocytopenia (ITP)	PREA Only
9/27/2018	Fycompa	perampanel	Partial onset seizures (POS), with or without secondarily generalized seizures	PREA + BPCA
9/12/2018	Botox	onabotulinumtoxinA	Prevention of headaches in patients with chronic migraine	PREA Only
9/12/2018	Actemra	tocilizumab	Systemic juvenile idiopathic arthritis	PREA + BPCA
8/29/2018	Jivi	Antihemophilic Factor (Recombinant), PEGylated-aucl	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
8/23/2018	Altreno lotion	tretinoin	Acne vulgaris	PREA Only
8/15/2018	Prepopik for oral solution	sodium picosulfate/magnesium	Cleansing of the colon as a preparation for colonoscopy	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
		oxide/anhydrous citric acid		
8/10/2018	Annovera	segesterone acetate/ethinyl estradiol	Prevention of pregnancy	PREA Only
8/8/2018	Jornay PM	methylphenidate	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
8/3/2018	Nuvessa	metronidazole	Bacterial vaginosis	PREA Only
8/2/2018	Panzyga	Immune Globulin Intravenous, human-ifas	Primary humoral immunodeficiency (PI) and 2) chronic immune thrombocytopenic purpura (ITP)	PREA Only
7/31/2018	Granix injection	tbo-filgrastim	Severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia	PREA + BPCA
7/30/2018	Kerydin topical solution	tavaborole	Onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes	PREA + BPCA
7/20/2018	Lotemax	loteprednol etabonate ophthalmic gel	Postoperative inflammation and pain following ocular surgery	PREA + BPCA
7/16/2018	Intelence	etravirine	HIV-1 infection	PREA + BPCA
6/29/2018	Yondelis injection	trabectedin	Pediatric histotypes of sarcoma	BPCA Only
6/28/2018	Qbrexza cloth	glycopyrronium	Primary axillary hyperhidrosis	PREA Only
6/15/2018	LymePak	doxycycline hyclate	Early Lyme disease due to Borrelia burgdorferi	PREA Only
6/7/2018	Mircera	Methoxy Polyethylene Glycol-Epoetin Beta	Anemia associated with chronic kidney disease (CKD) in patients on hemodialysis who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA	PREA Only
5/17/2018	Arnuity Ellipta	fluticasone furoate	Asthma	PREA Only
5/11/2018	Gilenya	fingolimod	Relapsing forms of multiple sclerosis	PREA + BPCA
5/11/2018	Actemra	tocilizumab	Polyarticular juvenile idiopathic arthritis (PJIA) and Systemic Juvenile Idiopathic Arthritis (SJIA)	PREA + BPCA
5/10/2018	Briviact	brivaracetam	Partial onset seizures (POS)	PREA Only
5/3/2018	Lyrica	pregabalin	Partial onset seizures (POS)	PREA + BPCA
4/30/2018	Amitiza	lubiprostone	Pediatric Functional Constipation (PFC)	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
4/3/2018	Emend Injection	fosaprepitant	Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)	PREA + BPCA
3/22/2018	Symfi	efavirenz/lamivudine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
3/5/2018	Latuda	lurasidone hydrochloride	Major depressive episodes associated with bipolar I disorder	PREA Only
3/2/2018	Otiprio	ciprofloxacin	Acute otitis externa due to Pseudomonas aeruginosa and Staphylococcus aureus	PREA Only
2/28/2018	Cimduo	lamivudine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
2/20/2018	Luzu cream	luliconazole	Tinea pedis and tinea cruris	PREA Only
2/15/2018	Cialis	tadalafil	Duchenne muscular dystrophy	BPCA Only
2/15/2018	Ampicillin Injection	ampicillin	Neonatal dosing for meningitis and septicemia	409I(BPCA)
2/6/2018	Pristiq	desvenlafaxine	Major Depressive Disorder (MDD)	PREA + BPCA
2/5/2018	Symfi Lo	efavirenz/lamivudine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
1/11/2018	Fluarix Quadrivalent	Influenza Vaccine	Active immunization of persons 6 months and older for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	PREA Only
12/26/2017	Draximage DTPA	Technetium Tc99m Pentetate	Lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging in patients when administered by nebulizer for inhalation and for renal visualization, assessment of renal perfusion, and estimation of glomerular filtration rate	PREA Only
12/22/2017	Lumify Ophthalmic Solution	brimonidine tartrate	Relief of redness of the eye due to minor eye irritations	PREA Only
12/22/2017	Procysbi	cysteamine bitartrate	Treatment-naïve nephropathic cystinosis	BPCA Only
12/11/2017	Xepi	ozenoxacin	Impetigo	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
12/8/2017	Omidria intraocular solution	phenylephrine/ketorolac	Prevention of intraoperative miosis and reduction of postoperative pain in patients who have undergone cataract surgery	BPCA Only
12/6/2017	Jakafi	ruxolitinib	Relapsed or refractory solid tumors, leukemias or myeloproliferative neoplasms	BPCA Only
11/22/2017	Isentress	raltegravir	HIV exposed neonates	PREA + BPCA
11/21/2017	Triumeq	abacavir sulfate/dolutegravir/lamivudine	HIV-1 infection	PREA Only
11/14/2017	Fasenra	benralizumab	Severe asthma with an eosinophilic phenotype	PREA Only
11/14/2017	Tekturna	aliskiren	Hypertension	PREA + BPCA
11/3/2017	Vimpat	lacosamide	Partial-onset seizures	PREA Only
10/13/2017	Butrans transdermal system	buprenorphine	Moderate-to severe chronic pain requiring continuous, around-the clock opioid treatment for an extended period of time	PREA Only
10/13/2017	Stelara	ustekinumab	Psoriasis	PREA Only
10/13/2017	Pegasys	peginterferon alfa-2a	Non-cirrhotic HBeAg-positive Chronic Hepatitis B virus infection	PREA Only
9/28/2017	Descovy	emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only
9/25/2017	Genvoya	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA + BPCA
9/20/2017	Rapivab	peramivir	Acute uncomplicated influenza	PREA Only
9/15/2017	Adzenys ER	amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
9/13/2017	Aptiom	eslicarbazepine acetate	Partial-onset seizures	PREA + BPCA
9/1/2017	Cubicin Injection	daptomycin	Staphylococcus aureus bacteremia	PREA + BPCA
8/31/2017	Afluria Quadrivalent	Influenza Vaccine	Active immunization for the prevention of influenza disease caused by virus types A and B contained in the vaccine	PREA Only
8/30/2017	Kymriah	tisagenlecleucel	B-cell precursor acute lymphoblastic leukemia (ALL)	BPCA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
8/27/2017	T.R.U.E TEST	Thin-Layer Rapid Use Epicutaneous Patch Test	Aid in the diagnosis of allergic contact dermatitis in persons whose history suggests sensitivity to one or more of the 35 allergens and 17 allergen mixes included on the T.R.U.E. TEST panels	PREA Only
8/25/2017	Dotarem	gadoterate meglumine	Contrast agent for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues to detect and visualize areas with disruption of the blood brain barrier and/or abnormal vascularity	PREA Only
7/26/2017	Fycompa	perampanel	Partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy	PREA Only
7/6/2017	Vimovo	naproxen/esomeprazole magnesium	Juvenile idiopathic arthritis (JIA)	PREA Only
6/22/2017	Simponi	golimumab	Active polyarticular juvenile idiopathic arthritis	PREA Only
6/20/2017	Mydayis	mixed salts of a single-entity amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
6/19/2017	Cotempla XR-ODT	methylphenidate	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
6/15/2017	Calcium Gluconate	calcium gluconate	Acute symptomatic hypocalcemia	PREA Only
6/7/2017	Fibryna	Fibrinogen (Human)	Acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia	PREA Only
5/31/2017	Rebinyn	Coagulation Factor IX (Recombinant), GlycoPEGylated	Hemophilia B	PREA Only
5/30/2017	Zerviate	cetirizine	Ocular itching associated with allergic conjunctivitis	PREA + BPCA
5/26/2017	Isentress HD	raltegravir	HIV-1 infection	PREA Only
5/23/2017	Sensipar	cinacalcet	Secondary HPT in pediatric patients with Chronic Kidney Disease on dialysis	BPCA Only
5/17/2017	Jevtana	cabazitaxel	Solid tumors	BPCA Only
4/7/2017	Harvoni	ledipasvir/sofosbuvir	Chronic hepatitis C virus genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis	PREA Only
4/7/2017	Sovaldi	sofosbuvir	Chronic hepatitis C virus genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis	PREA Only
4/5/2017	Visipaque	iodixanol	Coronary computed tomography angiography (CCTA) to assist diagnostic evaluation patients with suspected coronary artery disease	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
3/30/2017	Orencia	abatacept	Moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (pJIA)	PREA + BPCA
3/29/2017	Cubicin Injection	daptomycin	Complicated skin and skin structure infections (cSSSI)	PREA + BPCA
3/21/2017	Ciloxan ophthalmic solution	ciprofloxacin	Bacterial conjunctivitis	BPCA Only
3/21/2017	Zymar	gatifloxacin	Bacterial conjunctivitis	BPCA Only
3/14/2017	Vigamox Ophthalmic Solution	moxifloxacin	Bacterial conjunctivitis	BPCA Only
3/3/2017	Rubber Panel T.R.U.E. TEST	Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test	Diagnosis of allergic contact dermatitis in persons whose history suggests sensitivity to one or more of the 5 substances included on the Rubber Panel T.R.U.E. TEST	PREA Only
3/1/2017	Liquid E-Z-Paque	barium sulfate	Use in single contrast radiographic examinations of the esophagus, stomach, and small bowel to visualize the gastrointestinal (GI) tract	PREA Only
3/1/2017	Cerebyx	fosphenytoin sodium	Generalized tonic-clonic status epilepticus, for the prevention and treatment of seizures occurring during neurosurgery, and for short-term substitution for oral phenytoin	BPCA Only
2/23/2017	RotaTeq	Rotavirus Vaccine, Live, Oral, Pentavalent	Prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9	PREA Only
2/15/2017	Spiriva Respimat Inhalation Spray	tiotropium bromide	Asthma	PREA + BPCA
1/28/2017	Vyvanse	lisdexamfetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
1/27/2017	Ofirmev	acetaminophen	Pain and fever	PREA + BPCA
1/27/2017	Symbicort Inhalation Aerosol	budesonide/formoterol fumarate dihydrate	Asthma	PREA + BPCA
1/27/2017	Stribild	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	HIV infection	PREA Only
1/27/2017	ArmonAir RespiClick	fluticasone propionate	Asthma	PREA Only
1/27/2017	AirDuo RespiClick	fluticasone propionate/salmeterol	Asthma	PREA Only
1/27/2017	Latuda	lurasidone hydrochloride	Schizophrenia Irritability associated with autistic disorder	BPCA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
12/22/2016	Lumason	Sulfur Hexafluoride Lipid-Type A Microspheres	Evaluation of suspected or known vesicoureteral reflux	PREA Only
12/22/2016	Lyrica	pregabalin	Fibromyalgia	PREA Only
12/22/2016	Adynovate	Antihemophilic Factor (Recombinant), PEGylated	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
12/16/2016	Ryzodeg 70/30	insulin degludec/insulin aspart	Type 1 and type 2 diabetes mellitus	PREA Only
12/16/2016	Tresiba	insulin degludec	Type 1 and type 2 diabetes mellitus	PREA Only
12/14/2016	Eucrisa ointment	crisaborole	Mild to moderate atopic dermatitis	PREA Only
11/25/2016	Renvela	sevelamer carbonate	Control of serum phosphorus in patients with chronic kidney disease on dialysis	PREA Only
11/18/2016	FluLaval Quadrivalent	Influenza Virus Vaccine	Active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine	PREA Only
11/18/2016	FluLaval	Influenza Virus Vaccine	Active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine	PREA Only
11/10/2016	Naftin	naftifine hydrochloride	Tinea corporis	PREA Only
11/4/2016	Selzentry	maraviroc	CCR5-tropic HIV-1 infection	PREA + BPCA
11/4/2016	Enbrel	etanercept	Chronic moderate to severe plaque psoriasis (PsO)	PREA Only
10/18/2016	Zemplar	paricalcitol	Secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3, 4 and 5	PREA Only
10/14/2016	Varibar Pudding	barium sulfate	Evaluate the oral and pharyngeal function and morphology	PREA Only
10/7/2016	Gardasil 9	Human Papillomavirus 9-valent Vaccine, Recombinant	Two-dose regimen	PREA Only
10/6/2016	Pertzye	pancrelipase	Exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	PREA Only
9/27/2016	Avelox	moxifloxacin hydrochloride	Complicated intra-abdominal infections (cIAI)	PREA + BPCA

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
9/13/2016	Cuvitru	Immune Globulin Subcutaneous (Human), 20% Liquid	Primary humoral immunodeficiency (PI)	PREA Only
9/9/2016	Noxafil	posaconazole	Prophylaxis of invasive fungal infections	PREA + BPCA
9/9/2016	Q-Pan	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted	Prophylaxis of influenza A (H5N1)	PREA Only
9/2/2016	Canasa Suppositories	mesalamine	Mildly to moderately active ulcerative proctitis	PREA Only
8/30/2016	Blincyto	blinatumomab	Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	BPCA Only
8/16/2016	Kapvay Extended Release Tablets	clonidine	Juvenile animal toxicity study	PREA Only
7/29/2016	Dysport	abobotulinumtoxinA	Lower limb spasticity	PREA Only
7/12/2016	Effient	prasugrel	Vaso-occlusive crises in patients with sickle cell disease	BPCA Only
7/8/2016	Dexilant	dexlansoprazole	Healing of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD)	PREA Only
7/6/2016	Xolair	omalizumab	Moderate to severe persistent asthma	PREA Only
6/29/2016	Kovanaze Nasal Spray	tetracaine HCl/oxymetazoline HCl	Regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J	PREA Only
6/9/2016	Tivicay	dolutegravir	HIV-1 infection	PREA Only
5/27/2016	Ativan Injection	lorazepam	Status epilepticus	409I(BPCA)
5/27/2016	Teflaro Injection	ceftaroline fosamil	Acute Bacterial Skin and Skin Structure Infections (ABSSI) and Community Acquired Bacterial Pneumonia (CABP)	PREA Only
5/25/2016	Afstyla	Antihemophilic Factor (Recombinant), Single Chain	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
5/23/2016	Flucelvax Quadrivalent	Influenza Vaccine	Active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	PREA Only
5/23/2016	Flucelvax	Influenza Vaccine	Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
4/29/2016	Fycompa	perampanel	Partial-onset seizures; primary generalized tonic-clonic seizures	PREA Only
4/29/2016	Entocort EC	budesonide	Crohn's disease	PREA Only
4/29/2016	Otovel Otic Solution	ciprofloxacin/fluocinolone acetonide	Acute otitis media with tympanostomy tubes	PREA Only
4/28/2016	ProAir Digihaler	albuterol sulfate	Asthma	PREA Only
4/27/2016	Gadavist	gadobutrol	Evaluation of known or suspected supra-aortic or renal artery disease	PREA Only
4/14/2016	Trumenba	Meningococcal Group B Vaccine	Active immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B	PREA Only
4/4/2016	Descovy	emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only
3/31/2016	Lumason	Sulfur Hexafluoride Lipid-Type A Microspheres	Ultrasonography of the liver for characterization of focal liver lesions	PREA Only
3/23/2016	Cinqair	reslizumab	Asthma	PREA Only
3/18/2016	OraVerse Injection	phentolamine mesylate	Reversal of soft-tissue anesthesia	PREA Only
3/18/2016	Anthim	obiltoxaximab	Inhalational anthrax	PREA Only
3/16/2016	Kovaltry	Antihemophilic Factor (Recombinant), Full Length	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
3/10/2016	Truvada	emtricitabine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
3/1/2016	Odefsey	emtricitabine/rilpivirine/tenofovir alafenamide	HIV-1 infection	PREA Only
2/29/2016	Tetracaine Hydrochloride Ophthalmic Solution	tetracaine hydrochloride	Ophthalmic anesthesia	PREA Only
2/24/2016	Aczone Gel	dapsone	Acne vulgaris	PREA Only
2/23/2016	Complera	emtricitabine/rilpivirine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
2/3/2016	Prilosec	omeprazole magnesium	Erosive esophagitis due to gastroesophageal reflux disease	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
1/27/2016	Adzenys XR-ODT	amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
1/15/2016	Readi-Cat 2; Readi-Cat 2 Smoothie	barium sulfate	CT of the abdomen in pediatric patients	PREA Only
1/14/2016	Hiberix	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)	Active immunization for the prevention of invasive disease caused by Haemophilus influenzae type b	PREA Only
1/11/2016	E-Z-HD	barium sulfate	For use in double contrast radiographic examinations of the esophagus, stomach and duodenum to visualize the gastrointestinal tract	PREA Only
12/17/2015	Emend	aprepitant**	Chemotherapy induced nausea and vomiting	PREA + BPCA
12/10/2015	Otiprio	ciprofloxacin otic suspension	Bilateral otitis media with effusion undergoing tympanostomy tube placement	PREA Only
12/4/2015	Gamunex-C	Immune Globulin Injection (Human), 10%, Caprylate/Chromatography Purified	Primary Humoral Immunodeficiency	PREA Only
12/4/2015	QuilliChew ER	methylphenidate hydrochloride	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
11/20/2015	Caldolor Injection	ibuprofen	Mild to moderate pain; moderate to severe pain as an adjunct to opioid analgesics; fever	PREA + BPCA
11/18/2015	Narcan Nasal Spray	naloxone hydrochloride	Opioid overdose	PREA Only
11/13/2015	Adynovate	Antihemophilic Factor (Recombinant), PEGylated	Hemophilia A (congenital factor VIII deficiency)	PREA Only
11/5/2015	Genvoya	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only
11/4/2015	Nucala	mepolizumab	Severe asthma with an eosinophilic phenotype	PREA Only
10/19/2015	Dyanavel XR Oral Suspension	amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
9/24/2015	Reyataz Oral Powder	atazanavir	HIV-1 infection	PREA + BPCA
9/17/2015	Epzicom	abacavir sulfate/lamivudine	HIV-1 infection	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
9/15/2015	Spiriva Respimat Inhalation Spray	tiotropium bromide	Asthma	PREA Only
9/14/2015	Velcade	bortezomib	Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)	BPCA Only
9/9/2015	Delzicol	mesalamine**	Mildly to moderately active ulcerative colitis	PREA + BPCA
9/4/2015	Nuwiq	Antihemophilic Factor (Recombinant)	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
8/28/2015	Emend	aprepitant**	Chemotherapy induced nausea and vomiting	PREA + BPCA
8/26/2015	Edurant	rilpivirine	HIV-1 infection	PREA + BPCA
8/24/2015	Promacta	eltrombopag	Chronic immune (idiopathic) thrombocytopenia (ITP)	BPCA Only
8/14/2015	Procysbi	cysteamine bitartrate	Nephropathic cystinosis	BPCA Only
8/13/2015	Oxycontin Extended Release Tablets	oxycodone hydrochloride	Severe pain in opioid-tolerant patients	BPCA Only
8/5/2015	Wilate	von Willebrand Factor/Coagulation Factor VIII Complex (Human)	Control of bleeding episodes and perioperative management of bleeding	PREA Only
7/30/2015	Gammaplex	Immune Globulin Intravenous (Human) 5% Liquid	Primary immunodeficiency (PI)	PREA Only
7/15/2015	Epiduo Forte	adapalene/benzoyl peroxide	Acne vulgaris	PREA Only
7/15/2015	TachoSil	Absorbable Fibrin Sealant Patch	Local bleeding in patients undergoing hepatic resection surgery	PREA Only

* Conditions provided in this table do not necessarily represent an approval in pediatric patients. In some cases, the condition may have been evaluated in pediatric patients and found to be ineffective or unsafe.

Note that not all pediatric labeling changes have resulted from pediatric studies. In some cases, labeling may be updated based on other data sources such as pediatric extrapolation from adult data or the literature.

For complete details regarding these labeling changes, please see https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes.

From: Jungman, Elizabeth [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=5238A0CAEC064BA8B5D598115BC4F99F-ELIZABETH.J]
Sent: 9/10/2021 9:44:52 AM
To: Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]
Subject: RE: CDER Trade Press News Update September 10, 2021

I am open until 10, between 12 and 2, or at 4 – can send other times if those don't work. I know your day today is nuts.

Elizabeth Jungman, J.D., M.P.H. (she/her)
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From: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>
Sent: Friday, September 10, 2021 9:40 AM
To: Jungman, Elizabeth <Elizabeth.Jungman@fda.hhs.gov>
Subject: RE: CDER Trade Press News Update September 10, 2021

Could we speak about Propecia at the next opportunity?

Patrizia

From: CDER Trade Press <CDERTradePress@fda.hhs.gov>
Sent: Friday, September 10, 2021 9:29 AM
To: CDER Trade Press <CDERTradePress@fda.hhs.gov>
Subject: CDER Trade Press News Update September 10, 2021

Today's Headlines (click to go directly to the article):

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Premier Acquires Stake In Specialty Drug Maker To Ensure Supply Of At-Risk Drugs

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WCLC: AstraZeneca's detailed Imfinzi, tremelimumab data in metastatic NSCLC are far from a clear-cut win

Biogen CEO blames Aduhelm's rocky launch on 'too much confusion, misinformation and controversy'

Despite mixed phase 3 showing, Apellis hopes to push eye disorder drug past FDA's finish line

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Room Available In US Pharma Industry For OTC Switch Leader: Has Perrigo Made A Reservation?

(BioCentury)

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Cancer leads way to routine use of accelerated approval: Data Byte

If you are unable to access a link within an article, please respond to this email, and we will provide you the text of the linked article.

Biogen Declines To Say If It Seeks IG Advice On Aduhelm Giveaway

By Gabrielle Wanneh / September 9, 2021 at 10:42 AM

Biogen is giving free Aduhelm to patients at Florida-based First Choice Neurology, and that arrangement is at risk of being considered a kickback, a former HHS Inspector General official said. However, the company said its program is common practice and declined to say whether it seeks an advisory opinion from the IG that would help shield it from enforcement action.

"Biogen is committed to ensuring that appropriate patients have access to any Biogen medicines prescribed by their physicians," Biogen said. "It is common for pharmaceutical companies, including Biogen, to offer patient assistance programs designed to help remove non-clinical barriers to access to care, and Biogen designs and administers its access programs to comply with applicable laws and regulations."

Reuters reported that Biogen is providing its Alzheimer's drug for free while Medicare determines whether, and under what circumstances, to cover Aduhelm. FDA granted Aduhelm an accelerated approval in June against the advice of independent agency advisers. It's the first new Alzheimer's treatment in nearly two decades, but many insurers and doctors don't believe there is sufficient evidence that the drug works to outweigh the risk of serious side effects.

It's common for companies to offer free medications, and the legality of patient assistance programs depends on their details. Companies may seek advice from the IG on their programs, but they aren't required to get advisory opinions, and advisory opinions are not legally binding, according to Jennifer Michael, former chief of the Industry Guidance Branch at the IG.

Based on the description of Biogen's program in the Reuters article, Michael says there's a chance the IG would consider the arrangement to be a 'seeding' program. Seeding refers to the practice of giving free drugs to a subset of eligible patients to induce those patients to use drugs that federal health programs will eventually pay for.

"The government might be concerned that those types of seeding programs could result in the potential for overutilization or inappropriate utilization," Michael told *Inside Health Policy*. -- *Gabrielle Wanneh* (gwanneh@iwpnews.com)

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Premier Acquires Stake In Specialty Drug Maker To Ensure Supply Of At-Risk Drugs

By Gabrielle Wanneh / September 9, 2021 at 2:39 PM

The group purchasing organization Premier and 11 leading health systems have invested a small stake in specialty drug maker Exela Pharma Sciences to ensure the supply of essential drugs that face possible shortages due to sourcing problems spurred by the COVID-19 pandemic.

The participating health systems are expected to secure an uninterrupted supply of 19 pharmaceutical products, including generic injectables that often appear on the FDA drug shortage list and 503B compounded pharmaceutical products provided by Exela, which primarily sources active ingredients domestically and from Europe, through its manufacturing facility in North Carolina.

The move is a part of a longtime initiative of Premier's ProvideGx and is similar to actions by other hospital groups like CivicaRx that aim to avert drug shortages and prevent price gouging that often follows a drug scarcity. For more than a decade, several drug shortages have contributed to $230 million in additional drug costs as well as poorer health outcomes for patients, according to a 2018 study conducted by researchers at the University of Pittsburgh.

"Leveraging Exela's significant production capacity, this collaboration is expected to give Premier's participating members uninterrupted access to high-quality, U.S.-made pharmaceutical products and safety stock," Premier President and CEO Michael Alkire said in a statement Wednesday (Sept. 8). "With this investment, we are committing to support the domestic production of vital medicines for our members and the market and to bring much-needed solutions to help eliminate drug shortages."

The participating health systems have signed a multi-year commitment to buy a portion of their drugs from Exela through Premier's GPO. They include Baystate Health of Springfield, MA; Genesis Health System of Davenport, IA; Henry Ford Health System of Detroit, MI; McLaren Health Care of Grand Blanc, MI; Memorial Healthcare System of Hollywood, FL; OSF HealthCare of Peoria, IL; Riverside Health System of Newport News, VA; Saint Francis Health System of Tulsa, OK; Texas Health Resources of Arlington, TX; and Universal Health Services, Inc. Of King of Prussia, PA. -- *Gabrielle Wanneh* (gwanneh@iwpnews.com)

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REGULATORY FOCUS
Healthcare Product Regulation. In Focus.

FDA updates guidance on generic drug development during COVID

Posted 09 September 2021 | By Michael Mezher

The US Food and Drug Administration (FDA) on Wednesday revised its questions and answers guidance on generic drug development and abbreviated new drug application (ANDA) submissions during the COVID-19 public health emergency.

The revised guidance updates the agency's previous guidance on generic drug development during the COVID-19 pandemic that was released in April 2021. (RELATED: FDA offers guidance on generic drug development during COVID, *Regulatory Focus* 5 April 2021)

The revisions include a clarification about when FDA will accept requests to receive an ANDA with "less than the full complement of recommended stability data," and information on how to handle expired batches of test product in interrupted bioequivalence studies. FDA also says it has made some minor updates throughout the frequently asked questions section.

"FDA recognizes that the COVID-19 public health emergency may impact the development of generic drug products, interrupt or delay ANDA applicants' bioequivalence studies, and impact the submission of ANDAs to FDA for assessment. The ongoing development of generic drugs submitted as ANDAs to the FDA for assessment helps Americans continue to have access to safe, effective generic drugs," FDA says.

In the revised guidance, FDA now explains that it will "generally accept requests to receive an ANDA with less than the full complement of recommended stability data if the drug product is on FDA's Drug Shortage List or FDA confirms that the drug product is vulnerable to shortage." The agency also says it will also generally do so for products that meet its criteria for priority review to help address the COVID-19 pandemic.

FDA is also granting generic drugmakers additional flexibility when it comes to resuming bioequivalence studies that were interrupted due to the COVID-19 public health emergency. The revised guidance now provides recommendations allowing prospective applicants to potentially use a test product batch that is beyond the established expiration dating period to resupply bioequivalence studies, "as long as sufficient evidence can be provided to demonstrate the acceptability of the test product batch."

FDA further explains that applicants who wish to follow this approach "should submit data to ensure the test batch samples stored at the long-term stability conditions beyond the current expiration date are in compliance with the finished drug product shelf-life specifications at the time of conducting the [bioequivalence] BE study."

FDA

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Kaleido warned; FDA not persuaded by 'medical food' claim

Posted 09 September 2021 | By Joanne S. Eglovitch

The US Food and Drug Administration (FDA) recently issued a warning letter to Kaleido Biosciences for administering an investigational new COVID-19 treatment to patients without obtaining an investigational new drug (IND) application.

The company argued that the product under investigation was a food and not a drug, and therefore not subject to IND filing requirements. Yet the agency disagreed, saying that the endpoints used in the clinical trials went beyond 'dietary management' of COVID-19 and were more aligned with drug trials in assessing effectiveness of the treatment.

The 26 August warning letter was sent over "objectionable conditions" observed following a mid-February to early March inspection of Kaleido's Lexington, MA facility, conducted under the auspices of FDA's bioresearch monitoring program. At issue was the firm's clinical investigation of a molecule called KB109 for treating COVID-19. The treatment is a microbiome metabolic therapy, a synthetic glycan that is orally administered for treating COVID-19.

The warning letter focused on two protocols, Protocol K031-120, and Protocol K032-120. The first trial was a randomized, open-label prospective parallel group study to assess the natural history of COVID-19 and compare the effect of the treatment in patients undergoing supportive self-care (SSC). The other trial was an exploratory open-label clinical study to evaluate how the treatment affected the gut microbiota of adult patients with mild to moderate COVID-19.

Between the two multi-site trials, 399 patients were randomized.

Kaleido argued it was not obligated to submit an IND before initiating these clinical investigations because KB109 is a food rather than a drug. Specifically, Kaleido argued that the investigations were conducted "to evaluate the effect of KB109 on the microbiome" and to "determine the safety and tolerability of KB109 in the disease population," according to FDA's characterization of the firm's position.

These arguments failed to persuade FDA, which concluded that the "evidence collected during the inspection showed that KB109 was intended for use as a drug and not as a food."

FDA maintained that "even if there were distinctive nutritional requirements established for COVID-19, Protocols K031-120 and K032-120 went beyond 'dietary management' of COVID-19 to evaluate KB109's ability to treat COVID-19 by measuring the investigational product's effects on fever, oxygen saturation, viral load, and other biomarkers of COVID-19 infection, among other things."

Kaleido's argument that KB109 is a medical food fails on other counts as well, wrote FDA. Since no particular nutritional requirements that might help manage COVID-19 have yet been discovered, KB109 cannot be used in the dietary management of the disease, as would be required for a product classified as a medical food.

Also, the fact that an article has been established to be generally recognized as safe (GRAS) does not preclude its use as a drug. FDA clarified that "an article may be a drug as used in a clinical trial, even if it is considered a food as used in other contexts."

The company has 15 days to file a response.

Daniel Menichella, Kaleido's chief executive officer, told *Focus* in an email that "we are reviewing the letter currently and look forward to providing a response within the given timeframe and continuing our discussions with the FDA."

Kaleido warning letter

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FDANEWS

Advocacy Group Files Lawsuit Seeking FDA Action on Propecia

September 10, 2021

A new lawsuit filed against the FDA this week contends that the male pattern baldness drug Propecia (1 mg) should either be taken off the market or its prescribing information should include warnings about the risk of long-term erectile dysfunction, depression and suicide.

The consumer watchdog group Public Citizen filed the suit Sept. 8 in the U.S. District Court for the District of Columbia on behalf of the Post-Finasteride Syndrome Foundation (PFSF). The complaint asks the FDA to act on a petition the foundation filed in 2017, which has gone unanswered.

The case has more merit than it did when originally filed, Philip Roberts, PFSF's patient manager, told *FDAnews*. "Much more scientific information has come to light since then," he said, including two studies by Harvard investigators confirming the risk of long-term erectile dysfunction, depression, suicidal ideation and suicide; and epidemiologic data showing that the drug alters the expression of more than 3,700 genes in men who take the drug. The drug mimics a male hermaphroditism gene; people who have this are genetic males who sometimes look female and who never go bald.

The 2017 petition asked FDA to either withdraw 1 mg oral Propecia from the market or include a Black Box warning and send out a "Dear Healthcare Provider" letter, alerting clinicians to the risks associated with the medication. The petition included information on about a dozen men whose suicides were considered related to Propecia use and contraindications for patients with a history of sexual dysfunction and depression.

Since then, PFSF has amassed more data, including 17,953 adverse event reports filed in the International Drug Monitoring database. These include reports of erectile and sexual dysfunction (5,234) and 4,313 reports of psychiatric disorders, including anxiety (1,756) and depression (1,386). The database includes 88 cases of completed suicides, 39 attempts and 384 cases of suicidal ideation.

In light of Propecia's enormous global market (almost 9 million users in 2018, according to the website ClinCalc.com), the numbers are very small. Nevertheless, they represent an unnecessary tragedy that needs to be addressed, said Michael Kilpatrick, the Public Citizen attorney who filed the suit.

"It's a small percentage, but the number of prescriptions is so high that it's still a large number of people," he told FDAnews. "We think patients should know this. It's a drug for a cosmetic issue. If people knew there was even a slight change you could develop a significant, life-altering syndrome and even think about suicide, they might not want to take it."

The FDA has been sitting on the matter far too long, he said.

"A four-year wait is unreasonable. Our goal is to compel FDA to issue a decision on the original petition. We think it's a strong one and that the decision should be for granting a black box warning or even withdrawing the drug. This delay is in violation of the Administrative Procedure Act and given the seriousness of the issue and the quality of the petition, it should be resolved."

Merck didn't reply to a request for comment. The company has moved all of its Propecia patient and prescribing data to a new company spinoff, Organon, launched on June 3.

Read the PFSF complaint here: www.fdanews.com/09-09-21-Complaint.pdf. — Michele G. Sullivan

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Humanigen's Lenzilumab for COVID-19 Draws FDA Complete Response Letter

September 10, 2021

The FDA has declined to grant Humanigen an emergency use authorization (EUA) for its antibody lenzilumab for treatment of hospitalized COVID-19 patients.

The agency instead sent the Burlingame, Calif.-based company a Complete Response Letter (CRL), in which it said it was " unable to conclude that the known and potential benefits of lenzilumab outweigh the known and potential risks of its use as a treatment for COVID-19," Humanigen said.

But the agency also said in the letter that it is committed to working with Humanigen to develop lenzilumab and has invited the company to submit additional data as it becomes available, the company said.

Humanigen CEO Cameron Durrant said the National Institutes of Health's ACTIV-5/BET-B study, which is enrolling up to 500 patients, is expected to provide further data that may support a new EUA request. The company said it is also committed to completing the regulatory processes it has under way to seek a marketing authorization for lenzilumab to treat hospitalized COVID-19 patients in the UK and other territories.

Humanigen is focused on preventing and treating an immune hyper-response called 'cytokine storm,'" which has been a major problem for critically ill COVID-19 patients. Lenzilumab neutralizes granulocyte-macrophage colony-stimulating factor (GM-CSF) that plays a role in inflammation that can lead cytokine storm.

The company said its phase 3 LIVE-AIR study "suggests early intervention with lenzilumab may prevent consequences of a full-blown cytokine storm in hospitalized patients with COVID-19."

Humanigen is also studying the antibody for other inflammatory conditions such as acute graft versus host disease in patients undergoing allogeneic hematopoietic stem cell transplantation, eosinophilic asthma, and rheumatoid arthritis.
— Martin Berman-Gorvine

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DICKINSON'S FDA Webview

Apellis Pharma Plan NDAs for Geographic Atrophy

09/09/2021

Apellis Pharmaceuticals says it plans to file an NDA in the first half of 2022 after reporting top-line results from the Phase 3 DERBY and OAKS studies evaluating intravitreal pegcetacoplan, an investigational targeted C3 therapy, in 1,258 adults with geographic atrophy secondary to age-related macular degeneration. Geographic atrophy is a leading cause of blindness that affects about one million people in the U.S.

In the studies, pegcetacoplan demonstrated a clinically meaningful slowing of disease progression with an even stronger effect in geographic atrophy patients with extrafoveal lesions, the company says. "Monthly and every-other-month treatment with pegcetacoplan met the primary endpoint in OAKS, significantly reducing [geographic atrophy] lesion growth by 22% (p=0.0003) and 16% (p=0.0052), respectively, compared to pooled sham at 12 months," it says. "DERBY did not meet the primary endpoint, showing a reduction in GA lesion growth of 12% (p=0.0528) and 11% (p=0.0750) with monthly and every-other-month treatment, respectively, compared to pooled sham at 12 months."

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Myfembree sNDA for Endometriosis Pain

09/09/2021

FDA has accepted for review a Myovant Sciences and Pfizer supplemental NDA for Myfembree (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) for managing moderate to severe pain associated with endometriosis. The agency set a user fee review action target date of 5/6/2022.

The submission is based on data from the Phase 3 SPIRIT program, which included two multinational, replicate pivotal clinical studies (SPIRIT 1 and SPIRIT 2) in over 1,200 women with pain associated with endometriosis for 24 weeks, and an open-label extension study for eligible women through one year.

Endometriosis is an estrogen-dependent, inflammatory disease in which tissue similar to the uterine lining is found outside the uterine cavity, which results in chronic inflammation and can cause scarring and adhesions.

Myfembree is currently approved for managing heavy menstrual bleeding associated with uterine fibroids in premenopausal women, with a treatment duration of up to 24 months.

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New FDA Jardiance Breakthrough Therapy Designation

09/09/2021

FDA has granted breakthrough therapy designation to Boehringer Ingelheim and Lilly's Jardiance (empagliflozin) for treating heart failure with preserved ejection fraction. An *American Journal of Managed Care* online post says Jardiance is the first drug in its class to gain the designation. The post says results from the EMPEROR Preserved trial showed that Jardiance, a sodium glucose co-transporter 2 inhibitor reduced cardiovascular death and hospitalization for heart failure by 21%.

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FDA Rejects Lenzilumab EUA for Hospitalized Covid Patients

09/09/2021

FDA has rejected a Humanigen emergency use authorization (EUA) request for the use of its lenzilumab in newly-hospitalized Covid-19 patients. FDA reportedly told the company it was unable to conclude that the known and potential benefits of lenzilumab outweigh the known and potential risks of its use as a treatment for Covid-19.

The company says the agency committed to working with it in the development of lenzilumab and invited Humanigen to submit additional data as they become available. Humanigen says the National Institutes of Health ACTIV-5/BET-B study is expected to provide further data that may support a new EUA request.

Humanigen describes lenzilumab as a first-in-class antibody that binds to and neutralizes granulocyte-macrophage colony-stimulating factor.

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Congress Must Regulate CBD Since FDA Won't: Steve Mister

09/09/2021

Responding to an FDA objection to a new dietary ingredient notification submitted by Charlotte's Web to demonstrate that its full-spectrum hemp extract is reasonably expected to be safe, Council for Responsible Nutrition CEO **Steve Mister** says Congress must step in and regulate the CBD (cannabidiol) marketplace. Mister appeared with Charlotte's Web CEO **Deanie Elsner** in a "Short Legal Briefs" video posted by *Natural Products Insider*.

In the video, Elsner said she was disappointed in the way the agency made its decision to object to the notification for two reasons: that CBD products are excluded from the definition of a dietary supplement and that there were concerns about the sufficiency of the safety evidence.

She indicated that her company met multiple times with FDA officials before the notification was submitted to share data. The agency "ignored big parts of our application," she said.

Mister said the FDA denial letter showed that the agency is not going to solve the problem with CBD and thus Congress must act. He said the industry should turn its attention to persuading Congress to intervene. Regulation is needed, he said, because reputable companies that are concerned about the quality of their products are stuck in a "quagmire" with other companies that are not as concerned about quality, and consumers are being hurt.

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No dice: Court tells AbbVie it can't force Takeda to supply a drug that's in shortage worldwide

by Eric Sagonowsky | Sep 9, 2021 9:28am

Amid the global shortage of prostate cancer drug Lupron, AbbVie took its partner Takeda to court over alleged failures to live up to supply agreements. Now, a court has denied the company's plea to force Takeda to fill orders.

In an **opinion** (PDF) this week, Delaware Chancery Court Vice Chancellor Sam Glasscock III denied AbbVie's request to compel Takeda to fill supply orders from its plant in Hikari, Japan.

Under a deal between the companies, AbbVie sells the drug in the U.S. and Canada. Because Takeda is the sole supplier of the drug worldwide, AbbVie relies on the Japanese drugmaker for its product.

Problem is, the med has been in short supply worldwide after the FDA and Takeda in 2019 found "protocol violations" at the plant, Glasscock wrote in this week's opinion. Thanks to "remediation efforts" including a weeks-long production hold global supply hiccups and shortages have persisted to this day, Glasscock wrote.

AbbVie had asked the court to find that Takeda breached its contract plus issue damages and "injunctive relief," or an order forcing Takeda to supply the drug. In his new opinion, Glasscock said an injunction would be "unworkable" because it'd force the court to oversee Takeda's operations and would "inevitably lead to contempt hearings" over Takeda's ability to fulfill orders.

"In other words, even if I find that Takeda has breached its contract with AbbVie and that, as a result, AbbVie faces irreparable harm, the injunctive relief sought is unavailable," Glasscock wrote.

The Lupron saga started in November 2019, when FDA inspectors traveled to Japan to review production processes at the Hikari site. In a June 2020 warning letter, the FDA slapped Takeda for poor equipment maintenance, faulty documentation and quality shortfalls. The company has been working to resolve those concerns, but the Lupron problem has dragged on throughout this year.

Right now, the FDA **lists** most Lupron Depot dose forms as "available" in the U.S., but there's one dose that's not expected to become available until next January.

While Glasscock decided against an injunction forcing Takeda to fill orders, he hasn't made a ruling on whether the company breached its contract. He plans to issue a decision on that issue in "due course," he said, and another trial phase on damages could follow.

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WCLC: Jazz charts new path for small cell lung cancer drug Zepzelca after late-stage flop

by Angus Liu | Sep 9, 2021 11:00am

Jazz Pharmaceuticals wasn't able to ride a breakthrough FDA nod to a pivotal trial win for conditionally approved small cell lung cancer (SCLC) drug Zepzelca. But after talking with the FDA, the company and partner PharmaMar see a new path forward.

In previously treated SCLC, the combination of Zepzelca and doxorubicin failed to extend patients' lives over physician's choice of doxorubicin-based chemo or Hycamtin, according to data presented at the 2021 World Conference on Lung Cancer virtual meeting.

Jazz and PharmaMar first unveiled the phase 3 ATLANTIS failure in December. Now we know patients who mostly got the Zepzelca regimen as their second-line treatment lived a median 8.6 months, versus 7.6 months in the control arm.

If successful, the trial could have served as the confirmatory trial to convert Zepzelca's accelerated approval earned last June into a full one. In a previous single-arm study, Zepzelca monotherapy shrunk tumors in 35% of relapsed SCLC patients as measured by investigator assessment. The response lasted a median 5.3 months.

Pascal Besman, chief operating officer at PharmaMar, noted that the ATLANTIS study used a 2-mg/m^2 dose of Zepzelca, which is lower than the FDA-approved dose of 3.2-mg/m^2. Although the Zepzelca-doxorubicin combo didn't improve survival, "the overall results support the activity and tolerability of Zepzelca monotherapy in second-line therapy," Besman said in an email interview.

As ATLANTIS investigator Luis Paz-Ares, M.D., Ph.D., noted in a prepared presentation, the research team ran a so-called exposure-response analysis to gauge Zepzelca's contribution on patient survival. The model predicted that single-agent Zepzelca, at the 3.2-mg/m^2 dose, would have had a statistically significant advantage over the control arm at prolonging the lives of patients in the ATLANTIS study.

Jazz stands "firmly behind the favorable benefit/risk profile of monotherapy Zepzelca" in second-line SCLC as shown in its phase 2 trial, the company's chief medical officer, Rob Iannone, M.D., said in a separate email interview.

For now, Zepzelca will remain on the market. Jazz and PharmaMar have agreed "in principle" with the FDA to run another phase 3 as the confirmatory trial, Besman said.

The three-arm trial will test Zepzelca monotherapy at 3.2 mg/m^2, and a second experimental arm will combine the drug at 2 mg/m^2 with Pfizer's Camptosar (irinotecan).

Second-line patients in the control arm will get physician's choice or either Camptosar or Hycamtin. The trial, expected to launch this year, will also support a regulatory filing to the European Medicines Agency, Besman added.

In addition, Jazz is collecting data from an observational phase 4 trial to understand Zepzelca's real-world profile in second-line SCLC, Iannone noted.

Meanwhile, Jazz is also looking to move Zepzelca earlier in the treatment line. Through a partnership with Roche, a phase 3 trial dubbed ImForte will test Zepzelca with immunotherapy as a first-line maintenance therapy for patients with extensive-stage SCLC after induction chemotherapy. If successful, the new regimen could pressure AstraZeneca and its Imfinzi, which is currently dominating the front-line SCLC space.

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WCLC: AstraZeneca's detailed Imfinzi, tremelimumab data in metastatic NSCLC are far from a clear-cut win

by Angus Liu | Sep 9, 2021 11:00am

After two high-profile late-stage trial flops, AstraZeneca has finally scored a victory for Imfinzi and ill-fated tremelimumab in newly diagnosed metastatic non-small cell lung cancer (NSCLC). But in a lucrative field where immuno-oncology rivals Merck and Bristol Myers Squibb have established a solid presence, a detailed look at the data reveals a win that's perhaps too little, too late.

A cocktail of Imfinzi, investigational CTLA-4 inhibitor tremelimumab and chemotherapy **pared down** the risk of death by 23% over chemo alone in previously untreated patients, AZ announced Thursday at the 2021 World Conference on Lung Cancer virtual meeting.

The phase 3 POSEIDON trial came after two prior phase 3 flops for Imfinzi in metastatic NSCLC and marked the first positive pivotal readout for treme after many more failures in multiple indications. But the data don't look favorable compared to Merck's Keytruda or Bristol Myers' Opdivo, and efficacy in some patient subgroups showed imbalances that could limit an eventual FDA approval if AZ gets one.

First off, the combination of Imfinzi and chemo failed to significantly outdo chemo alone at extending patients' lives. That pairing only reduced the risk of death by 14% over chemo alone. That already makes Imfinzi look inferior to current standard-of-care Keytruda.

Keytruda's combo with chemo is well known for its impressive 51% death risk reduction over chemo alone in front-line non-squamous NSCLC. Those were the results at an interim analysis in the phase 3 Keynote-189 trial, while the final analysis at 31 months of follow-up showed a 44% risk decrease. As for front-line squamous cell NSCLC, Keytruda and chemo reduced death risk by 36% at interim and 29% at final analysis in the KEYNOTE-407 trial.

Luckily for AZ, treme finally pulled through to help Imfinzi. The CTLA-4 agent has a bad track record with Imfinzi and has been marred with failures in NSCLC as well as small cell lung, head and neck and bladder cancers. In front-line NSCLC alone, the dual immunotherapy combo of Imfinzi and treme flopped the phase 3 **MYSTIC trial** in a broad patient group and the **NEPTUNE trial** in patients with high tumor mutation burden.

Now that the Imfinzi-treme-chemo doesn't appear likely to shake up Keytruda's dominance, what about less competitive Opdivo? Data don't look very promising for AZ.

For one thing, while the chemo-free regimen of Imfinzi and treme failed, Opdivo's own CTLA-4 combo with Yervoy is **approved** for front-line NSCLC patients whose tumors express PD-L1.

For a better apple-to-apple comparison, the Opdivo-Yervoy-chemo combo won an FDA nod last year for front-line NSCLC patients regardless of PD-L1 status. In the CheckMate 9LA trial, Opdivo, Yervoy and chemo were able to show a survival benefit early, having cut patients' risk of death by 31% over chemo after a minimum follow-up of 8.1 months. After a longer follow-up of at least 24.4 months, the rate stood at 28%, as patients on the Opdivo-Yervoy-chemo regimen lived a median 15.8 months versus 11 months for the solo chemo group.

Imfinzi-treme-chemo's 23% death reduction looks slightly weaker than Opdivo-Yervoy-chemo's 28%, but cross-trial comparisons have their problems. In POSEIDON, patients on the AZ therapy lived a median 14 months, versus 11.7 months for those who took chemo alone.

To further complicate the front-line NSCLC landscape, Roche's PD-L1 inhibitor Tecentriq is allowed as a monotherapy for PD-L1-high patients thanks to data from the IMpower110 trial. And its combo with Avastin and chemo has an approval for non-squamous disease after showing it reduced the risk of death by 22% over Avastin and chemo.

Sanofi and Regeneron's Libtayo also bears a monotherapy nod in front-line PD-L1-high NSCLC. The companies recently found that adding Libtayo on top of chemo could further prolong the lives of first-line patients in the phase 3 EMPOWER-lung 3 trial.

Eli Lilly and Innovent Biologics have a front-line non-squamous NSCLC filing for their China-approved PD-1 inhibitor Tyvyt under review at the FDA. The application **includes** data from a China trial that showed a combination of Tyvyt, Lilly's Alimta and platinum chemo could stave off tumor progression or death over chemotherapy alone.

For AZ, non-squamous NSCLC might be just what it could eventually reach for with the Imfinzi-treme-chemo pairing.

As POSEIDON lead investigator Melissa Johnson, M.D., noted during a prepared presentation Thursday, among patients with the squamous histology, progression-free survival (PFS) "and overall survival were poor across all treatment arms, with little separation of the curves for PFS or overall survival."

In the squamous subgroup, Imfinzi, treme and chemo only managed to reduce the risk of death by 12% over chemo.

What's more, the AZ therapy also showed some worrisome signs in other patient subgroups. Notably, women and Asian patients didn't seem to experience any additional survival benefits from Imfinzi and treme.

The one upside? The efficacy of Imfinzi, treme and chemo didn't seem to be bound by a patient's PD-L1 expression level.

Still, with the mixed bag of data and a poor track record, AZ could face a limited FDA label and a hard time winning over market share in front-line NSCLC. Imfinzi is currently approved to treat stage 3 NSCLC and extensive-stage small cell lung cancer. In the first half of 2022, AZ plans to read out data from PEARL, an IMpower110 counterpart trial that evaluates Imfinzi monotherapy against chemo as front-line treatment for PD-L1-high patients.

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Biogen CEO blames Aduhelm's rocky launch on 'too much confusion, misinformation and controversy'

by Eric Sagonowsky | Sep 9, 2021 1:44pm

Before Biogen scored an FDA approval for Alzheimer's drug Aduhelm, the company probably hoped its launch would go much smoother than the last three months have been. It turns out Biogen's CEO Michel Vounatsos is willing to say so publicly.

Speaking at a Morgan Stanley healthcare **event** Thursday, Vounatsos said there's "clearly too much confusion, misinformation and controversy surrounding our data and the approval process." The launch has been "even more gradual than we had expected," he added.

The company is facing "near-term challenges," Vounatsos told the virtual audience, noting that "everybody can see that." Now, months after the drug's approval, he said it's "imperative" that "society moves its attention [from] the clinical data to the patients in need."

After Aduhelm's accelerated approval in June, a firestorm quickly engulfed the new Alzheimer's drug. Lawmakers and medical experts have questioned the data Biogen used to support an approval plus the FDA's procedures that led to the accelerated nod.

The criticism grew so intense that the FDA and Biogen, in an unusual move, **walked back** Aduhelm's broad label just weeks into the launch. The FDA originally endorsed the drug for all Alzheimer's patients but later restricted the label to those with mild cognitive impairment or mild dementia.

In another big setback for the rollout, the Department of Veteran's Affairs last month decided against covering the drug, citing a "risk of significant adverse drug events" and a "lack of evidence of a positive impact on cognition."

Looking forward, one key question mark for the rollout remains in the Centers for Medicare & Medicaid Services' coverage decision on the drug. That's expected in January and will determine whether federal insurance programs get behind the treatment.

Meanwhile, the company is working to improve the public's understanding of the clinical data and on generating additional data, Vounatsos said. It's also aiming to bring more treatment centers online and negotiate reimbursement deals to "maximize access," he added.

Biogen's drug launched with big sales expectations, but its initial stumbles have dampened some of the enthusiasm on Wall Street. In a note about Vounatsos' Thursday presentation, Jefferies analysts said the Street is "very negative on the early launch." Analysts still expect the drug to bring in multiple billions of dollars per year once it gets rolling.

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Despite mixed phase 3 showing, Apellis hopes to push eye disorder drug past FDA's finish line

by Noah Higgins-Dunn | Sep 9, 2021 4:05pm

Apellis Pharmaceuticals' pegcetacoplan posted mixed results in two late-stage trials studying the C3 inhibitor in patients living with geographic atrophy (GA). Despite the mixed showing, CEO Cedric Francois thinks the med's performance was strong enough to warrant an FDA nod.

Apellis studied pegcetacoplan, the active ingredient in rare disease drug Empaveli, in two phase 3 trials, known as Oaks and Derby, as a monthly and every-other-month treatment in 1,258 patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). For the studies, investigators weighed efficacy by measuring change in the total area of GA lesions from baseline.

In Oaks, pegcetacoplan met its primary endpoint in both dosing groups, significantly reducing GA lesion growth by 22% in the monthly arm and 16% in the every-other-month group compared with sham injections after 12 months, Apellis said.

The drug failed to do the same in Derby, reducing lesions by just 12% and 11%, respectively. The drug didn't produce any significant safety concerns in both trials, although its use was associated with slightly higher rates of exudation, or emitted fluid.

Despite the conflicting readouts, Apellis is "unbelievably happy" with the results given the totality of pegcetacoplan clinical trial performance, CEO Cedric Francois said in an interview. The company plans to file the med with the FDA in the first half of 2022.

There are no FDA-approved treatments for the condition, an advanced form of AMD that eventually leads to vision loss and blindness in older people.

"This is a drug that, in our opinion, has absolutely no doubt around its efficacy and comes out with a safety profile that I think exceeds our own and other people's expectations," Francois said.

Meanwhile, the drug posted another late-stage upside, Francois argued. In a prespecified analysis of the combined trials, pegcetacoplan was more effective in patients with extrafoveal lesions at the start of the trials, decreasing GA lesion growth in that group by as much as 26% in the monthly arm and 23% in the every-other-month group.

GA patients typically present first with extrafoveal lesions, which then progress toward the fovea where central vision is impacted, Apellis says. That's important because the disease is like a forest fire in the retina, continuously destroying photoreceptor cells until someone's blind with no way to turn it around, Francois said.

There are roughly 1 million Americans living with the condition and 5 million people globally. If Apellis is able to do what others have failed, it could be looking at $3 billion in peak sales, Jefferies analysts recently **predicted**.

Pharma has tried and failed to push GA treatments over the FDA's finish line in recent years, including an effort by Roche on its complement-inhibiting drug lampalizumab. That drug, however, **crashed** out of two phase 3 trials in 2017.

This has already been a busy year for Apellis, which **scored** its first-ever FDA nod in May for pegcetacoplan in patients with the rare blood disorder paroxysmal nocturnal hemoglobinuria (PNH). That has teed-up a showdown between Apellis' C3 inhibitor and Alexion's heavyweight C5 inhibitors Soliris and its follow-up Ultomiris, which target a different enzyme.

"If this drug gets approved, it will be the first time that complements control would get approved in a large speciality, rather than in a rare disease like PNH," Francois said. "I think it opens up a new era for what a complement can do in many of these conditions across multiple therapeutic areas."

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Room Available In US Pharma Industry For OTC Switch Leader: Has Perrigo Made A Reservation?

09 Sep 2021
ANALYSIS

Malcolm Spicer@TheTanSheet malcolm.spicer@informa.com

Executive Summary

Acquiring HRA Pharma, Perrigo could take OTC switch lead, likely starting with HRA's daily oral contraceptive before moving to numerous other potential candidates. Pharmas previously busy in switch have other priorities for their consumer health businesses.

The US pharma industry has a vacancy for an OTC switch leader as longtime sponsors of applications to make additional ingredients available nonprescription prioritize reorganizing their consumer health businesses over expanding their product portfolios.

By acquiring HRA Pharma, Perrigo Company PLC could fill the space in the pharma industry. Its switch proposals likely will start with HRA's daily oral contraceptive before moving to numerous other potential candidates.

"There aren't a lot of switch powerhouses out there. I think there's an opportunity for a new player to emerge as a switch powerhouse, given the changing market dynamics," says pharma industry consultant Susan Levy .

"I think this alignment, HRA with Perrigo's scale, is just what the industry needs," said switch consultant Susan Lavine Coleman, president of NCI Consulting in Moorestown, NJ.

Levy and Coleman spoke with HBW Insight following Perrigo's 8 September announcement of an agreement to acquire Paris-based HRA, listed in France as Héra SAS, for €1.8bn ($2.1bn) in a cash deal.

Perrigo's predominant revenue stream has been private label/store brand OTC drugs, although it has added brands with its 2014 move into Europe's consumer health market and by acquiring the Prevacid 24 HR (lansoprazole/15 mg) proton pump inhibitor in 2019 and licensing the Burt's Bees brand in May to make and market a line of organic baby formulas and supplements for babies and children.

"I think there's an opportunity for a new player to emerge as a switch powerhouse, given the changing market dynamics." – Susan Levy

But while it consistently is first to launch generic equivalents for brand switches, its name hasn't been linked to submitting proposals for making additional drug ingredients available OTC.

Bringing HRA, including management, under its roof changes the switch outlook for Perrigo.

"These are pros. They know what they're doing," Perrigo president and CEO Murray Kessler said about HRA's management during a briefing about the deal. "They've all agreed to stay on with Perrigo."

Slow Time For Switch NDAs

The HRA acquisition isn't the only reason Perrigo could become a top OTC switch sponsor in the US. Other pharmas are leaving the top spot open.

Looking over the current lineup of major OTC marketers in the US, Levy, founder and principal of Susan B. Levy Consulting LLC in Cranford, NJ, doesn't see any interested in sponsoring new drug applications for OTC switches.

"If you look at who has historically been a driver for OTC switches, you've got GSK, Novartis and Pfizer, but they're all one [consumer health] company now, and it's being spun out. It's kind of unclear to what extent they are positioned right now to invest in expensive growth programs," she said.

GlaxoSmithKline plc is the majority owner of a joint venture with Pfizer Inc. marketing the two firms' consumer health product lines. GSK, with products including brands it acquired after previously operating a consumer health JV with Novartis AG, plans to spin out its current consumer health business. (Also see "McNamara To Lead GSK's Standalone Consumer Healthcare Business" - HBW Insight, 23 Jul, 2021.)

"Then you've got Sanofi," Levy added.

The French firm is known to be considering proposing switches for flu treatment Tamiflu (oseltamivir) and erectile dysfunction drug Cialis (tdalafil), but it too looks to separate its consumer health business. (Also see "Sanofi To Divest 60% Of Brands In Consumer Healthcare Overhaul" - HBW Insight, 10 Feb, 2021.)

"It's unclear where they want to put their bets right now as a result of being spun out independently," she said.

Bayer AG earlier in 2021 received Food and Drug Administration approval for OTC sales of Astepro Allergy (azelastine hydrochloride nasal spray, 205.5 mcg per spray). Bayer plans to launch the first-in-class switch, the first ingredient available OTC that is a first-generation H1 (histamine receptor inhibitor) antihistamine, in 2022. (Also see "Market Exclusivity Decision Pending For Bayer's First-In-Class OTC Switch Astepro Allergy" - HBW Insight, 24 Jun, 2021.)

Levy pointed out the previous OTC switch for a product the German firm markets in the US was Oxytrol for Women overactive bladder treatment, a first-in-class switch when it was approved in in 2013 when US firm Merck & Co., Inc. owned the brand. After acquiring Merck & Co.'s consumer business in 2014, Bayer relinquished OTC rights to the 3.9mg oxybutynin transdermal patch to Allergan PLC less than a year later.

J&J Large In Consumer, Not In Switch

Johnson & Johnson may be synonymous with OTC drugs due to its market-leading brands, but like Perrigo it hasn't been a switch driver.

"Who could be the powerhouses? … J&J has not historically been a switch player. They don't have an experienced team of switch professionals," Levy said.

"It speaks to the fact that there is a gap in the marketplace because these switch programs are very expensive for an OTC company. They are somewhat risky, and they're much longer-term than typical OTC innovation. … If you're heading up a consumer health care company and thinking about where you're going to put your R&D bets, much more incentives are there to do some of the shorter-term, easier innovation."

The FDA is encouraging firms to study making available nonprescription drug ingredients indicated for chronic conditions; in 2012 it opened a docket for recommendations on changing its OTC switch NDA rules to allow for "novel switches" targeting chronic conditions, indications more complicated than most currently available OTC drugs have.

The agency launched the initiative expecting labeling for novel switches to be subject to the same limits as other OTCs, with all necessary information available on a product's Drug Facts label. However, it has since indicated in a 2018 guidance that switch sponsors could tap into digital media and other extra-label tools to help demonstrate that consumers can assess whether an OTC drug is appropriate for them and they can use the

product safely. (Also see "Before Asking FDA For Novel OTC Switch, Be Sure DFL Alone 'Can't Get There'" - HBW Insight, 23 May, 2019.)

In a recent FDA workshop conducted online, industry experts and other stakeholders said some problems with OTC DFLs are worse than others and some likely can be corrected with minor changes to the format, but other changes, notably for supporting OTC labeling for drugs that currently are available Rx-only and are indicated for chronic conditions aren't minor and won't happen within the limits of one-dimensional text media printed on nonprescription drug containers, packages and inserts. (Also see "Progress On Adding OTC Drugs To US Market? Room To Move But Label Format Limits Options" - HBW Insight, 18 Jun, 2021.)

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BIOCENTURY

Sept. 9 Quick Takes: Obsidian readies for IPO with $115M crossover round

PLUS: VENTURE ROUNDS FOR LEXEO, EVOMMUNE, ALAMAR, AND SETBACKS FOR HUMANIGEN, SANOFI AND MORE

BY BIOCENTURY STAFF

SEP 9, 2021 | 9:44 PM EDT

Cell and gene therapy play Obsidian Therapeutics Inc. looks set to seek a public listing after raising $115 million in a series B round led by The Column Group Crossover Fund. Other new investors included RA Capital, Surveyor Capital, Cowen Healthcare Investments, Deep Track Capital, Logos Capital, Pivotal BioVenture Partners, Samsara BioCapital and Soleus Capital. Existing investors Atlas Venture, Vertex Ventures HC, Amgen Ventures, Bristol Myers Squibb Co. (NYSE:BMY) and Vertex Pharmaceuticals Inc. (NASDAQ:VRTX) also participated. Obsidian's lead tumor infiltrating lymphocyte (TIL) program, cytoTIL15, is expected to enter the clinic next year.

$100M SERIES B TO SUPPORT LEXEO'S GENE THERAPIES

Adding to an $85 million January series A, Lexeo Therapeutics raised $100 million in a series B led by D1 Capital Partners and Eventide Asset Management. Also backing the round were CAM Capital, Verition Fund Management, Laurion Capital Management, Gray's Creek Capital Partners, and existing investors Longitude Capital, Omega Funds, Lundbeckfonden Ventures, PBM Capital, Janus Henderson Investors, Woodline Partners LP, Invus Capital and Alexandria Venture Investments. The company has three lead AAV-mediated gene therapy programs: LX2006, which is in preclinical testing for cardiomyopathy associated with Friedreich's ataxia, and LX1004 for CLN2 Batten disease and LX1001 for APOE4-associated Alzheimer's disease, both of which are in Phase I/II testing. The company is also developing recently acquired cardiac gene therapies from Stelios Therapeutics Inc. and additional preclinical programs targeting Alzheimer's disease.

EVOMMUNE RAISES $83M IN SERIES A

Evommune Inc., which was founded in 2020 by Dermira Inc. alums, raised $83 million in series A round with participation from Andera Partners, LSP, global syndicate of investors and Pivotal BioVenture Partners, the seed investor, to enable development of therapies to treat inflammatory diseases through industry and academic collaborations. Evommune has exclusive rights to three of the four candidates in its pipeline, from Dermira, now a Eli Lilly and Co. (NYSE:LLY) company.

SHERPA LEADS ALAMAR'S $80M SERIES B

An $80 million series B round led by Sherpa Healthcare Partners will enable Bay Area-based proteomics company Alamar Biosciences Inc. to accelerate the development of its NULISA and Attobody technology platforms to deliver single-digit attomolar detection sensitivity. NULISA (NUcleic acid-Linked Immuno-Sandwich Assay) seeks to provide "ultra-high sensitivity and massively parallel scale" to proteomic analysis, while Attobody, the company says, yields highly specific picomolar affinity antibodies. Other firms participating in the round included new investors Morningside Ventures and Samsara Biocapital and

existing investors Qiming Venture Partners, which lead the series A, and Illumina Ventures. The company has now raised $110 million.

LILLY TAKES EQUITY STAKE IN LYCIA AS PART OF $70M SERIES B

New Lycia Therapeutics, Inc. partner Eli Lilly and Co. (NYSE:LLY) has invested in the South San Francisco company's $70 million series B, which Redmile Group led. Founding investor Versant Ventures and new investors Cowen Healthcare Investments, Invus, RTW Investments and Alexandria Venture Investments also participated. The financing comes two weeks after Lycia picked Lilly as its collaborator to develop LYTACs against targets implicated in the pharma's areas of focus.

FIRST APPROVAL FOR PFIZER'S ORAL ATOPIC DERMATITIS THERAPY COMES IN U.K.

The U.K.'s MHRA approved Cibinqo abrocitinib from Pfizer Inc. (NYSE:PFE) to treat atopic dermatitis, marking the first global approval for the JAK1 inhibitor. FDA pushed back the therapy's PDUFA date due to a class-wide safety review. Last month, the oral therapy demonstrated superiority to leading atopic dermatitis therapy Dupixent dupilumab in the Phase III JADE DARE trial.

CENTESSA REPORTS FIRST POSITIVE DATA READOUT SINCE FORMATION

Asset-centric play Centessa Pharmaceuticals plc (NASDAQ:CNTA) had its first positive data readout since the company was formed this year by Medicxi. Centessa subsidiary ApcinteX Ltd. said that in the Phase IIa portion of a Phase I/IIa trial, the high dose of SerpinPC over six months led to an 88% reduction in annualized bleeding rate compared with a pre-exposure observation period in patients with either hemophilia A or hemophilia B. The PROC inhibitor was well tolerated with no cases of sustained elevation of D-dimer, a marker of excess thrombin generation. Data from an open-label extension of the study are expected next year. Centessa rose $1.21 to $22.26

HUMANIGEN SINKS AFTER FDA DECLINES TO ISSUE EUA

Shares of Humanigen Inc. (NASDAQ:HGEN) shed nearly half their value Thursday after the biotech said FDA declined to grant an emergency use authorization for lenzilumab, its mAb targeting GM-CSF, to treat hospitalized patients with COVID-19. Humanigen said FDA could not yet conclude that lenzilumab's benefits outweigh its risks, but the biotech believes the NIH-funded ACTIV-5/BET-B study may generate data sufficient to support the mAb's emergency authorization. Humanigen lost $7.14 (47%) to $7.97 on Thursday.

ACQUIRED IN PRINCIPIA DEAL, SANOFI'S BTK MISSES IN PEMPHIGUS

Sanofi (Euronext:SAN; NASDAQ:SNY) said Btk inhibitor rilzabrutinib failed to significantly improve remission rates in the Phase III PEGASUS trial to treat pemphigus, missing the study's primary endpoint. The pharma gained the molecule via its $3.4 billion buyout of Principia Biopharma Inc. (NASDAQ:PRNB) last year. Rilzabrutinib is also in a Phase III study to treat chronic immune thrombocytopenia.

AZ-AVILLION COMBO MEETS MARK IN ASTHMA READOUTS

AstraZeneca plc (LSE:AZN; NYSE:AZN) and Avillion LLP said PT027, the partners' fixed-dose combination of albuterol and budesonide, met the primary endpoints in the Phase III DENALI and MANDALA trials to treat asthma. The treatment significantly improved lung function compared with each of its components in DENALI, and significantly reduced exacerbations compared with albuterol alone as a rescue medicine in MANDALA. Blackstone Life Sciences, Abingworth and Royalty Pharma plc (NASDAQ:RPRX) are backing the PT027 development program in a risk-sharing arrangement.

POSITIVE READOUT FOR A SUBCUTANEOUS GENMAB BISPECIFIC

Epcoritamab, a subcutaneously administered CD3 x CD20 bispecific antibody from Genmab A/S (CSE:GMAB; NASDAQ:GMAB), led to an 88% ORR in relapsed or refractory diffuse B cell lymphoma patients, providing support that the formulation may compete with more burdensome IV infusions on efficacy. Among eight patients who received the recommended Phase II dose of 48 mg, 38% achieved a complete response. ORR was 90% and CR was 50% in the 10 follicular lymphoma patients treated across dose ranges in the dose-escalation study. There was no Grade 3 of higher cytokine release syndrome.

Odronextamab (REGN1979), a CD3 x CD20 bispecific from Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), led to an ORR of 92.9% in follicular lymphoma patients in a Phase I readout last year, though a partial clinical hold was place on the program in December due to incidence of Grade 3 and higher CRS during step-up dosing.

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Cancer leads way to routine use of accelerated approval: Data Byte

AN ANALYSIS FROM BIOCENTURY'S 2021 BACK TO SCHOOL PACKAGE

BY SELINA KOCH, EXECUTIVE EDITOR

SEP 9, 2021 | 7:08 PM EDT

Accelerated approval is becoming the *de facto* route for approvals of new molecular entities in cancer.

In three of the past five years, the number of new cancer drugs granted accelerated approval by FDA has outnumbered those given full approval. Halfway through this year, the count stood at eight accelerated to four standard approvals.

BioCentury's annual Back to School project explored cancer as a case study of the promise and problems of accelerated approval, and argued for changes that could usher in routine use of the pathway for all serious diseases with unmet needs.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date: November 15, 2021

Reviewer(s): Amy I Chen, PharmD, Safety Evaluator
Division of Pharmacovigilance-I (DPV-I)

David Croteau, MD, Medical Officer
DPV-I

Acting Team Leader: Daniel Woronow, MD, FACC
DPV-I

Division Director: Cindy Kortepeter, PharmD
DPV-I

Product Name(s):

Drug name	Active ingredient	Application	Applicant
Lupron Depot-Ped	Leuprolide acetate	020263	AbbVie Endocrine Inc
Fensolvi	Leuprolide acetate	213150	Tolmar
Synarel	Nafarelin	019886	Pfizer
Supprelin LA	Histrelin	022058	Endo Pharm
Triptodur	Triptorelin	208956	Arbor Pharms LLC

Subject: Idiopathic intracranial hypertension (pseudotumor cerebri)

Application Type/Number: NDA 020263

Submission Number: S-049

Applicant/Sponsor: AbbVie Endocrine Inc.

OSE RCM #: 2021-171

SS ID # 1004605

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EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of General Endocrinology (DGE) an evaluation of idiopathic intracranial hypertension (IIH) [pseudotumor cerebri (PTC)] reported with the use of gonadotropin-releasing hormone (GnRH) agonists that are indicated for the treatment of pediatric patients with central precocious puberty (CPP) from the FDA Adverse Event Reporting System (FAERS) and medical literature. The information and recommendations in this review will assist DGE to determine if IIH (PTC) should be added to labeling for the GnRH agonist class. In addition, this review will assist DGE to determine the approvability of a Prior Approval Supplement (PAS) for Lupron-Depot Ped (NDA 020263, S-049) to update the Warnings and Precautions and Adverse Reactions Postmarketing Experience sections of the United States Prescribing Information (USPI) to include IIH (PTC) in patients treated for CPP.

Based on information identified in this review, DPV concludes there is evidence to support an association between leuprolide acetate and IIH (PTC) including four cases with a temporal relationship with leuprolide therapy, general absence of alternative etiologies for IIH (PTC), and three of these cases with lack of IIH (PTC) recurrence after acetazolamide discontinuation. Evidence from the case series also supports an association between triptorelin and IIH (PTC) based on temporal relationship and general absence of alternative etiologies for IIH (PTC). DPV determined that the cases of IIH (PTC) included in this review were clinically serious with medically important outcomes to warrant the inclusion of IIH (PTC) in the Warnings and Precautions section of the leuprolide acetate and triptorelin label to communicate the risk of IIH (PTC) in pediatric patients diagnosed with CPP. Although we do not have cases for the other two GnRH agonists, nafarelin and histrelin, the biological mechanism is similar for members of the drug class; therefore, DPV does not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

DPV will continue to monitor the class of GnRH agonists for cases of IIH (PTC), with special attention to drugs with no identifiable cases in our current case series.

Based on this review DPV recommends the following:

- Add information proposed by the Applicant regarding IIH (PTC) to Section 5 of the leuprolide acetate product labeling (for products indicated for CPP):

  WARNINGS AND PRECAUTIONS:

  Pseudotumor cerebri (idiopathic intracranial hypertension)

  Pseudotumor cerebri (idiopathic intracranial hypertension) has been reported in pediatric patients receiving leuprorelin[1] acetate. Monitor patients for signs and symptoms of

[1] Leuprorelin is the generic name of the drug and its International Nonproprietary Name (INN) and British Approved Name (BAN) while leuprolide acetate is its United States Adopted Name (USAN) and established (nonproprietary) name in the United States Pharmacopeia (USP). The current Lupron Depot-Ped® USPI does not use nomenclature for leuprorelin acetate, but rather, leuprolide acetate throughout the label.

pseudotumor cerebri, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea.

(b) (4)

ADVERSE REACTIONS

Nervous system disorders: pseudotumor cerebri (idiopathic intracranial hypertension)

- Add language to the PATIENT COUNSELING INFORMATION regarding IIH (PTC) such as unusual headaches and visual disturbances.

- Add similar language to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS AND PATIENT COUNSELING INFORMATION section of triptorelin product labeling (for products indicated for CPP).

- Although we do not have cases for all the products within the pharmaceutical class of the GnRH agonists, we do not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

1 INTRODUCTION

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of General Endocrinology (DGE) an evaluation of idiopathic intracranial hypertension (IIH) [pseudotumor cerebri (PTC)] reported with the use of gonadotropin-releasing hormone (GnRH) agonists that are indicated for the treatment of pediatric patients with central precocious puberty (CPP) [i.e., not for gynecologic or oncologic indications] from the FDA Adverse Event Reporting System (FAERS) and medical literature. The information and recommendations in this review will assist DGE to determine if IIH (PTC) should be added to labeling for the GnRH agonist class. In addition, this review will assist DGE to determine the approvability of a Prior Approval Supplement (PAS) for Lupron-Depot Ped (NDA 020263, S-049) to update the Warnings and Precautions and Adverse Reactions Postmarketing Experience sections of the United States Prescribing Information (USPI) to include IIH (PTC) in patients treated for CPP.

On July 30, 2021 DGE consulted DPV-I to evaluate reports of IIH (PTC) with leuprolide acetate (Lupron-Depot Ped®) to determine if DPV-I agrees with the addition of language proposed by the Applicant in the PAS for Lupron-Depot Ped. DGE also requested DPV assess whether a newly identified safety signal (NISS) should be opened for IIH (PTC) across the class of GnRH agonist products approved for CPP. DPV-I subsequently opened NISS ID #1004605, and moved to the Evaluation Phase after conferring with DGE, which is the basis for this review.

1.1 BACKGROUND

1.1.1 PAS for Leuprolide acetate (NDA 020263, S-049)

On June 18, 2021 AbbVie Endocrinology identified a potential safety signal concerning IIH (PTC) with the use of leuprolide acetate (Lupron-Depot Ped®) in pediatric patients diagnosed with CPP and reported their findings in the AbbVie Leuprolide Clinical Overview.[1] The signal was triggered by a medical literature report describing IIH (PTC) in a 6-year-old female treated with leuprolide for CPP.[2] IIH (PTC) was previously evaluated as a safety signal in December 2016, based on a medical literature report describing a 9-year-old female who developed IIH (PTC) after a dose increase of leuprolide to treat CPP.[3] Given the totality of the data, the previous assessment concluded that there was insufficient information at the time to confirm or rule out a causal association between leuprolide and the occurrence of IIH (PTC). An additional report was identified in the medical literature of a 12-year 5-month-old transgender male, birth assigned female, who developed IIH (PTC) after initiating leuprolide acetate to suppress puberty.[4]

Based on the information in the three literature reports, especially the two reports describing pediatric patients treated with leuprolide for CPP, the Applicant recommended changes to the product labeling for the pediatric CPP population as follows:

Warnings and Precautions:

Pseudotumor cerebri/idiopathic intracranial hypertension

Pseudotumor cerebri (PTC)/idiopathic intracranial hypertension has been reported in pediatric patients receiving leuprorelin acetate. Monitor patients for signs and symptoms of PTC, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. (b) (4)

(b) (4)

Adverse Reactions:

Nervous system disorders: pseudotumor cerebri/idiopathic intracranial hypertension

1.1.2 GnRH agonists

GnRH is a decapeptide synthesized in the cell bodies of hypothalamic neurons and secreted by their axon terminals directly into the hypophyseal-portal blood supply.[5] GnRH selectively stimulates gonadotropic cells in the anterior pituitary to release the heterodimeric gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). In turn, LH and FSH stimulate gonadal production of sex steroids and gametogenesis, respectively.[6]

In general, GnRH agonists are derived from native GnRH by substitution of a D-amino acid for the native L-amino acid at position 6 in the decapeptide. GnRH has a short half-life because of the rapid cleavage of the bonds between amino acids at selective positions (5-6, 6-7, 9-10). Substitution at position 6 yields an agonist which is resistant to degradation with an extended half-life and receptor occupancy time.[7] Several unique features mark the physiology of GnRH. First, its secretion is pulsatile in nature and gonadotropic cells require this intermittent form of stimulus-secretion coupling in order to secrete gonadotropins in a physiologic pattern. Second, continuous stimulation of the pituitary either by natural sequence GnRH or by long-acting GnRH agonists desensitizes gonadotropin secretion, resulting in a gonadal suppression that has important clinical applications.[8] A constant intravenous infusion of GnRH or administration of GnRH agonists causes an initial agonistic action, followed by downregulation of receptor concentrations, which desensitizes the pituitary to continued stimulation. Within three to four weeks, a hypogonadotropic hypogonadal state is induced. Initially, the response is due to desensitization and downregulation of the receptors; however, gradual loss of receptors and the uncoupling of the receptor from its effector system occurs over time.[7]

GnRH or its analogs are employed clinically in two different modes. Applications designed to restore fertility in GnRH-deficient men and women must use and intermittently deliver natural-sequence GnRH and hence rely on external delivery devices designed to mimic the physiologic frequency of endogenous GnRH secretion.[9,10] In the second mode of clinical use, a selective and reversible suppression of the pituitary-gonadal axis is sought. This mode of GnRH use (i.e., a biochemical castration) can be achieved by continuous administration of natural sequence GnRH or by the use of long-acting GnRH agonists or antagonists. Single daily injections or depot formulations of GnRH agonists have been introduced in several clinical applications, each of which relies upon complete extinction of gonadotropin secretion with subsequent suppression of gonadal steroids to castrate levels.

CPP, also known as gonadotropin-dependent precocious puberty or true precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis. It is characterized by sequential maturation of breasts and pubic hair in girls, and of maturation of the testes, penis, and pubic hair in boys. CPP is idiopathic in 80 to 90 percent of cases in girls, whereas intracranial lesions are detected in 40 to 75 percent of boys with CPP.[11]

When warranted, pubertal progression in CPP can be treated by administration of a GnRH agonist. GnRH agonists work by providing continuous stimulation to the pituitary gonadotrophs, instead of physiologic pulsatile stimulation from hypothalamic GnRH. Continuous stimulation leads to desensitization of the gonadotroph cells and suppression of gonadotropins, resulting in decreased sex steroid production,[12] a phenomenon referred to as pituitary-gonadal axis suppression. This treatment can be used for patients with idiopathic or neurogenic CPP[13,14] or for secondary activation of CPP, which may occur in patients who initially present with peripheral precocity. For children with CPP, GnRH agonist administration results in an initial transient stimulation of gonadotropin secretion from the pituitary, followed by a complete, but reversible, suppression of the pituitary-gonadal axis.

1.1.3 IIH (PTC)

IIH is also called PTC, designated herein as IIH. For the purposes of this review, we will use PTC and IIH synonymously, except when quoting an external source. IIH is a disorder defined by clinical criteria that include symptoms and signs isolated to those produced by increased intracranial pressure (ICP) (e.g., headache, papilledema, vision loss), elevated ICP with normal cerebrospinal fluid (CSF) composition, and no other cause of intracranial hypertension evident on neuroimaging or other evaluations. While once called "benign intracranial hypertension" to distinguish it from secondary intracranial hypertension produced by a malignancy, it is not a benign disorder. Many patients suffer from intractable, disabling headaches, and there is a risk of severe, permanent vision loss. Even patients with mild vision loss have an associated reduction in quality of life.[15]

The annual incidence of IIH is 1 to 2 per 100,000 population.[16,17] There is a higher incidence in obese women between the ages of 15 and 44 years (4 to 21 per 100,000).[17,18] IIH is a disorder that primarily affects women of childbearing age who are overweight.[17] In a national prospective population-based cohort study of 185 children with IIH , the national annual incidence (95% CI) of IIH in children aged 1–16 years was 0.71 (0.57 to 0.87) per 100,000 population increasing with age and weight to 4.18 and 10.7 per 100,000 in obese boys and girls aged 12–15 years, respectively.[19] Incidence rates under 7 years were similar in both sexes. From 7 years onwards, the incidence in girls was double that in boys, but only in overweight (including obese) children. In children aged 12–15 years, an estimated 82% of the incidence of IIH was attributable to obesity.[19]

When IIH is associated with factors other than obesity, recent weight gain, and polycystic ovarian syndrome, it is referred as IIH-like syndrome because it is no longer idiopathic. Many case reports and case series describe associations between certain medications and intracranial hypertension. Such medications include vitamin A (hypervitaminosis A) and the vitamin A derivatives isotretinoin and all-trans-retinoic acid, antibiotics (e.g., tetracycline, minocycline,

nalidixic acid, fluoroquinolones, sulfa drugs), hormonal medications (e.g., growth hormone, oral contraceptives, progesterone, danazol), corticosteroid withdrawal (especially among children), and lithium.[20,21,22,23,24,25,26,27,28,29,30,31,32]

Various systemic diseases have been associated with IIH, including systemic lupus erythematosus, underlying malignancies, anemia, Addison's disease, hyperthyroidism and hypothyroidism, and uremia.[33,34,35,36,37,38] Dural venous sinus thrombosis has long been recognized as being associated with intracranial hypertension.[39] Dural sinus occlusion leads to increased venous pressure and higher CSF pressures, with clinical findings of papilledema and headaches. Certain systemic conditions and medications may be associated with IIH via a hypercoagulable state leading to dural sinus thrombosis. These conditions include malignancies, systemic lupus erythematosus, protein C and S deficiencies, antithrombin III deficiency, Factor V Leiden mutations, anticardiolipin antibodies, oral contraceptive use, and pregnancy.[40,41,42,43,44]

Other venous abnormalities that can elevate intracranial venous pressures, including dural arteriovenous fistulae and carotid-cavernous fistulae, have been associated with IIH.[45,46] Iatrogenic disruption of venous drainage, for example, after acoustic neuroma resection, radical neck dissection or catheter-induced subclavian vein thrombosis has also been associated with elevated intracranial venous and CSF pressures.[47,48,49] Venous sinus compression by tumors (e.g., meningiomas) has also been reported.[50]

The pathophysiologic mechanisms of pediatric IIC have not been studied to the same extent as adult IIH. In its most fundamental level, IIC is related to abnormal CSF dynamics, either impaired CSF outflow, or aberrant CSF production, or both. With respect to impaired CSF outflow, increased resistance of CSF flow through arachnoid granulations may contribute to raised ICP. Impaired CSF lymphatic outflow (the "glymphatic pathway"), a CSF drainage pathway recently appreciated in the CNS, may also be contributing. In the pediatric population, IIH is characterized by a multifaceted relationship between age, obesity, pubertal status, and sex, factors which, in truth, may be acting to influence CSF production or outflow. However, many studies have focused on their influence on CSF production. The interaction of these factors may change with age, producing age-dependent phenotypes likely driven by distinct factors with possibly different pathophysiology. For example, adiposity clearly contributes to the presentation of disease in early and late adolescents, who are more frequently obese and female, likely similar to those in adults. Whereas factors other than adiposity likely contribute to the phenotype of young, prepubertal children with IIH, who are less likely to be obese, are equally male and female, and may present without symptoms of headache or visual blurring. Pediatric adiposity has complex pathophysiology and includes potential contributions from alterations in growth hormone and gonadal hormones, factors also known to play a role in IIH-like syndrome.[51,52] Transverse sinus stenoses (TSS) have been found in a large majority of patients with IIH.[53] It is, however, not clear whether they are incidental, secondary to increased ICP, or causal.[54,55]

Headache is the most common symptom of IIH and observed in nearly all patients. IIH headaches are typically generalized, episodic, throbbing, and worse in the morning. They are often aggravated by Valsalva maneuvers (straining or coughing) and may be associated with retro-orbital pain.[56] Neck, shoulder, and arm pain is often involved. In addition, transient visual

symptoms (obscurations, blurring, and scotomata) and diplopia are frequently noted.[57] Pulsatile tinnitus is common and may be the initial complaint.[58]

After recording a complete history, the evaluation should continue with complete neurological and ophthalmological examinations. Papilledema, as a criterion for the condition, is observed for virtually all patients with IIH and is the most important sign. However, there have been numerous case reports of patients with IIH for whom papilledema was not observed, and the absence of papilledema is thus not an exclusionary criterion.[59] Abducens palsy, a false localizing sign thought to be attributable to traction of the sixth cranial nerve resulting from intracranial hypertension is observed in approximately 20% of cases.[60] Facial palsy may also be observed. In cases of suspected IIH, an ophthalmoscopic examination is critical. Papilledema is usually the only objective finding in physical examinations for patients with IIH. The ophthalmoscopic appearance of IIH is usually characterized by bilateral optic nerve head swelling. However, this can be quite subtle and cases of IIH without papilledema have been reported. The magnetic resonance imaging (MRI) findings in IIH are generally reported as unremarkable, but abnormalities may be present in IIH. The abnormalities include a partially empty sella, flattening of the posterior sclera, dilation and tortuosity of the optic nerve sheath, and sometimes gadolinium enhancement of the optic disc.[61] However, the findings are often too subtle and nonspecific to allow the diagnosis of IIH on the basis of MRI scans alone. If the findings on MRI scans do not provide compelling evidence of ICP elevation, then a lumbar puncture, with direct measurement of the lumbar subarachnoid pressure, should be performed in cases of suspected papilledema.

For initial treatment of patients with IIH, the carbonic anhydrase inhibitor acetazolamide is recommended. Carbonic anhydrase inhibitors are believed to reduce the rate of CSF production and have been associated with modestly improved outcomes in patients with IIH.[62] Furosemide is also a diuretic but has little effect on CSF production; it may be used for patients who cannot tolerate acetazolamide. A short course of intravenous glucocorticoids may be helpful for patients with acute visual loss resulting from fulminant papilledema. Serial lumbar punctures or lumbar drainage can be a useful temporizing measure as a prelude to surgery.[55] However, these are not useful for long-term management of IIH in most patients.

Surgical intervention is required as soon as medical treatment fails. The two main surgical procedures in IIH are optic nerve sheath fenestration (ONSF) and cerebrospinal fluid (CSF) shunting procedures. ONSF is usually performed using a medial orbital approach. The optic nerve sheath is identified and a window is cut in the sheath, allowing CSF egress into the orbit. Common complications include diplopia, efferent pupillary dysfunction from ciliary ganglion damage, and vision loss. Vision loss can result from vascular complications, trauma, infections, hemorrhage into the optic nerve sheath, and other operative events.[63] CSF shunting procedures include ventriculoperitoneal shunt (VPS) or lumboperitoneal shunt (LPS). Shunt failure requiring revision is the most common complication of LPS and occurs in approximately half of patients, with a few patients requiring multiple (10 to 38) shunt revisions.[64] In rare cases, shunt failure is accompanied by visual loss that can be rapid and severe.[65] Other complications of shunting include shunt infection, abdominal pain, and over drainage causing low pressure. Rare complications include cerebellar tonsillar herniation, syringomyelia, subdural and subarachnoid hemorrhage, and bowel perforation.

1.2 REGULATORY HISTORY

GnRH agonists are used for a variety of indications including the treatment of infertility and to lower sex hormone levels in the treatment of hormone-sensitive cancers such as prostate cancer and breast cancer, gynecological disorders such as endometriosis and uterine leiomyomas, and the treatment of CPP in pediatric patients. There are five FDA-approved GnRH analogs currently marketed in the U.S for the treatment of CPP in pediatric patients. The first GnRH agonist, nafarelin (Synarel®) was approved by the FDA on February 13, 1990. Table 1 lists the currently available GnRH agonists in the U.S. indicated for the treatment of CPP in pediatric patients.

Table 1. GnRH Agonists Approved by FDA for Treatment of CPP in the U.S.

Active ingredient	**Leuprolide acetate**	**Leuprolide acetate**	**Nafarelin**	**Histrelin**	**Triptorelin pamoate**
Trade name	Lupron-Depot Ped	Fensolvi	Synarel	Supprelin LA	Triptodur
Application NDA	020263	213150	019886	022058	208956
Approval date	4/16/93	5/1/20	2/13/90	5/3/07	6/29/17
Dosage form	IM injection	SQ injection	Nasal spray	SQ implant	IM injection
Dose	7.5 mg, 11.25 mg, 15 mg QMO 11.25 mg, 30 mg Q3MO	45 mg Q6MO	1600-1800 mcg QD	50 mg QYR	22.5 mg Q24 WK

1.3 RELEVANT PRODUCT LABELING

GnRH agonists indicated for the treatment of CPP in pediatric patients are not labeled for IIH.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION AND SELECTION CRITERIA[66]

Case definition of IIH

The case definition of IIH requires the following:

Category I

A reported lumbar puncture opening pressure of ≥250 mm H_2O in adults and ≥280 mm H_2O in children [250 mm if the child is not sedated and not obese][2] AND the following:

A. Papilledema
B. Normal neurological examination except for cranial nerve abnormalities
C. Normal CSF composition[3]
D. Neuroimaging consistent with normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI,

[2] If criteria A–D are met but the measured CSF pressure is lower than specified here, a diagnosis of IIH is still conceivable but less robust

[3] If CSF values or neurological examination findings are not specifically reported it is appropriate to assume they are unremarkable

with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced computerized tomography (CT) may be used[3]

OR

Cases lacking papilledema but otherwise fulfilling other criteria above AND with a unilateral or bilateral abducens neuropathy

Category II

Clinical diagnosis including any the following terms:

A. Pseudotumor cerebri
B. Benign intracranial hypertension
C. Idiopathic intracranial hypertension

Selection Criteria

- Inclusion criteria
  - Met the case definition for IIH
  - Reasonable temporal relationship to GnRH agonist exposure
- Exclusion criteria
  - Non-CPP or non-puberty indication[4] (e.g. gynecological or oncological indication)
  - Duplicate report
  - Pediatric patient not reported
  - GnRH agonist use not reported
  - Insufficient information to assess causality

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	September 6, 2021
Time period of search	Through September 5, 2021
Search type	FBIS Product Manufacturer Reporting Summary
Product terms	Product active ingredient: leuprolide; leuprolide acetate; leuprolide acetate\lidocaine hydrochloride; leuprolide acetate\norethindrone acetate; nafarelin; nafarelin acetate; histrelin; histrelin acetate; triptorelin; triptorelin acetate; triptorelin pamoate; goserelin; goserelin acetate; elagolix; elagolix sodium; elagolix sodium\estradiol\norethindrone

[4] We included a case, also identified in the Applicant's clinical overview, of a transgender 12-year-old male (birth assigned female) who received leuprolide acetate to suppress puberty.

Table 2. FAERS Search Strategy*	
MedDRA search terms (Version 24.0)	HLT: *Increased intracranial pressure disorders* PT: *Idiopathic intracranial hypertension; CSF pressure increased; Intracranial pressure increased; Papilloedema; Reduction of increased intracranial pressure*
Serious†	Yes
* See Appendix A for a description of the FAERS database. † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening hospitalizations (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SOC=System Organ Class, HLGT=High Level Group Term, HLT=High Level Term, PT=Preferred Term	

2.3 DRUG UTILIZATION

Please see Appendix B for a pediatric patient focused drug utilization review of GnRH agonists.[67]

2.4 LITERATURE SEARCH

DPV searched the medical literature with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Date of search	September 5, 2021
Database	PubMed
Search terms	(gonadotropin releasing hormone agonists OR gonadotropin releasing hormone analogs OR gonadorelin derivative OR gonadorelin agonist OR leuprorelin OR leuprolide OR nafarelin OR histrelin OR triptorelin OR goserelin OR elagolix OR "lupron depot ped" OR “Lupron-depot ped” OR fensolvi OR synarel OR “supprelin la” OR triptodur) AND (idiopathic intracranial hypertension OR pseudotumor cerebri OR brain pseudotumor)
Years included in search	All

2.5 APPLICANT'S EVALUATION[1]

AbbVie Endocrinology submitted a clinical overview evaluating IIH, as part of the PAS (NDA 020263, S-049) to update the Warnings and Precautions (Section 5) and Adverse Reactions Postmarketing Experience (Section 6.2) of the USPI for leuprolide acetate (Lupron-Depot Ped®) injection.

3 RESULTS

3.1 FAERS CASE SELECTION

After applying the case selection criteria in Section 2 to both the FAERS and medical literature search results and accounting for duplicate reports, we included six GnRH agonist cases of IIH. (see Figure 2). Appendix B contains a line listing of the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the five GnRH agonist FAERS cases in this case series. The one literature case for GnRH agonist (triptorelin) is cited in the references section.

Figure 2. FAERS Case Selection

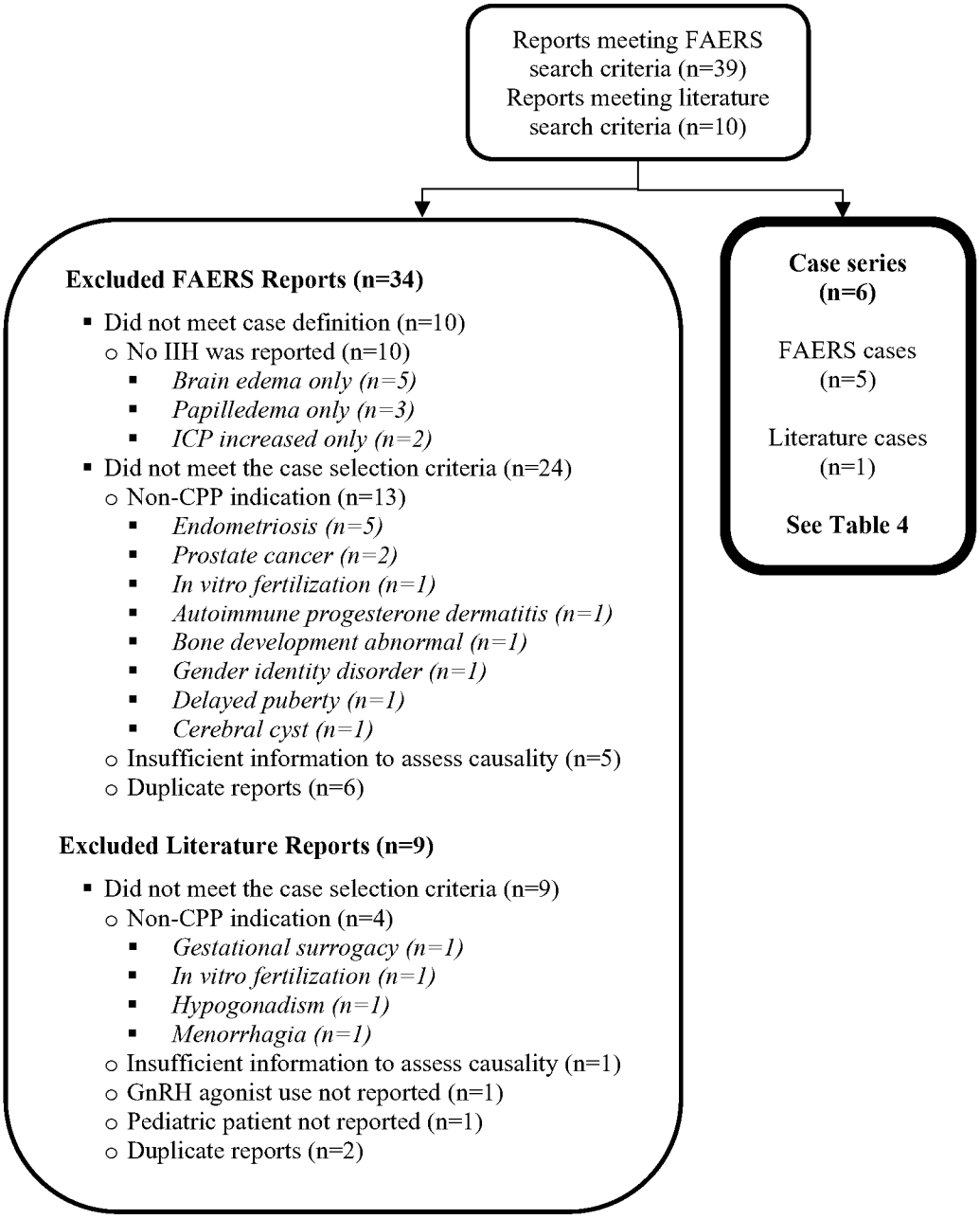

Table 4 summarizes our case series consisting of six FAERS and literature cases of IIH reported with GnRH agonist.

Table 4. Descriptive Characteristics of Cases Reporting IIH in Pediatric Patients with GnRH Agonists in FAERS[*] and the Published Medical Literature[†] Received by FDA or Published through September 5, 2021 (n=6)

Characteristic	Leuprolide acetate (n=4)	Triptorelin (n=2)	Total (n=6)
Case source			
FAERS	4	1	5
Literature	0	1	1
Report type			
Expedited	4	1	5
Patient sex			
Female	4	2	6
Male	0	0	0
Age (years)			
Number of cases	4	2	6
Median	10	7	9
Range	6-12	5-9	5-12
Country[‡]			
Domestic	0	0	0
Foreign	4	2	6
Case Definition Category			
Category I	2	1	3
Category II	2	1	3
Year received by FDA or published			
2000-2010	1	0	1
2011-2020	2	2	4
2021	1	0	1
Serious outcome[§]			
Other serious	4	1	5
Reporter Type			
Physician	4	1	5
HCP, NOS	0	1	1
Time to onset from the first dose of GnRH agonist (days)[‖]			
Number of cases	4	2	6
Median	135	62	120
Range	60-240	3-120	3-240
GnRH agonist dose (mg) (non-mutually exclusive)	3.75 (2) 22.5 (1) 11.25 (1) 7.5 (1) 5.6 (1)	3.75 (1)	NA
BMI (kg)			
Number of cases	2	2	4
Median	21	20	20
Range	17-25	18-21	17-25
Reported signs and symptoms (non-mutually exclusive)	Visual disturbances (5) Headache (2) Papilledema (2) Abducens neuropathy(1)	Non-specific findings (4) Headache or vomiting (3) Papilledema (1) Blood pressure increase (1)	Visual disturbances (5) Headache or vomiting (5) Non-specific findings (5) Papilledema (3)

Table 4. Descriptive Characteristics of Cases Reporting IIH in Pediatric Patients with GnRH Agonists in FAERS* and the Published Medical Literature† Received by FDA or Published through September 5, 2021 (n=6)			
Characteristic	**Leuprolide acetate (n=4)**	**Triptorelin (n=2)**	**Total (n=6)**
	Non-specific findings (1)		Abducens neuropathy (1) Blood pressure increase (1)
Lumbar puncture opening pressure (mm H_2O) **Number of cases** **Median** **Range**	 2 380 310-450	 1 460 NA	 3 450 310-460
Treatment or intervention	Acetazolamide (4) Ventriculoperitoneal shunt (1)	Acetazolamide (1)	Acetazolamide (5) Ventriculoperitoneal shunt (1)
Leuprolide discontinued	Yes (2)¶ NR (2)	Yes (1) NR (1)	Yes (3) NR (3)
Patient disposition	Resolved (2) Resolving (1) Not resolved (1)	Resolved (1)	Resolved (3) Resolving (1) Not resolved (1)

* FAERS - includes any case identified in either FAERS alone or in both FAERS and the literature.
† Literature - includes cases only identified in the literature.
‡ Six foreign cases from Brazil (1), Kenya (1), Canada (1), Great Britain (1), Spain (1), Turkey (1).
§ Other serious was the only serious outcome reported. Literature cases are not coded for serious outcomes
‖ Time to onset calculated from the initiation of GnRH agonist to the onset of IIH symptoms or diagnosis, whichever is first.
¶ Case 12789628 reported improvement in conjunction with VPS.
Abbreviations: BMI=body mass index, GnRH=gonadotropin-releasing hormone, HCP= Healthcare professional, NA=not applicable, NOS= not otherwise specified, NR=not reported

REPRESENTATIVE CASES (N=4)

FAERS 12789628 (Brazil, BR-ABBVIE-16P-020- 1734538-002016, September 2016):[3]
A physician reported a 9-year-old female who developed "PTC" four months after receiving leuprolide acetate 3.75 mg once monthly to treat CPP. She presented with axillary odor, accelerated growth velocity and thelarche onset at the age of 7 years, 6 months. On work-up, she showed advancement of bone age (11 years, 6 months, chronological age 9 years), gonadotropins at pubertal levels (FSH 3.3 U/L, LH 2 U/L), and uterine volume of 12.3 ml. The patient's weight was within normal limits [body mass index (BMI) 17.1 kg/m^2, 75^{th} percentile] and no recent weight gain was noted. No medication beyond leuprolide was used before or at the time of the medical visit. In the fourth month of treatment, the dosage of leuprolide acetate was increased to 11.25 mg in once quarterly doses. After four weeks of the first intramuscular (IM) injection of 11.25 mg leuprolide, she presented with moderate holocranial headache. Ten days after the onset of headache, she complained of transient visual obscuration followed by progressive visual loss. Despite the complaints, she received two further doses of 11.25 mg leuprolide as the cause of her headache was still being investigated. After six months, she persisted with holocranial headache and progressive visual loss associated with ocular deviation. Neuro-ophthalmological examination revealed visual acuity of 20/200 in the right eye and 20/40 in the left eye, with relative afferent pupillary defect in the right eye and edema of the optic disc in both eyes. Extrinsic ocular motility examination showed hypofunction of the lateral rectus muscle in both eyes, consistent with bilateral involvement of the abducens nerve. Manual perimetry showed increased blind spot and generalized constriction of the isopters in both eyes. Neurological

examination revealed no significant deficit. CSF analysis showed an opening pressure of 450 mm H_2O. No other alterations were found on CSF examination. MRI of the brain and orbit detected flattening of the posterior sclera and absence of mass or other alteration associated with PTC or optic neuropathy. Magnetic resonance angiography showed no signs of cerebral venous thrombosis. Because of severe visual loss, treatment with acetazolamide was started and leuprolide was discontinued. Headache and transient visual obscuration showed "significant" improvement (day of the lumbar puncture). After one month the CSF pressure was 170 mm H_2O. The acetazolamide was discontinued in less than three months due to metabolic acidosis. After two weeks, headache and transient blurred vision recurred. On that occasion the CSF pressure was 220 mm H_2O. A VPS was performed to control ICP as an alternative to acetazolamide treatment. The follow-up at eighteen months showed CSF pressure of 140 mm H_2O, stabilization of visual acuity and visual field, and resolution of papilledema with persistent optic disc atrophy.

Reviewer's comment: This case fulfills our Category I case definition criteria. The patient presented with symptoms of IIH four months after initiating leuprolide acetate 3.75 mg once monthly to treat CPP. The time to onset from the most recent dose increase of leuprolide acetate to 11.25 mg once quarterly to the onset of the event was four weeks. This case met the Category I case definition of PTC as the patient's lumbar puncture reported an elevated opening pressure of 450 mm H_2O. The patient experienced bilateral papilledema reported as edema of the optic disc in both eyes. Her neurological examination was normal, except for hypofunction of the lateral rectus muscle bilaterally, consistent with bilateral involvement of the sixth cranial nerve (abducens nerve), and this finding is consistent with PTC.[60] Except for flattening of the posterior sclera, a suggestive sign of PTC, no mass or structural lesions were detected on MRI. The onset of PTC temporal to the initiation of leuprolide acetate supports an association between PTC and leuprolide acetate. No alternative etiologies or risk factors for IIH were reported. Although PTC resolved upon discontinuation of leuprolide acetate with acetazolamide, including a reduction in the CSF pressure, the event recurred upon discontinuation of acetazolamide. Pharmacokinetic studies performed following a single leuprolide acetate 11.25 mg or 30 mg for 3-month administration to pediatric patients with CPP showed mean leuprolide plasma concentration remained constant from month 1 to month 3 for both 11.25 and 30 mg doses.[68] It is plausible the acetazolamide was withdrawn before the end of the 11.25 mg leuprolide 3-month effect, thereby causing a recurrence in ICP elevation. The VP shunt, which was placed during this three month interval, exemplifies the seriousness of this case. On 18 month follow-up, the patient continued to do well without recurrence of IIH, which supports a drug-associated etiology, although we acknowledge the contribution of the VPS in improving ICP. Overall, the temporal relationship between the initiation of leuprolide acetate and onset of IIH and the lack of risk factors and alternative etiologies for IIH support a drug-event causal association. Additionally, the Applicant assessed this case as "no alternative etiology."[1]

FAERS 18649727 (Kenya, KE-ABBVIE-20K-089- 3687126-00, December 2020):[2]
A physician reported a 6-year-6 months-old female who developed PTC two months after receiving leuprolide acetate 3.75 mg monthly every 28 days to treat CPP. She was referred to the pediatric endocrinology clinic for breast development and rapid growth for the past six months. There was no significant past medical or family history. On examination her weight was 26.5 kg (75th-90th centile), height 125.5 cm (75th-90th centile), and blood pressure 90/40

mm Hg. Pubertal examination revealed left breast at Tanner 3 and right breast at Tanner 2. Pubic hair was at Tanner 1 and no axillary hair was noted. Investigations revealed bone age at seven years, pelvic ultrasound revealed uterus of 4.2 ml (Tanner 3), right ovarian volume of 3 ml (Tanner 4), and left ovarian volume of 4 ml (Tanner 5). Endometrial thickness of 2 mm was also noted. GnRH stimulation test done with leuprolide acetate revealed LH at 7.78 mIU/ml and FSH at 14.52 mIU/ml. A diagnosis of precocious puberty was made and the patient was started on leuprolide acetate 3.75 mg every 28 days. After two doses of leuprolide acetate 3.75 mg, the patient developed double vision with partial vision loss. There was no history of headache, vomiting, or convulsions. Neurologic and other systemic examination was normal. The patient was referred to an ophthalmologist for a fundoscopy examination. She also had a head tilt to the left with normal extraocular movements. On fundoscopy, there was "severe" bilateral papilledema with blurring of the optic disc margins. The rest of the fundus was normal. Cranial and pituitary MRI did not reveal any space occupying lesion. The patient was not on other medications apart from leuprolide acetate. Because of "severe" papilledema and visual loss leuprolide acetate was discontinued "immediately" and acetazolamide initiated. After six weeks of treatment with acetazolamide, the visual acuity as well as papilledema resolved, and the acetazolamide was then also discontinued, without recurrence of ophthalmologic findings.

Reviewer's comment: This case fulfills our Category II case definition criteria. This patient developed signs of IIH including double vision and partial vision loss two months after starting leuprolide acetate 3.75 mg monthly to treat CPP. The patient's neurologic examination was normal with normal cranial and pituitary MRI. However, a fundoscopy examination showed marked bilateral papilledema with blurred disc margins. Although there was no CSF analysis or pressure measured, papilledema has good sensitivity and specificity for the diagnosis of increased ICP, especially when documented by an ophthalmologist. This, in conjunction with the unremarkable brain MRI, supports the diagnosis of IIH in this patient.[69] This case was characterized by temporal association to the initiation of leuprolide acetate, lack of a clear alternative etiology for IIH, and resolution of IIH after leuprolide discontinuation with medical treatment supporting a causal relationship between IIH and leuprolide acetate. Notably, acetazolamide was discontinued after six weeks of treatment with no recurrence of IIH. Additionally, the Applicant assessed this case as "no alternative etiology."[1]

FAERS 19098245 (Canada, CA-ABBVIE-21K-028-3846355-00, April 2021):[4]
A physician reported a 12 5/12-year-old trans-gender male (birth-assigned female), who developed PTC five months after receiving leuprolide acetate to suppress puberty. The patient started depot leuprolide acetate to suppress puberty at 11 10/12 years of age (early Tanner 2 breast development). He received leuprolide acetate 7.5 mg intramuscularly (IM) for four doses, then 22.5 mg IM every 13 weeks thereafter. Five months after his first injection, a routine eye examination revealed bilateral papilledema and enlarged blind spots, which was confirmed by a pediatric ophthalmologist. He was asymptomatic. There was no marked weight gain in the previous year with a BMI of 24.5 kg/m^2. His blood pressure was 110–123 mm Hg systolic and 71–85 mm Hg diastolic. Neurological examination was normal. Head CT was normal. Cranial MRI showed slight flattening of the optic nerve heads, mild engorgement of optic nerve sheath fluid, and no space-occupying mass. A sedated lumbar puncture revealed elevated opening pressure of 310 mm H2O. CSF analysis, including pathology, was benign. He was managed with acetazolamide. Based on these findings, he was diagnosed with PTC secondary to the

GnRH agonist. Follow-up by the ophthalmologist one month after starting acetazolamide showed significant improvement of the papilledema.

Reviewer's comment: This case fulfills our Category I case definition criteria. This patient received a lumbar puncture with an opening pressure of 310 mm H2O, ophthalmological examination which revealed bilateral papilledema, normal neurological examination, and cranial MRI with no space occupying mass. Although the papilledema improved with the use of acetazolamide, it was unclear if therapy with leuprolide acetate was discontinued. In addition, this report did not provide information regarding the patient's past medical history or concomitant medications.

Literature case (Gul et al., 2016)[70]

A nine-year-old female was admitted because of breast development which had started ten months before. Rapid height growth, adult body odor, and vaginal discharge were reported. The patient had no history of drug use or chronic illness. On physical examination, weight was 34 kg, height 138.3 cm, and blood pressure 100/60 mm Hg. Thelarche Tanner stage 3, pubic hair stage 2, and axillary hair was not detected. Her BMI was normal (17.7 kg/m^2) and she did not have a history of recent weight gain. The patient's bone age was 10.5 years. On pelvic ultrasonography, the length of the uterus (45 mm) and ovarian volumes (2.5 ml and 3.1 ml) were observed in pubertal size. The hypophysis MRI was normal. Gonadotropin levels were within pubertal range (FSH 1.97 mIU/ml, LH 1 mIU/ml). The patient's bone age demonstrated fast progress of one and a half years in six months, and annual follow-up height growth was 7.5 cm. Triptorelin acetate 3.75 mg depot per month was started due to early puberty. The patient had headaches after the fourth dose and her blood pressure was 130/80 mmHg (>99th percentile). Past medical history revealed no history of hypertension and her blood pressure increased after treatment. Multiple measurements showed systolic and diastolic blood pressure in the range of 130-155/85-110 mm Hg. Other system examinations were normal. Complete blood count, renal function tests, and serum electrolyte levels were within normal limits. Echocardiography analysis and renal doppler ultrasound were normal. Plasma renin activity and aldosterone levels were within normal limits. There was no abnormality related to the patient's neurological examination except bilateral papilledema. On cranial MRI, space-occupying mass was not observed and the ventricular system was intact. The orbital section of the MRI revealed bilateral optic nerve enlargement. Lumbar puncture was performed and an elevated initial CSF opening pressure was detected (460 mm H_2O, normal range: 15-25 cm H_2O). Based on the findings, the patient was diagnosed with PTC and triptorelin therapy was discontinued. Except for the GnRH agonist, there were no other risk factors that might lead to PTC such as obesity, renal failure, or other drugs associated with PTC. The patient improved with acetazolamide and the CSF pressure and fundoscopic examinations returned to normal.

Reviewer's comment: This case fulfills our Category I case definition criteria. This patient developed IIH four months after receiving triptorelin acetate 3.75 mg monthly to treat CPP. She experienced symptoms consistent with a diagnosis of IIH including elevated opening pressure of 460 mm H_2O on lumbar puncture and bilateral papilledema on neurological examination. No space occupying mass was observed on MRI; however, the orbital area revealed bilateral optic nerve enlargement, which may be due to enlargement of the perioptic subarachnoid space as previously associated with IIH.[71] *The temporal relationship, and lack of an alternative etiology*

to explain the occurrence of IIH support a causal role of triptorelin with IIH. The patient also developed hypertension during triptorelin therapy, which resolved upon discontinuation, and in ranges not associated with hypertensive encephalopathy. Triptorelin is labeled for hypertension under the Adverse Reactions Postmarketing Experience section of product labeling.[72]

3.2 DRUG UTILIZATION

Please see Appendix B for a pediatric patient focused drug utilization review of GnRH agonists.[67]

3.3 LITERATURE SEARCH

The literature search in Table 3 retrieved ten citations from PubMed, and after de-duplication, a total of eight citations were obtained. Abstracts of these citations were reviewed to identify relevant articles for the development of IIH and GnRH agonists. Three citations reported the use of GnRH agonists for non-CPP indications. One citation did not pertain to the topic of this review. One citation reported GnRH agonist use in pediatric patients with limited information. One citation did not report the use of GnRH agonist and the remaining citation reported GnRH agonist use in an adult. The remaining citation by Gul et al[70] is discussed in Section 3.1.

3.4 APPLICANT'S EVALUATION

AbbVie Endocrinology conducted a signal evaluation for IIH associated with leuprolide acetate. The evaluation included a search of AbbVie's global safety database Adverse Event Global Information System (AEGIS) using the High Level Term (HLT) Intracranial pressure disorders to identify postmarketing cases through January 21, 2021, and the medical literature.

Postmarketing

Of the 44 cases identified in the AbbVie global safety database coded with a Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) from the above HLT, the Applicant noted the following:

- 29 were excluded from further analysis as the cases did not contain follow-up information since the data lock date of the previous assessment.
- Of the 15 remaining cases:
    - 4 cases were newly received after the data lock date of the previous assessment
        - 2 cases contained limited information
        - 1 case was confounded by endoscopic endonasal surgery for olfactory neuroblastoma and concomitant medications (e.g., hormone therapies)
        - 1 case had no alternate etiology [described as the publication that triggered the updated evaluation (Omar et al)][2]
    - 5 cases were assessed as no alternate etiology from the previous assessment
        - 3 cases were confounded by underlying disease e.g., obesity, family history of IIH or concomitant medications (e.g., potential contraceptive use)
        - 1 case reported benign intracranial hypertension in an adult female
        - 1 case had no alternate etiology [described as the publication that triggered the previous evaluation (Germano et al)][3]

- 6 cases reported a pediatric patient or indication of CPP if age was unknown
  - 1 case did not report IIH
  - 4 cases were confounded by underlying disease (e.g., obesity, papilledema, medulloblastoma, hydrocephalus) and malfunction of ventriculoperitoneal shunt
  - 1 case contained limited information

Scientific literature
AbbVie also included the publication by Omar et al[2] (FAERS 18649727) and Gazzaz et al[4] (FAERS 19098245) noted in Section 3.1 of the review.

AbbVie's conclusion
Based on a comprehensive review of the literature and postmarketing cases of IIH in the AbbVie global safety database, the Applicant concluded the evidence is sufficient to support a causal association between IIH and leuprolide acetate. The Applicant recommends a change to the product labeling for the CPP pediatric population treated with leuprolide acetate.

4 DISCUSSION

This review identified six cases in FAERS and the medical literature of IIH associated with the use of GnRH agonists including leuprolide acetate (4) and triptorelin (2). We will provide a separate discussion of IIH with the two GnRH agonists below.

Leuprolide acetate
The evidence from the FAERS cases supports an association between leuprolide acetate and IIH. The median time to onset from the initiation of leuprolide acetate to the onset of IIH was 135 days (range 60 days to 240 days). In one case the time to onset from the most recent dose increase of leuprolide acetate was 28 days. In two of the four cases IIH resolved with discontinuation of leuprolide although we acknowledge a VPS was used in one case. Acetazolamide in all cases was used to treat symptomatic IIH. In one of these cases the recurrence of IIH symptoms was triggered by the discontinuation of acetazolamide after leuprolide withdrawal. The withdrawal occurred within a three-month window when plasma concentrations of leuprolide would be expected to persist in the body, thereby causing a recurrence in symptoms. Eighteen months after discontinuation of leuprolide the symptoms resolved. One case reported resolution of IIH with acetazolamide, however, it was unclear whether leuprolide was discontinued. In the fourth case it was unclear if leuprolide therapy was discontinued. Although acetazolamide is an invalidating intervention affecting the interpretation of dechallenge information, it may be challenging to identify FAERS cases that do not report the use of acetazolamide, as this intervention is normally used to treat patients with IIH symptoms.[62] In the majority of cases, a lumbar puncture was performed where the median opening pressure was 380 mm H_2O (range 310-450 mm H_2O) in two cases. In one of these cases the opening pressure decreased to 140 mm H_2O after discontinuation of leuprolide acetate. In the third case a lumbar puncture was performed revealing "raised intracranial pressure" however no numeric value of the opening pressure was reported. Half of the cases were assessed as having no alternative etiology for the occurrence of IIH. One case did not provide information regarding the patient's past medical history or concomitant medications. In the other case IIH was confounded by underlying cerebellar medulloblastoma and concomitant use of somatropin

(Genotropin) which is labeled for intracranial hypertension in the Warnings and Precautions and Adverse Reactions section of product labeling.[73] The specificity of the case definition utilized in this review allowed us to capture true cases of IIH including three cases that reported elevated CSF opening pressures on lumbar puncture and four cases that were reported by a physician or neurologist.

Triptorelin

Two cases reported the onset of IIH associated with the use of triptorelin to treat CPP. In the first case the time to onset was 120 days from the initiation of triptorelin to onset of the event. An elevated CSF opening pressure of 460 mm H_2O on lumbar puncture was reported in this case. The event resolved upon discontinuation of triptorelin with medical treatment. This patient had no reported risk factors that could explain the occurrence of IIH such as obesity, renal failure, or concomitant medications. The other case reported the onset of "benign intracranial hypertension" in a 5-year-old female three days after the initiation of triptorelin to treat CPP. It was unknown if triptorelin was discontinued and outcome of the event was also unknown. This patient was reported to be overweight with a weight of 30 kg, BMI of 21 (units not provided), and adiposity in the trunk and abdomen.[74] The dose of triptorelin was not reported, however, the authors recommended weight-based dosing, especially in obese children, to avoid clinically relevant adverse drug reactions such as benign intracranial hypertension in pediatric patients.

Drug Utilization

Drug utilization patterns of GnRH agonist use from 2014 – 2016 (Appendix B) showed that the majority of use among pediatric patients (aged 0-17 years) was for leuprolide acetate (Lupron Dept-Ped®) followed by histrelin (Supprelin LA®), and nafarelin (Synarel®).[67] This finding is consistent with the FAERS data which showed that Lupron Depot Ped was the most commonly reported GnRH agonist in our case series reporting pediatric patients with CPP. Lupron Depot-Ped also accounted for the majority of patients aged 6-12 with a prescription and or medical procedure claim, followed by Supprelin LA and Synarel. Note that the drug use review was conducted in 2016 and did not include triptorelin pamoate (Triptodur®), which received FDA approval in 2017.

Case Series Demographics

Notably all the patients in our case series were female. The national annual incidence (95% CI) of IIH in children aged 1–16 years was 0.71 (0.57 to 0.87) per 100,000 population increasing with age and weight to 4.18 and 10.7 per 100,000 in obese boys and girls aged 12–15 years, respectively.[19] There is a strong female predominance of children evaluated for precocious puberty. In a retrospective review of 104 consecutive children referred for evaluation of precocious puberty, 87 percent were female.[75] Whether this represents a true biologic difference or referral bias is not understood. Given the incidence of IIH in patients with CPP is unknown, it is difficult to determine if female patients with CPP are at increased risk of developing IIH with the use of GnRH agonists. Most of the patients in our series were not overweight. Studies examining the differences between prepubertal and postpubertal IIH show that there is a strong female predominance and association with obesity in postpubertal IIH similar to idiopathic IIH in adults. Therefore, the relative lack of obesity in our case series, is consistent with IIH that is generally observed in prepubertal pediatric patients. Also, presenting symptoms of IIH may differ between children and adults. Headache is a less universal finding among younger children

compare with adults. Furthermore, in addition to abducens neuropathy, other cranial nerve deficits may be more common in prepubertal children than in older patients.[76]

Biological Plausibility

Although the etiology of IIH is unknown, increased serum testosterone, and increased CSF testosterone and androstenedione have been observed in women with IIH implicating the role of androgens in disease pathogenesis.[77] GnRH agonists cause a short-term increase of sex steroids that may result in a hypercoagulable state, and it has been hypothesized this may predispose to dural venous sinus thrombosis.[78] Dural venous sinus thrombosis would have led to exclusion of such reports based on our case definition. Furthermore, no such reports were encountered. It has also been hypothesized that GnRH agonists may cause non-obstructive microthrombosis of the dural venous sinuses and consequently impede CSF drainage.[79,80] Such microthrombi may be of insufficient size to be seen on neuroimaging studies.

Considerations for Labeling

The Applicant proposed the addition of IIH (PTC) to the Warnings and Precautions and Adverse Reactions section of the USPI for Lupron Depot-Ped injection. According to the FDA guidance *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling*[81] factors to consider for inclusion in the Warnings and Precautions section of labeling include 1) the frequency of reporting 2) seriousness of the event 3) evidence of a causal association between drug and the adverse event. In general, IIH is a chronic and disabling condition characterized by elevated ICP. If untreated, severe outcomes such as papilledema and residual visual field deficits, including permanent visual loss could occur. It is a clinically significant adverse event because it has implications for prescribing decisions or patient management. Based on 1) serious outcomes associated with IIH in patients receiving leuprolide 2) clinical significance of the adverse event, and 3) evidence to support a causal association between IIH and leuprolide acetate, DPV concurs with the Applicant to add IIH to the Warnings and Precautions and Adverse Reactions section of the leuprolide acetate labeling for products indicated for CPP. DGE requested DPV to assess whether class labeling for the GnRH agonists approved for CPP is warranted. Based on the evidence in FAERS and the medical literature, DPV also recommends the addition of IIH to the Warnings and Precautions and Adverse Reactions section of the triptorelin labeling. Although we do not have cases for the other two GnRH agonists, nafarelin and histrelin, likely due to low usage for CPP in pediatric patients, the biological mechanism is similar for members of the drug class; therefore, DPV does not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

5 CONCLUSION

DPV concludes there is evidence to support a causal association between leuprolide acetate and IIH in pediatric patients diagnosed with CPP. The evidence also supports a causal association between triptorelin and IIH in pediatric patients diagnosed with CPP. DPV determined that the cases of IIH included in this review were clinically serious with medically important outcomes to warrant the inclusion of IIH in the Warnings and Precautions section of the leuprolide acetate and triptorelin labeling to communicate the risk of IIH in pediatric patients diagnosed with CPP. Although DPV did not identify cases for all members of the GnRH agonists, the biological mechanism is similar for members of the drug class; therefore, DPV does not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

DPV will continue to monitor the class of GnRH agonists for cases of IIH (PTC), with special attention to drugs with no identifiable cases in our current case series.

6 RECOMMENDATIONS

Based on this review DPV recommends the following

- Add information proposed by the Applicant regarding IIH (PTC) to Section 5 of leuprolide acetate product labeling (for products indicated for CPP):

  WARNINGS AND PRECAUTIONS:

  Pseudotumor cerebri (idiopathic intracranial hypertension)

  Pseudotumor cerebri (idiopathic intracranial hypertension) has been reported in pediatric patients receiving leuprorelin acetate. Monitor patients for signs and symptoms of pseudotumor cerebri, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea.

  (b) (4)

  ADVERSE REACTIONS

  Nervous system disorders: pseudotumor cerebri (idiopathic intracranial hypertension)

- Add language to the PATIENT COUNSELING INFORMATION regarding IIH such as unusual headaches and visual disturbances.

- Add similar language to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS AND PATIENT COUNSELING INFORMATION section of triptorelin product labeling (for products indicated for CPP).

- Although we do not have cases for all of the products within the pharmaceutical class of the GnRH agonists, we do not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. GNRH AGONISTS DRUG UTILIZATION REVIEW IN PEDIATRIC PATIENTS

GnRH agonist DUR review.pdf

Attached below is a Summary Table from the Drug Utilization Review on GnRH agonist utilization in pediatric patients as of July 2016, and the complete Review is attached above.

Number of pediatric patients with prescription and/or procedure claims* for Lupron Depot-PED, Supprelin LA and Synarel from study a sample, stratified by patient age (0-17 years)***, August 2014 through July 2016, annually**

	Year 1 (August 2014-July 2015)		Year 2 (August 2015-July 2016)	
	Patients (N)	Share (%)	Patients (N)	Share (%)
Total GnRH agonist	(b) (4)			
Lupron Depot-PED				
0-5 year				
6-12 year				
13-17 year				
Supprelin LA				
0-5|year				
6-12 year				
13-17 year				
Synarel				
0-5 year				
6-12 year				
13-17 year				

* Claims are from U.S.Commercial, medicare Part D, Cash, and Medicaid plans

**Claims data from sample of 80 pharmacies & 6,366 clinics, hospitals and physician offices

*** Age is at first claim during examined time period. Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years of age (17 years and 11 months).

Source: Symphony Health Solutions' Integrated Dataverse (IDV)™ . August 2014-July 2016. Extracted October 2016. File: 2016-2369-CPA-GnRH Agonist stratified by products (brand names) and age. 11.03.2016

8.3 APPENDIX C. FAERS LINE LISTING OF IIH IN PEDIATRIC PATIENTS WITH CPP CASE SERIES

Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
11/18/2015	11749523	1	ES-WATSON-2015-19356	Expedited (15-DAY)	5	Female	Spain	OT
09/28/2016	12789628	1	BR-ABBVIE-16P-020-1734538-00	Expedited (15-DAY)	9	Female	Brazil	OT
12/22/2020	18649727	1	KE-TOLMAR, INC.-20KE024472	Expedited (15-DAY)	6	Female	Kenya	OT
04/06/2021	19098245	2	CA-ABBVIE-21K-028-3846355-00	Expedited (15-DAY)	12	Female	Canada	OT
11/22/2002	3870025	1	THQ2002A01439	Expedited (15-DAY)	10	Female	Great Britain	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: OT=other medically significant

8.4 APPENDIX D. CASE CHARACTERISTICS OF IIH IN PEDIATRIC PATIENTS WITH CPP REPORTED WITH GNRH AGONIST USE (N=6)

FAERS Case # Literature report	Age (years)	Sex	Time to onset (days)	PT	Clinical signs and symptoms	Other diagnostic criteria	Country	Opening pressure (mm H_2O)	BMI (kg/m^2)	DC	Comments
LEUPROLIDE CASES (N=4)											
12789628	9	F	120	Idiopathic intracranial hypertension	Bilateral papilledema, abducens neuropathy, progressive visual loss, headache	Lumbar puncture, MRI unremarkable brain structures	Brazil	450	17	yes	Resolved with acetazolamide. and VPS
18649727	6	F	60	Idiopathic intracranial hypertension	Bilateral papilledema, visual loss	Fundoscopy MRI unremarkable brain structures	Kenya	NA	NR	yes	Acetazolamide DC after 6 weeks. No IIH recurrence
19098245	12	F*	150	Idiopathic intracranial hypertension	Bilateral papilledema	Lumbar puncture, MRI unremarkable brain structures	Canada	310	25	NR	Discontinuation status unknown. IIH resolved
3870025	10	F	240	Idiopathic intracranial hypertension	Headache	Lumbar puncture	Great Britain	"raised ICP"	NR	unclear	Medulloblastoma and concomitant somatropin. Discontinuation status unknown IIH not resolved
TRIPTORELIN CASES (N=2)											
11749523	5	F	3	Idiopathic intracranial hypertension	Headache, vomiting	MRI unremarkable brain structures	Spain	NA	21	NR	Overweight Discontinuation status unknown. IIH outcome unknown
Gul et al	9	F	120	Idiopathic intracranial hypertension	Bilateral papilledema, hypertension	Lumbar puncture, MRI unremarkable brain structures	Turkey	460	18	yes	Resolved with acetazolamide

*Transgender male, birth assigned female
Abbreviations: BMI=body mass index, DC=discontinued, F=female, ICP=intracranial pressure, IIH=idiopathic intracranial hypertension, MRI=magnetic resonance imaging, NA=not applicable, NR=not reported, PT=preferred term, VPS=ventriculoperitoneal shunt

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/s/

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U.S. FOOD & DRUG
ADMINISTRATION

FY 2020

PERFORMANCE REPORT TO CONGRESS

for the

Prescription Drug User Fee Act

Commissioner's Report

I am pleased to present to Congress the Food and Drug Administration's (FDA's or the Agency's) fiscal year (FY) 2020 Prescription Drug User Fee Act (PDUFA) performance report. This report marks the 28th year of PDUFA and the third year of PDUFA VI (which covers FY 2018 through FY 2022).

This report presents updated data on FDA's progress in meeting FY 2019 performance goals, preliminary data on FDA's progress in meeting FY 2020 review performance goals, and data on other commitments under PDUFA VI as of September 30, 2020.

FY 2020 turned out to be a unique year, creating unforeseen challenges and obstacles due to the COVID-19 pandemic. Despite an increased workload, the use of expedited development and review pathways for new therapeutics to address the public health emergency, and a remote workforce, FDA rose to the challenge and maintained its high level of performance in meeting PDUFA goals and initiatives.

FDA continues its longstanding commitment to meeting all PDUFA performance goals related to human drug review. In FY 2020, the Agency engaged in sustained efforts to recruit and hire new talent for the human drug review program to better enable FDA to meet increasing demands on the program, particularly in the area of meeting management goals. Moving forward into FY 2021, FDA will continue to enhance the program's staffing and strengthen efforts to improve the program's performance while maintaining a focus on ensuring that safe, effective, and high-quality new drugs and biological products are reviewed in an efficient and predictable time frame.

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs

Acronyms

ARIA – Active Risk Identification and Analysis
BEST – Biologics Effectiveness and Safety Initiative
BLA – Biologics License Application
BT – Breakthrough Therapy
BQP – Biomarkers Qualification Program
BTD – Breakthrough Therapy-Designated
CBER – Center for Biologics Evaluation and Research
CDER – Center for Drug Evaluation and Research
CE – Continuing Education
CID – Complex Innovative Design
COA – Clinical Outcome Assessment
DDT – Drug Development Tool
EHR – Electronic Health Record
EMA – European Medicines Agency
EOP – End of Phase
ESG – Electronic Submissions Gateway
ETASU – Elements to Assure Safe Use
FDA – Food and Drug Administration
FD&C Act – Federal Food, Drug, and Cosmetic Act
FDARA – FDA Reauthorization Act of 2017
FTE – Full-Time Equivalent
FY – Fiscal Year (October 1 to September 30)
IMEDS – Innovation in Medical Evidence Development and Surveillance
IND – Investigational New Drug
IT – Information Technology
MAPP – Manual of Policies and Procedures
MIDD – Model-Informed Drug Development
NDA – New Drug Application
NISS – Newly Identified Safety Signal (NISS)
NME – New Molecular Entity
OC – Office of the Commissioner
ORA – Office of Regulatory Affairs

PD – Position Description

PDUFA – Prescription Drug User Fee Act

POC – Point of Contact

RDT – Rare Diseases Team

REMS – Risk Evaluation and Mitigation Strategy

RMAT – Regenerative Medicine Advanced Therapies

RWE – Real-World Evidence

SOP – Standard Operating Procedure

SOPP – Standard Operating Policy and Procedure

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Executive Summary

The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 and authorized the Food and Drug Administration (FDA or the Agency) to collect user fees from pharmaceutical and biotechnology companies for the review of certain human drug and biological products. In return, FDA committed to certain review performance goals, procedural and processing goals, and other commitments that are part of the Agency's agreement with the regulated industry.

PDUFA has been reauthorized by Congress every 5 years. The fifth reauthorization (known as PDUFA VI) occurred on August 18, 2017, when the President signed into law the FDA Reauthorization Act of 2017. As directed by Congress, FDA developed proposed enhancements for PDUFA VI in consultation with drug industry representatives, patient and consumer advocates, health care professionals, and other public stakeholders. These discussions led to the current set of performance goals for the fiscal year (FY) 2018 to FY 2022 period, detailed in a document commonly known as the PDUFA VI Commitment Letter.[1]

This report summarizes FDA's performance results in meeting PDUFA goals and commitments for FY 2019 and FY 2020. Specifically, this report updates performance data for submissions received in FY 2019 (initially reported in the FY 2019 PDUFA Performance Report)[2] and presents preliminary data on FDA's progress in meeting FY 2020 goals. Updates on FDA's accomplishments related to additional PDUFA VI commitments for FY 2020 and historical review trend data are also included. Appendices include details of review cycle data on all original new drug applications (NDAs) and biologics license applications (BLAs) approved during FY 2020, the number and characteristics of applications filed by review division, and definitions of key terms used in this report. In addition, descriptions of the various submission types are included on page 4 of this report.

The estimated[3] median approval times for priority and standard NDAs and BLAs received in FY 2019 decreased compared to the estimated median approval times for priority and standard NDAs and BLAs received in FY 2018. The preliminary data show that the percentage of priority and standard applications filed in FY 2019 and approved during the first review cycle were 73 percent and 68 percent, respectively.

Achievements in FY 2020

In March 2020, FDA experienced the unexpected onset of a public health emergency, the impact of which continued through the remainder of that fiscal year. The COVID-19 pandemic resulted in a shift to 100 percent virtual work for the majority of the Agency's staff. The Agency appropriately shifted limited resources to prioritize work focused on addressing the pandemic.

[1] www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf.
[2] www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm2007449.htm.
[3] The median approval time is estimated because an application can receive an approval after multiple review cycles, thus impacting the median approval time for all applications in a given receipt cohort. Some applications may be approved several years after their original receipt.

Also, the Agency experienced a significant increase of 17 percent in PDUFA workload. For example, in FY 2020, there was a 24 percent increase in formal meeting requests alone. Despite all this, FDA is on track to meet or exceed all its review performance goals for the FY 2020 cohort.

Review Performance Results

The FY 2019 cohort had a workload of 2,916 goal closing actions. FDA met or exceeded the 90 percent performance level for 11 of the 12 review performance goals for FY 2019.

For the FY 2020 cohort, FDA had completed 2,006 actions as of September 30, 2020. FDA is currently meeting or exceeding 12 of the 12 review performance goals for FY 2020. With 1,420 submissions currently under review and still within the PDUFA goal date, FDA has the potential to meet or exceed all 12 review performance goals for FY 2020.

Procedural and Processing Performance Results

For the FY 2019 cohort, FDA's workload for activities related to procedural and processing goals and commitments (i.e., meeting management, procedural responses, and procedural notifications) totaled 10,196 actions. FDA met or exceeded the performance level for 9 of the 20 procedural and processing goals for FY 2019.

For the FY 2020 cohort, FDA is currently meeting or exceeding 7 of the 20 procedural and processing goals. With 1,322 submissions currently under review and still within the PDUFA goal date, FDA has the potential to meet or exceed 7 of the 20 procedural and processing goal commitments for FY 2020.

Additional PDUFA VI Commitments

During FY 2020, FDA made significant progress implementing other important PDUFA VI commitments, including enhancing patient input and benefit-risk assessments in regulatory decision-making, enhancing regulatory science, exploring the use of real-world evidence, enhancing regulatory decision tools to support drug development and review, enhancing and modernizing FDA's drug safety system, and improving the efficiency of human drug review through the required electronic submission and standardization of electronic drug application data. These achievements, as well as information about FDA's information technology accomplishments, are included in this report.

To highlight just a few of these achievements, there were a number of important PDUFA commitments completed in FY 2020, including the following:

- Published guidances addressing combination products, the collection of patient and caregiver input on drug development, drug development tools, and complex innovative trial design,

- Published a final report on the assessment of FDA-sponsor communication practices during the IND stage of drug/biologic development, and
- Held public meetings to discuss use of real-world evidence, patient-focused drug development, the use of Sentinel (FDA's medical product safety surveillance system), and financial transparency and efficiency.

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Introduction

On August 18, 2017, the President signed the FDA Reauthorization Act of 2017 (FDARA) into law, which included the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) for fiscal year (FY) 2018 through FY 2022, known as PDUFA VI. PDUFA VI continues to provide the Food and Drug Administration (FDA or the Agency) with a consistent source of funding to help maintain a predictable and efficient review process for human drugs and biological products. In return forthis funding, FDA agreed to certain review performance goals, such as reviewing and acting on new drug application (NDA) and biologics license application (BLA) submissions within predictable time frames.

Since the enactment of PDUFA I in 1992, FDA has used PDUFA resources to significantly reduce the time needed to evaluate new drugs and biological products without compromising its rigorous standards for a demonstration of safety, efficacy, and quality of these products before approval. The efficiency gains under PDUFA have revolutionized the drug review process in the United States and enabled FDA to ensure more timely access to innovative and important new therapies for patients.

More information on the history of PDUFA is available on FDA's website.[4]

Information Presented in This Report

This report presents PDUFA performance and workload information for two different types of goals: (1) the review of applications and other submissions pertaining to human drugs and biological products and (2) meeting management and other procedural goals related to responses and notifications in the human drug review process. PDUFA workload information for these goals is included in the tables that follow. Significant components of the PDUFA workload (such as reviews of investigational new drug (IND) applications, labeling supplements, and annual reports, as well as the ongoing monitoring of drug safety in the postmarket setting) are not captured by PDUFA goals and are therefore not presented in this report.

PDUFA performance information related to achieving these two types of goals includes reviews of submissions pending from the previous fiscal year as well as reviews of submissions received during the current fiscal year. This report presents the final performance results for the FY 2019 cohort of submissions based on actions completed in FY 2019 and FY 2020. In addition, this report includes the preliminary performance results for the FY 2020 cohort of submissions that had actions completed or due for completion in FY 2020. Final performance for the FY 2020 cohort will be presented in the FY 2021 PDUFA Performance Report and will include actions for submissions still pending within the PDUFA goal date as of September 30, 2020.

The following information refers to FDA's performance presented in this report.

[4] www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm2007449.htm.

- The following terminology is used throughout this document:

    - *Application* means a new, original application.
    - *Supplement* means a request to approve a change in an application that has been approved.
    - *Resubmission* means a resubmitted application or supplement in response to a complete response, approvable, not approvable, or tentative approval letter.
    - *New molecular entities (NMEs)* refer only to NMEs that are submitted for approval under NDAs (not BLAs).
    - *Submission* applies to all of the above.
    - *Action* refers to an FDA decision on any of the above, including an approval, a tentative approval, a complete response, or withdrawal of the submission by the sponsor.

- Under PDUFA VI, the preliminary counts of NMEs in workload tables for the current fiscal year may not reflect the final determination of NME status for that fiscal year. FDA often receives multiple submissions for the same NME (e.g., different dosage forms). All such submissions are initially designated as NMEs, and once FDA approves the first of the multiple submissions, the other submissions will be designated as non-NMEs, and workload numbers will be appropriately updated in later years.

- The data presented in this report do not include biosimilar INDs or biosimilar BLAs. These data are presented in the annual Biosimilars User Fee Act (BsUFA) Performance Reports located on FDA's website.[5]

- FDA files applications only that are sufficiently complete to permit a substantive review. The Agency makes a filing decision within 60 days of an original application's receipt by FDA. FDA's review of an application begins once the application is received. For NME NDAs and original BLAs reviewed under the program (see the PDUFA VI Commitment Letter[6] for more information), the PDUFA clock begins after the conclusion of the 60-day filing period. For all other submissions, the PDUFA clock begins upon FDA's receipt of the application.

- FDA annually reports PDUFA performance data for each fiscal year receipt cohort (defined as submissions filed from October 1 to September 30 of the following year). In each fiscal year, FDA receives submissions that will have associated goals due in the following fiscal year. For these submissions, FDA's performance data will be reported in subsequent fiscal years, either after the Agency takes an action or when the goal becomes overdue, whichever comes first.

- Submission types (e.g., responses to clinical holds) with shorter (e.g., 30-day) review-time goals tend to have a larger percentage of reviews completed by the end of the fiscal

[5] www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm384244.htm.
[6] www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf.

year, and these submissions types' preliminary performance data are a more reliable indicator of their final performance results. However, submission types (e.g., standard NME NDA/BLA) with longer (e.g., within 10 months of the 60-day filing date) review-time goals tend to have a smaller percentage of reviews completed, and these submission types' preliminary performance data are a less reliable indicator of their final performance results.

- Final performance results for FY 2019 submissions are shown as the percentage of submissions that were reviewed within the specified goal timeline. Submission types with 90 percent or more submissions reviewed by the goal date are shown as having met the goal.

- Preliminary performance results for FY 2020 submissions are shown as the percentage of submissions reviewed on time as of September 30, 2020, excluding actions pending within the PDUFA goal date. Submission types with a current performance result of 90 percent or more reviewed by the goal date are shown as currently meeting the goal. The highest possible percent of reviews that may be completed on time (i.e., the highest possible performance results) if all non-overdue pending reviews are completed within the goal is also shown.

- Filed applications and supplements include submissions that have been filed or are in pending filing status. Data do not include submissions that are unacceptable for filing because of nonpayment of user fees, have been withdrawn within 60 days of receipt, or have been refused to file.

- FY 2020 workload and performance figures include applications that are identified as *undesignated*, which means they are still within the 60-day filing date and have not yet had a review designation, standard or priority, made.

- For resubmitted applications, the applicable performance goal is determined by the fiscal year in which the resubmission is received, rather than the year in which the original application was submitted.

- Unless otherwise noted, all performance data are as of September 30, 2020.

- Definitions of key terms used throughout this report can be found in Appendix E.

Submission Types Included in This Report

- **NDA** – When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA an NDA. The application must contain data from specific technical viewpoints for review, including chemical, pharmacological, medical, biopharmaceutical, and statistical. If the NDA is approved, the product may be marketed in the United States.
- **NME** – An NME is an active ingredient that contains no active moiety that has been previously approved by FDA in an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or has been previously marketed as a drug in the United States.
- **BLA** – A BLA is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and the clinical effects of a biological product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.
- **Resubmission** – A resubmitted original application or supplement is a complete response to an FDA action letter that addresses all identified deficiencies.
- **Supplement** – A supplement is an application to allow a company to make changes in a product that already has an approved NDA or to seek FDA approval for new uses of an approved drug. The Center for Drug Evaluation and Research (CDER) must approve all major NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are still being met.
- **Source:** www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm.

Review Workload: FY 2015 to FY 2020

In the table below, preliminary workload numbers from FY 2020 are compared to the previous 5-year averages for original NDAs and BLAs, resubmissions, and supplements. FDA noted a large increase in the number of original priority NMEs and BLAs, original priority non-NME NDAs submissions, Class 2 resubmitted NDAs and BLAs, priority NDA and BLA efficacy supplements, Class 2 resubmitted NDA and BLA efficacy supplements, and NDA and BLA manufacturing supplements requiring prior approval in FY 2020.

Definitions of Class 1 and Class 2 resubmissions and other terms are found in Appendix E. The data presented in this section represent receipts by FDA of the submission types listed in the table.

Workload for Applications and Submissions

Submission Type	FY 15	FY 16	FY 17	FY 18	FY 19*	FY 20	FY 15 to FY 19 5-Year Average	FY 20 Compared to 5-Year Average
Original Priority NMEs and BLAs	25	23	31	48	44	53	34	56%
Original Standard NMEs and BLAs	32	24	22	22	35	31	27	15%
Original Priority Non-NME NDAs	9	12	24	16	16	22	15	47%
Original Standard Non-NME NDAs	84	72	81	69	68	52	75	-31%
Class 1 Resubmitted NDAs and BLAs	7	5	8	9	8	5	7	-29%
Class 2 Resubmitted NDAs and BLAs	37	31	49	50	41	57	42	36%
Priority NDA and BLA Efficacy Supplements	52	54	78	97	81	116	72	61%
Standard NDA and BLA Efficacy Supplements	136	145	173	177	197	180	166	8%
Class 1 Resubmitted NDA and BLA Efficacy Supplements	0	3	3	3	4	3	3	0%
Class 2 Resubmitted NDA and BLA Efficacy Supplements	11	11	11	11	2	20	9	122%
NDA and BLA Manufacturing Supplements Requiring Prior Approval	765	842	968	992	973	1,191	908	31%
NDA and BLA Manufacturing Supplements Not Requiring Prior Approval	1,614	1,475	1,540	1,610	1,450	1,696	1,538	10%

* FY 2019 numbers were changed to reflect updates to the data presented in the FY 2019 PDUFA Performance Report.

Final FY 2019 Review Goal Performance Results

The final FY 2019 review goal performance results are presented in the table below. The final performance results for submission types that met the goal (i.e., 90 percent or more actions were completed by the goal date) are shown in bold text. FDA met or exceeded the 90 percent performance level for 11 of the 12 review performance goals in FY 2019.

Submission Type	Goal: Act on 90 Percent Within	Total	FY 2019 Performance
Original Priority NMEs and BLAs	6 months of filing date	44 of 44 on time	**100%**
Original Standard NMEs and BLAs	10 months of filing date	33 of 33 on time	**100%**
Original Priority non-NME NDAs	6 months	16 of 16 on time	**100%**
Original Standard non-NME NDAs	10 months	67 of 68 on time	**99%**
Class 1 Resubmitted NDAs and BLAs	2 months	7 of 8 on time	88%
Class 2 Resubmitted NDAs and BLAs	6 months	37 of 41 on time	**90%**
Priority NDA and BLA Efficacy Supplements	6 months	78 of 81 on time	**96%**
Standard NDA and BLA Efficacy Supplements	10 months	178 of 196 on time	**91%**
Class 1 Resubmitted NDA and BLA Efficacy Supplements	2 months	4 of 4 on time	**100%**
Class 2 Resubmitted NDA and BLA Efficacy Supplements	6 months	2 of 2 on time	**100%**
NDA and BLA Manufacturing Supplements Requiring Prior Approval	4 months	953 of 973 on time	**98%**
NDA and BLA Manufacturing Supplements Not Requiring Prior Approval	6 months	1,436 of 1,450 on time	**99%**

Final FY 2019 Review Goal Performance Details

The following tables detail the final performance data for the FY 2019 cohort of submissions. These data include the number of submissions reviewed *on time* (i.e., acted on by the PDUFA goal date) or *overdue* (i.e., acted on past the goal date or pending past the goal date) and the final *percent on time* (i.e., final performance with no actions pending within the PDUFA goal date). The performance data presented here have been updated from the preliminary performance information reported in the FY 2019 PDUFA Performance Report.

Original Applications

Original Application Type	Goal: Act on 90 Percent Within	Filed	On Time	Overdue	Percent on Time
Priority NMEs & BLAs	6 months of filing date	44	44	0	100%
Standard NMEs & BLAs	10 months of filing date	35	33	0	100%*
Priority Non-NME NDAs	6 months	16	16	0	100%
Standard Non-NME NDAs	10 months	68	67	1	99%

* Two NMEs are still pending within goal. This table represents data as of September 30, 2020.

Resubmitted Original Applications

Resubmitted Application Type	Goal: Act on 90 Percent Within	Received	On Time	Overdue	Percent on Time
Class 1	2 months	8	7	1	88%
Class 2	6 months	41	37	4	90%

Efficacy Supplements

Efficacy Supplement Type	Goal: Act on 90 Percent Within	Filed	On Time	Overdue	Percent on Time
Priority	6 months	81	78	3	96%
Standard	10 months	197	178	18	91%*

* One efficacy supplement is still pending within goal. This table represents data as of September 30, 2020.

Resubmitted Efficacy Supplements

Resubmitted Efficacy Supplement Type	Goal: Act on 90 Percent Within	Received	On Time	Overdue	Percent on Time
Class 1	2 months	4	4	0	100%
Class 2	6 months	2	2	0	100%

Manufacturing Supplements

Manufacturing Supplement Type	Goal: Act on 90 Percent Within	Filed	On Time	Overdue	Percent on Time
Prior Approval Required	4 months	973	953	20	98%
Prior Approval Not Required	6 months	1,450	1,436	14	99%

Preliminary FY 2020 Review Goal Performance Results

The preliminary FY 2020 review goal performance results are presented in the table below.

- The *progress* (i.e., the number of reviews completed) and the total number of submissions received for each submission type are shown in the second column. *Current performance* includes submissions reviewed *on time* (i.e., acted on by the PDUFA goal date) or *overdue* (i.e., acted on past the goal date or pending past the goal date). The current performance results for submission types with a greater proportion of reviews completed will be more representative of the final performance results. The *highest possible final performance* is the best potential final performance result, which accounts for actions pending within the PDUFA goal date.

- The current performance results for submission types that are meeting the performance goal (i.e., 90 percent or more reviews were completed by the goal date) as of September 30, 2020, are shown in bold text. FDA is currently meeting or exceeding the 90 percent performance level for all 12 review performance goals.

- If all non-overdue pending submissions are reviewed on time, FDA will achieve the performance results presented in the Highest Possible Final Performance column. FDA has the potential to meet or exceed the 90 percent performance level for all 12 review performance goals.

Submission Type	Progress*	Goal: Act on 90 Percent Within	FY 2020 Current Performance	Highest Possible Final Performance
Original Priority NMEs and BLAs	18 of 48 complete	6 months of filing date	**94%**	98%
Original Standard NMEs and BLAs	1 of 31 complete	10 months of filing date	**100%**	100%
Original Priority non-NME NDAs	8 of 12 complete	6 months	**100%**	100%
Original Standard non-NME NDAs	7 of 52 complete	10 months	**100%**	100%
Class 1 Resubmitted NDAs and BLAs	5 of 5 complete	2 months	**100%**	100%
Class 2 Resubmitted NDAs and BLAs	30 of 57 complete	6 months	**90%**	95%
Priority NDA and BLA Efficacy Supplements	58 of 105 complete	6 months	**100%**	100%
Standard NDA and BLA Efficacy Supplements	54 of 180 complete	10 months	**100%**	100%
Class 1 Resubmitted NDA and BLA Efficacy Supplements	2 of 3 complete	2 months	**100%**	100%
Class 2 Resubmitted NDA and BLA Efficacy Supplements	11 of 20 complete	6 months	**91%**	95%
NDA and BLA Manufacturing Supplements Requiring Prior Approval	812 of 1,191 complete	4 months	**98%**	98%
NDA and BLA Manufacturing Supplements Not Requiring Prior Approval	1,000 of 1,696 complete	6 months	**99%**	99%

* This column does not include undesignated applications in the total. Undesignated applications have only pending status.

Preliminary FY 2020 Review Goal Performance Details

The following detailed performance information for the FY 2020 cohort submissions includes the number of submissions *filed*, reviewed *on time* (i.e., acted on by the PDUFA goal date), and *overdue* (i.e., acted on past the goal date or pending past the goal date). The number of submissions not yet acted on but still pending within the PDUFA goal date (*pending within goal*) is also provided, along with the highest possible percent of reviews that may be completed on time (*highest possible percent on time*).

Original Applications

Original Application Type	Goal: Act on 90 Percent Within	Filed	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Priority NMEs & BLAs	6 months of filing date	48	17	1	30	94%	98%
Standard NMEs & BLAs	10 months of filing date	31	1	0	30	100%	100%
Priority Non-NME NDAs	6 months	12	8	0	4	100%	100%
Standard Non-NME NDAs	10 months	52	7	0	45	100%	100%
Review Priority Undesignated*	N/A	15	--	--	15	--	--
Total		158	33	1	124	--	--

* These applications have not yet received a review priority designation.

Resubmitted Original Applications

Resubmitted Application Type	Goal: Act on 90 Percent Within	Received	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Class 1	2 months	5	5	0	0	100%	100%
Class 2	6 months	57	27	3	27	90%	95%

Efficacy Supplements

Efficacy Supplement Type	Goal: Act on 90 Percent Within	Filed	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Priority	6 months	105	58	0	47	100%	100%
Standard	10 months	180	54	0	126	100%	100%
Review Priority Undesignated*	N/A	11	--	--	11	--	--

* These applications have not yet received a review priority designation.

Resubmitted Efficacy Supplements

Resubmitted Efficacy Supplement Type	Goal: Act on 90 Percent Within	Received	On Time	Overdue	Pending Within Goal	Current Percent On Time	Highest Possible Percent On Time
Class 1	2 months	3	2	0	1	100%	100%
Class 2	6 months	20	10	1	9	91%	95%

Manufacturing Supplements

Manufacturing Supplement Type	Goal: Act on 90 Percent Within	Filed	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Prior Approval Required	4 months	1,191	793	19	379	98%	98%
Prior Approval Not Required	6 months	1,696	990	10	696	99%	99%
Review Priority Undesignated*	N/A	0	--	--	0	--	--

* These applications have not yet received a review priority designation.

Procedural and Processing Workload: FY 2015 to FY 2020

The FY 2020 procedural and processing workload, which includes activities related to meeting management, procedural responses, and procedural notifications, is compared to the previous 5-year averages in the table below. The upward trend of meeting management workload continued into FY 2020.

A new category of Type B meeting, Type B End of Phase (EOP), was created under PDUFA VI; therefore, when comparing PDUFA VI (i.e., FY 2019 and FY 2020) data to previous years' data, it is important to combine both Type B meeting categories. This new category also included a new meeting metric, Type B (EOP) Preliminary Response. Meeting type definitions and other terms can be found in Appendix E. The table shows updated final FY 2019 performance and presents new reporting required under PDUFA VI.

Beginning in FY 2019, FDA committed to establish timelines for the review and comment on protocols for Human Factor studies of combination drug-device and biologic-device products. This additional goal is reflected in the number of procedural and processing goals reported.

Meeting Management, Procedural Responses, and Procedural Notifications Workload

Submission/Request Type	FY 15	FY 16	FY 17	FY 18	FY 19*	FY 20	FY 15 to FY 19 5-Year Average	FY 20 Compared to 5-Year Average
Type A Meeting Requests	121	135	175	146	153	279**	146	91%
Type B Meeting Requests	1,664	1,738	1,850	1,609	1,725	2,390	1,717	39%
Type B (EOP) Meeting Requests	--	--	--	343	343	346	--†	--†
Type C Meeting Requests	1,237	1,372	1,391	1,403	1,550	1,663	1,391	20%
Type A Meetings Scheduled	107	123	159	127	130	244**	129	89%
Type B Meetings Scheduled	1,204	1,183	1,293	945	936	877	1,112	-21%
Type B (EOP) Meetings Scheduled	--	--	--	324	325	316	--†	--†
Type C Meetings Scheduled	603	596	660	640	732	684	646	6%
Type A Written Response	--	--	--	6	6	13	--†	--†
Type B Written Response	382	469	482	578	719	1,384	526	163%
Type B (EOP) Written Response	--	--	--	14	11	25	--†	--†
Type C Written Response	546	658	652	686	728	877	654	34%
Type B (EOP) Preliminary Response	--	--	--	303	305	300	--†	--†
Meeting Minutes	1,517	1,500	1,679	1,541	1,638	1,511	1,575	-4%

Submission/Request Type	FY 15	FY 16	FY 17	FY 18	FY 19*	FY 20	FY 15 to FY 19 5-Year Average	FY 20 Compared to 5-Year Average
Responses to Clinical Holds	161	232	193	199	197	264	196	35%
Major Dispute Resolutions	15	17	20	23	28	35	21	67%
Special Protocol Assessments	231	215	173	160	158	149	187	-20%
Review of Proprietary Names Submitted During IND Phase	178	158	176	159	212	223	177	26%
Review of Proprietary Names Submitted with NDA/BLA	213	202	255	228	230	250	226	11%
Human Factors Protocol Submissions	--	--	--	--	70	79	--†	--†

* FY 2019 numbers were changed to reflect updates to the data presented in the FY 2019 PDUFA Performance Report.
** Some meeting requests and the subsequent scheduling of meetings are for requests where the type cannot be initially determined. There were 101 undesignated meetings counted as Type A meeting *requests* and *scheduled* in the table above. Performance in all categories will change once designations are made for these requests and scheduling and will be updated in the FY 2021 PDUFA Performance Report.
† Because of changing reporting requirements, no past average is presented for this area.

Final FY 2019 Procedural and Processing Performance Results

The table below presents the final performance results for FY 2019 submissions in meeting goals related to meeting management, procedural responses, and procedural notifications. The final performance results for submission types that met the goal (i.e., 90 percent or more reviews were completed by the goal date) are shown in bold text. FDA exceeded the performance level for 9 of the 20 procedural and processing goals in FY 2019.

Submission/Request Type	Goal: 90 Percent	Total	FY 2019 Performance
Type A Meeting Requests	Respond within 14 days	137 of 153 on time	**90%**
Type B Meeting Requests	Respond within 21 days	1,577 of 1,725 on time	**91%**
Type B (EOP) Meeting Requests	Respond within 14 days	282 of 343 on time	82%
Type C Meeting Requests	Respond within 21 days	1,375 of 1,550 on time	89%
Type A Meetings Scheduled	Schedule within 30 days	92 of 130 on time	71%
Type B Meetings Scheduled	Schedule within 60 days	613 of 936 on time	65%
Type B (EOP) Meetings Scheduled	Schedule within 70 days	247 of 325 on time	76%
Type C Meetings Scheduled	Schedule within 75 days	553 of 732 on time	76%
Type A Written Response	Respond within 30 days	4 of 6 on time	67%
Type B Written Response	Respond within 60 days	581 of 719 on time	81%

Submission/Request Type	Goal: 90 Percent	Total	FY 2019 Performance
Type B (EOP) Written Response	Respond within 70 days	8 of 11 on time	73%
Type C Written Response	Respond within 75 days	591 of 728 on time	81%
Preliminary Response for Type B (EOP) Meetings	Issue no later than 5 days prior to meeting date	264 of 305 on time	87%
Meeting Minutes	Issue within 30 days after meeting date	1,506 of 1,634 on time	**92%**
Responses to Clinical Holds	Respond within 30 days	189 of 197 on time	**96%**
Major Dispute Resolutions	Respond within 30 days	27 of 28 on time	**96%**
Special Protocol Assessments	Respond within 45 days	149 of 158 on time	**94%**
Review of Proprietary Names Submitted During IND Phase	Review within 180 days	203 of 212 on time	**96%**
Review of Proprietary Names Submitted with NDA/BLA	Review within 90 days	225 of 230 on time	**98%**

Submission/Request Type	Goal: 50 Percent	Total	FY 2019 Performance
Human Factors Protocol Submissions	Respond within 60 days	62 of 70 on time	**89%**

Final FY 2019 Procedural and Processing Goal Performance Details

The following tables detail the final performance data for the FY 2019 cohort of submissions. These data include the number of submissions reviewed *on time* (i.e., acted on by the PDUFA goal date) or *overdue* (i.e., acted on past the goal date or pending past the goal date) and the final *percent on time* (i.e., final performance with no actions pending within the PDUFA goal date). The performance data presented here have been updated from the preliminary performance information reported in the FY 2019 PDUFA Performance Report.

Meeting Management

Type	Goal: 90 Percent	Received*	On Time	Overdue	Percent on Time
Type A Meeting Requests	Respond within 14 days	153	137	16	90%
Type B Meeting Requests	Respond within 21 days	1,725	1,577	148	91%
Type B (EOP) Meeting Requests	Respond within 14 days	343	282	61	82%
Type C Meeting Requests	Respond within 21 days	1,550	1,375	175	89%
Type A Meetings Scheduled	Schedule within 30 days	130	92	38	71%
Type B Meetings Scheduled	Schedule within 60 days	936	613	323	65%
Type B (EOP) Meetings Scheduled	Schedule within 70 days	325	247	78	76%
Type C Meetings Scheduled	Schedule within 75 days	732	553	179	76%
Type A Written Response	Respond within 30 days	6	4	2	67%
Type B Written Response	Respond within 60 days	719	581	138	81%
Type B (EOP) Written Response	Respond within 70 days	11	8	3	73%
Type C Written Response	Respond within 75 days	728	591	137	81%
Preliminary Response for Type B (EOP) Meetings	Issue no later than 5 days prior to meeting date	305	264	41	87%
Meeting Minutes	Issue within 30 days after meeting date	1,638	1,506	128	92%†

* Not all meeting requests are granted; therefore, the number of meetings scheduled may differ from the number of meeting requests received. Not all scheduled meetings are held; therefore, the number of meeting minutes may differ from the number of meetings scheduled.

† Four meeting minutes are still pending within goal. This table represents data as of September 30, 2020.

Responses to Clinical Holds

Goal	Received	On Time	Overdue	Percent on Time
Respond to 90 percent within 30 days	197	189	8	96%

Major Dispute Resolutions

Goal	Responses*	On Time	Overdue	Percent on Time
Respond to 90 percent within 30 days	28	27	1	96%

* This figure represents the number of FDA-generated 30-day responses to requests for review that have been received. This figure is not representative of the number of unique appeals received that have been reviewed as there may be more than one response to an original appeal.

Special Protocol Assessments

Goal	Received	On Time	Overdue	Percent on Time
Respond to 90 percent within 45 days	158	149	9	94%

Special Protocol Assessment Resubmissions

SPAs with Resubmissions	Applications with 1 Resubmission	Applications with 2 Resubmissions	Applications with 3 Resubmissions	Applications with 4 Resubmissions	Total Resubmissions
28	23	5	0	0	33

Drug/Biological Product Proprietary Names

Submission Type	Goal: 90 Percent	Received	On Time	Overdue	Percent on Time
Submitted During IND Phase	Review and respond within 180 days	212	203	9	96%
Submitted with NDA/BLA	Review and respond within 90 days	230	225	5	98%

Human Factor Protocol Submissions

Submission Type	Goal: 50 Percent	Received	On Time	Overdue	Percent on Time
Human Factors Protocol Submissions	Respond within 60 days	70	62	8	89%

Preliminary FY 2020 Procedural and Processing Performance Results

The table below presents preliminary performance results for FY 2020 submissions in achieving goals related to meeting management, procedural responses, and procedural notifications as outlined under PDUFA VI.

- The *progress* (i.e., the number of review activities completed or pending overdue) and the total number of submissions received for each submission type are shown in the second column. *Current performance* includes the number of submissions reviewed *on time* (i.e., acted on by the PDUFA goal date) or *overdue* (i.e., acted on past the goal date or pending past the goal date). *Highest possible final performance* is the best potential final performance result, which accounts for actions pending within the PDUFA goal date.
- The current performance results for submission types that are meeting the performance goal as of September 30, 2020, are shown in bold text. FDA is currently meeting or exceeding the performance level for 7 of the 20 procedural and processing goals. If all pending submissions are reviewed on time, FDA has the potential to meet 7 of the 20 goals, as seen in the Highest Possible Final Performance column.

Submission/Request Type	Progress	Goal: 90 Percent	FY 2020 Current Performance	Highest Possible Final Performance
Type A Meeting Requests	198 of 279 complete	Respond within 14 days	83%	88%
Type B Meeting Requests	2,350 of 2,390 complete	Respond within 21 days	**92%**	92%
Type B (EOP) Meeting Requests	341 of 346 complete	Respond within 14 days	82%	83%
Type C Meeting Requests	1,630 of 1,663 complete	Respond within 21 days	89%	89%
Type A Meetings Scheduled	154 of 244 complete	Schedule within 30 days	69%	81%
Type B Meetings Scheduled	836 of 877 complete	Schedule within 60 days	74%	75%
Type B (EOP) Meetings Scheduled	307 of 316 complete	Schedule within 70 days	79%	80%
Type C Meetings Scheduled	646 of 684 complete	Schedule within 75 days	78%	79%
Type A Written Response	12 of 13 complete	Respond within 30 days	75%	77%
Type B Written Response	1,210 of 1,384 complete	Respond within 60 days	82%	85%
Type B (EOP) Written Response	19 of 25 complete	Respond within 70 days	79%	84%
Type C Written Response	695 of 877 complete	Respond within 75 days	79%	83%

Submission/Request Type	Progress	Goal: 90 Percent	FY 2020 Current Performance	Highest Possible Final Performance
Preliminary Response for Type B (EOP) Meetings	261 of 300 complete	Issue no later than 5 days prior to meeting date	81%	84%
Meeting Minutes	1,122 of 1,511 complete	Issue within 30 days after meeting date	**92%**	94%
Responses to Clinical Holds	235 of 264 complete	Respond within 30 days	**96%**	96%
Major Dispute Resolutions	33 of 35 complete	Respond within 30 days	88%	89%
Special Protocol Assessments	128 of 149 complete	Respond within 45 days	**96%**	97%
Review of Proprietary Names Submitted During IND Phase	133 of 223 complete	Review and respond within 180 days	**98%**	99%
Review of Proprietary Names Submitted with NDA/BLA	206 of 250 complete	Review and respond within 90 days	**100%**	100%

Submission/Request Type	Progress	Goal: 70 Percent	FY 2020 Current Performance	Highest Possible Final Performance
Human Factors Protocol Submissions	71 of 79 complete	Respond within 60 days	**90%**	91%

Preliminary FY 2020 Procedural and Processing Goal Performance Details

The following detailed performance information for FY 2020 cohort submissions includes the number of submissions *received*, reviewed *on time* (i.e., acted on by the PDUFA goal date), and *overdue* (i.e., acted on past the goal date or pending past the goal date). The number of submissions not yet acted on but still pending within the PDUFA goal date (*Pending Within Goal*) is also provided, along with the highest possible percent of reviews that may be completed on time (*Highest Possible Percent On Time*).

Meeting Management

Type	Goal: 90 Percent	Received*	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Type A Meeting Requests†	Respond within 14 days	279	164	34	81	83%	88%
Type B Meeting Requests	Respond within 21 days	2,390	2,163	187	40	92%	92%
Type B (EOP) Meeting Requests	Respond within 14 days	346	281	60	5	82%	83%
Type C Meeting Requests	Respond within 21 days	1,663	1,450	180	33	89%	89%
Type A Meetings Scheduled†	Schedule within 30 days	244	107	47	90	69%	81%
Type B Meetings Scheduled	Schedule within 60 days	877	621	215	41	74%	75%
Type B (EOP) Meetings Scheduled	Schedule within 70 days	316	243	64	9	79%	80%
Type C Meetings Scheduled	Schedule within 75 days	684	504	142	38	78%	79%
Type A Written Response	Respond within 30 days	13	9	3	1	75%	77%
Type B Written Response	Respond within 60 days	1,384	998	212	174	82%	85%
Type B (EOP) Written Response	Respond within 70 days	25	15	4	6	79%	84%
Type C Written Response	Respond within 75 days	877	547	148	182	79%	83%
Preliminary Response for Type B (EOP) Meetings	Issue no later than 5 days prior to meeting date	300	212	49	39	81%	84%
Meeting Minutes	Issue within 30 days after meeting date	1,511	1,035	87	389	92%	94%

* Not all meeting requests are granted; therefore, the number of meetings scheduled may differ from the number of meeting requests received. Not all scheduled meetings are held; therefore, the number of meeting minutes may differ from the number of meetings scheduled.

† Some meeting requests and subsequent scheduling of meetings are for requests where the type cannot be initially determined. There were 101 undesignated meetings counted as Type A meeting *requests*" and *scheduled* in the table above. Performance in all categories will change once designations are made for these requests and scheduling and will be updated in the FY 2021 PDUFA Performance Report.

Responses to Clinical Holds

Goal	Received	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Respond to 90 percent within 30 days	264	225	10	29	96%	96%

Major Dispute Resolutions

Goal	Responses*	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Respond to 90 percent within 30 days	35	29	4	2	88%	89%

* This figure represents the number of FDA-generated 30-day responses to requests for review that have been received. This figure is not representative of the number of unique appeals received that have been reviewed as there may be more than one response to an original appeal.

Special Protocol Assessments

Goal	Received	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Respond to 90 percent within 45 days	149	123	5	21	96%	97%

Special Protocol Assessment Resubmissions

SPAs with Resubmissions	Applications with 1 Resubmission	Applications with 2 Resubmissions	Applications with 3 Resubmissions	Applications with 4 Resubmissions	Total Resubmissions
15	14	1	0	0	16

Drug/Biological Product Proprietary Names

Submission Type	Goal: 90 Percent	Received	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Proprietary Names Submitted During IND Phase	Review and respond within 180 days	223	131	2	90	98%	99%
Proprietary Names Submitted with NDA/BLA	Review and respond within 90 days	250	205	1	44	100%*	100%*

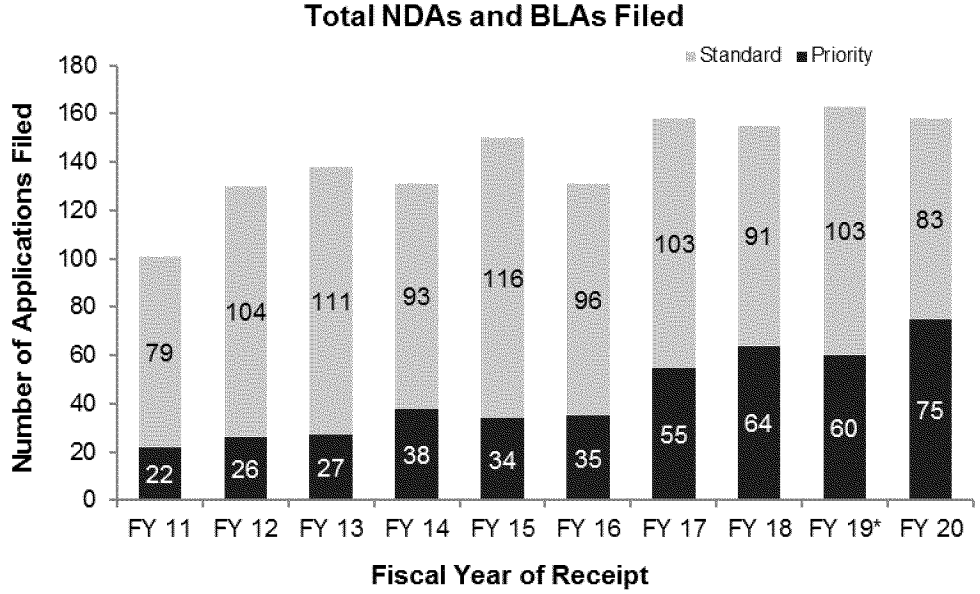
* The reported percentage is rounded up from 99.5%.

Human Factors Protocol Submissions

Submission Type	Goal: 70 Percent	Received	On Time	Overdue	Pending Within Goal	Current Percent on Time	Highest Possible Percent on Time
Human Factors Protocol Submissions	Respond within 60 days	79	64	7	8	90%	91%

PDUFA Trend Graphs

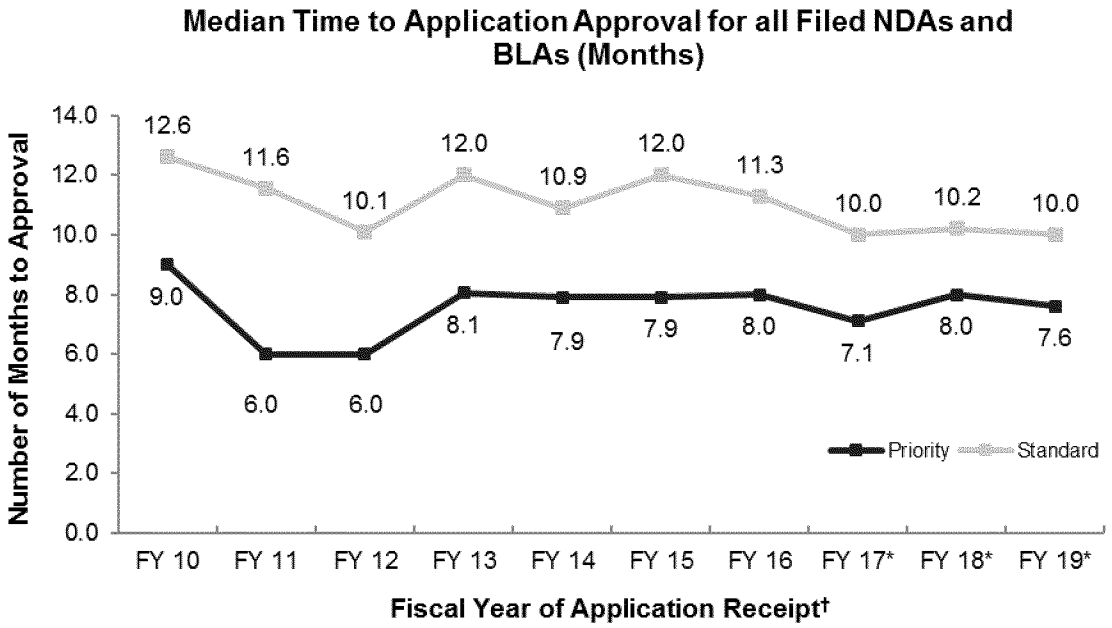
The number of NDAs and BLAs filed from FY 2011 to FY 2020 is presented in the graph below. The total number of all original applications (NDAs and BLAs) filed in FY 2020 decreased slightly from the number filed in FY 2019, and the total number of priority applications filed reached a new high in FY 2020.



* FY 2019 numbers were changed to reflect updates to the data presented in the FY 2019 PDUFA Performance Report.

The median total times to approval for priority and standard applications received from FY 2010 through FY 2019 are presented in the graph below.[7] The data represented in the graph are updated based on the approvals reported in Appendix A. FY 2020 data are too preliminary to estimate the median approval time.

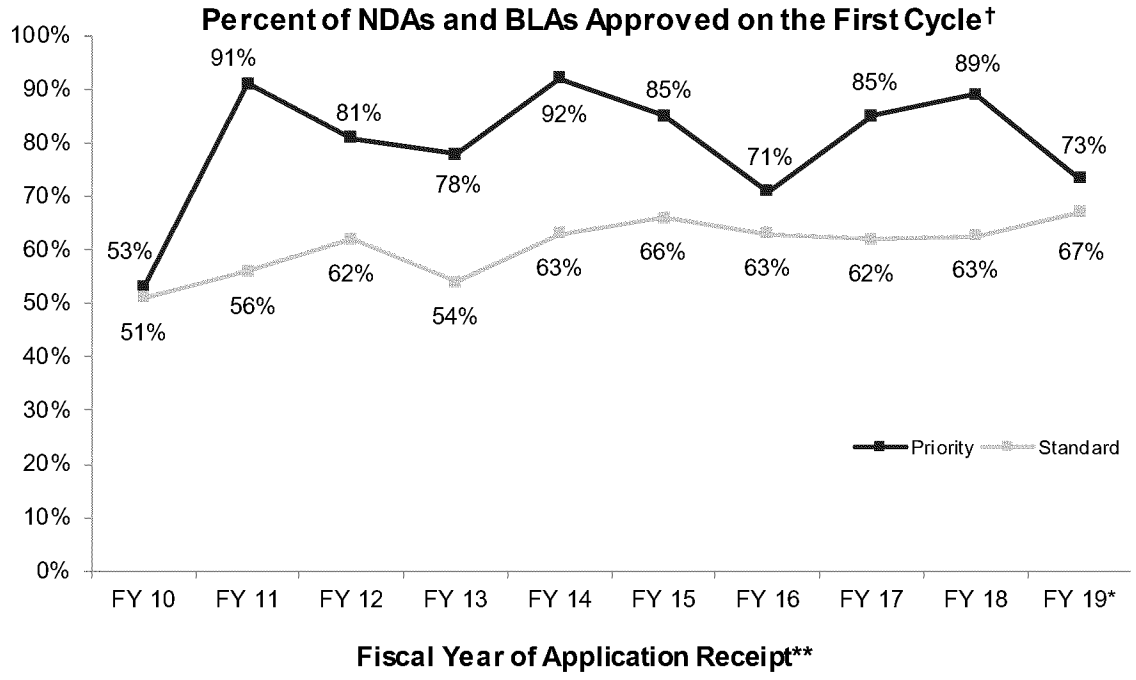
[7] The total time for applications that are approved in the first cycle includes only FDA response times. Applications that are approved after multiple review cycles include both FDA and sponsor times. The median total approval time is the median of all application times for a given cohort, including applications that have gone through multiple review cycles.



* The median approval times for the 3 most recent years are estimated.

† The data represented in this graph are based on the approvals reported in Appendix A.

The graph below depicts the percentages of priority and standard NDAs and BLAs approved in the first review cycle for the receipt cohorts from FY 2010 to FY 2019. These percentages are based on the approvals reported in Appendix A. The percentage of standard applications in first-cycle approvals increased in FY 2018 and FY 2019. For the FY 2019 cohort, which is still preliminary, 67 percent of standard applications were approved on the first cycle. First-cycle approvals for approved priority applications decreased in FY 2019, with 73 percent of approved priority applications being approved on the first cycle. The FY 2020 data are too preliminary to estimate the percent of first-cycle approvals.



* First-cycle approvals are still possible for FY 2019 standard applications, so the data are preliminary.
† The data were changed to reflect upates to the data presented in the FY 2019 PDUFA Performance Report.
** The data represented in this graph re based on the approvals reported in Appendix A.

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Additional PDUFA VI Commitments

Under Section VI of the PDUFA VI Commitment Letter, FDA committed to report its progress on the specific commitments identified in the following sections of the Commitment Letter:[8]

- Section I.I: Enhancing Regulatory Science and Expediting Drug Development,
- Section I.J: Enhancing Regulatory Decision Tools to Support Drug Development and Review,
- Section I.K: Enhancement and Modernization of the FDA Drug Safety System,
- Section II: Enhancing Management of User Fee Resources,
- Section III: Improving FDA Hiring and Retention of Review Staff, and
- Section IV: Information Technology Goals

Further, section 736B(a) of the FD&C Act, as amended by section 103 of FDARA, requires FDA to report on the Agency's performance under PDUFA VI.

FDA and industry designed these enhancements to improve the efficiency of drug development and the human drug review process. The progress reports in this section detail the work FDA performed in FY 2020 on commitments in Sections I.I-K of the Commitment Letter. In addition, this report includes updates on FDA's accomplishments under Section II: Enhancing Management of User Fee Resources, Section III: Improving FDA Hiring and Retention of Review Staff, and Section IV: Information Technology Goals. The Section II progress reports are duplicated in the FY 2020 PDUFA VI Financial Report. Each accomplishment includes a reference to a specific section of the Commitment Letter. External references are also provided to published guidances, meeting summaries, and other pertinent public information.

FDA is dedicated to the goals outlined in these sections of the Commitment Letter. When applicable, for each section, additional information is included on other activities FDA has conducted that are not specifically required but further the goals outlined in the Commitment Letter.

[8] www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf.

Section I.I: Enhancing Regulatory Science and Expediting Drug Development

Commitment Title	FY 2020 Accomplishments
I.I.1 Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development	• The contractor that FDA hired to perform a third-party assessment of communication between FDA and sponsors during drug development continued data collection efforts in FY 2020, including attending and assessing FDA-sponsor meetings and conducting post-meeting surveys and interviews with FDA review teams and sponsors (I.I.1.a). • FDA published the final report on the assessment of FDA-sponsor communication practices during the IND stage of drug/biologic development on June 17, 2020 (see www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-assessment-fda-sponsor-communication-practices-during-ind-stage-drugbiologic-development) (I.I.1.a). • FDA hosted a public meeting to present and discuss the findings of the report.

I.I.2 Ensuring Sustained Success of Breakthrough Therapy Program	• Under the Breakthrough Therapy (BT) Program,[9] FDA:
	  ○ Received 140 BT Designation Requests.
	  ○ Granted 66 BT Designation Requests.
	  ○ Approved 27 original and 8 supplemental marketing applications for BT-Designated (BTD) products.[10]
	• Under the Regenerative Medicine Advanced Therapies (RMAT) Program, FDA:
	  ○ Received 34 RMAT Designation Requests.
	  ○ Granted 11 RMAT Designation Requests.
	  ○ Granted no approvals for RMAT-Designated products.

I.I.3 Early Consultation on the Use of New Surrogate Endpoints	• FDA developed and fully implemented the internal process for the new Type C novel surrogate endpoint meeting. To date, FDA has had approximately nine requests for this new meeting type involving products by both Centers.
I.I.4 Advancing Drug Development of Drugs for Rare Diseases	• The Center for Drug Evaluation and Research's (CDER's) Rare Diseases Team (RDT) held meetings with the Center for Biologics Evaluation and Research (CBER) to coordinate efforts in documenting FDA's progress in advancing the development of drugs for rare diseases through review of applications/submissions, training, and stakeholder engagement activities. • In FY 2020, CDER's RDT was consulted or contributed to rare diseases programs in the majority of the Office of New Drugs review divisions. • At an annual training on Advancing Rare Disease Drug Development Through Innovative Thinking and Collaboration held in May 2020, a record 417 FDA staff were in attendance. The theme of the training was *Breaking Through the Silos*,

[9] www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm.

[10] Note that BTD approvals are tracked and posted on the FDA.gov website by calendar year (see www.fda.gov/drugs/nda-and-bla-approvals/breakthrough-therapy-approvals). However, the BT approval numbers included in this PDUFA report are reflective of FY 2020.

	focusing on regulatory and scientific considerations in rare disease drug development to increase an understanding of trial considerations in rare disease research to drug review practices. • Further, as part of training, in FY 2020, CDER's RDT initiated the Rare Disease Quarterly series, focusing on promoting awareness and sharing knowledge regarding drug development for rare diseases across the Centers. • In FY 2020, CDER's RDT launched the Zebragram, a monthly internal newsletter, distributed across FDA, highlighting innovative approaches to rare disease drug development, precedent-setting regulatory decisions, publications, and important upcoming rare disease events. • As part of furthering consistency (specifically with other regulatory agencies), CDER's RDT administers the International Rare Diseases Cluster, which includes FDA, European Medicines Agency, and Health Canada. Health Canada was added as a standing cluster participant in March 2020. Cluster meetings were held regularly to discuss rare disease product-specific and general topics to facilitate alignment across scientific evaluation requirements and drug development. Since the inception of the International Rare Diseases Cluster in September 2016, 43 cluster meetings have been held, covering approximately 124 agenda topics. • CDER's RDT continues to work on cross-cutting guidances regarding key issues for the Center concerning rare disease drug development. • CBER's Rare Disease Program continued the series of case study presentations of flexibility in the review of biological products as a CBER Rare Disease Coordinating Committee meeting activity. • CBER continues to track rare disease-related stakeholder engagement activities. In FY 2020, CBER staff participated in a minimum of 113 outreach activities intended to support development of biological products for rare diseases. These activities included presentations (60%), publications (19%), and poster/abstracts (21%). • In January 2020, CBER issued three rare disease-related final guidance documents regarding the development of gene therapy products. • On March 3, 2020, CBER held a public workshop, titled *Facilitating End-to-end Development of Individualized Therapeutics*, to foster the development of gene therapies and phage therapies for the treatment of rare diseases that affect one or a very small number of patients. • CBER continued to collaborate with CDER and the Office of Orphan Products Development in activities to advance the development of drugs and biological products for rare diseases, such as in planning for and providing the annual rare disease training for FDA review staff on May 28, 2020, and the public meeting *FDA Rare Disease Day 2020: Supporting the Future of Rare Disease Product Development* on February 24, 2020.
I.I.5 Advancing Development of Drug-Device and Biologic-Device Combination Products Regulated by CBER and CDER	• FDA continues to expand its hiring and enhance its training of staff to develop the capacity and capability to review combination products effectively across the Centers (I.I.5.a). • FDA published an independent contractor's final report of an assessment of combination drug products. The report included best practices and areas of improvement regarding submission procedures for human factors protocols and the review and

	submission of combination product applications (see Assessment of Combination Product Review Practices in PDUFA VI at www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-assessment-combination-product-review-practices-pdufa-vi) (I.I.5.g). • In December 2019, FDA published the draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products* (see www.fda.gov/media/133676/download) (I.I.5.h.i).
I.I.6 Enhancing Use of Real World Evidence for Use in Regulatory Decision-Making	• FDA satisfied the commitment to complete the public workshop *A Framework for Regulatory Use of Real-World Evidence (RWE)* in September 2017, and the Agency continues to host public meetings on RWE such as the two-day public workshop *Establishing a High-Quality Real-World Data Ecosystem* in July 2020 and *Considerations for the Use of Real-World Evidence to Assess the Effectiveness of Preventive Vaccines* on September 17-18, 2020. (PI.I.6.a). • FDA satisfied the commitment to initiate RWE activities in FY 2017 and continues to oversee additional demonstration projects and activities aimed at addressing evolving concerns and considerations in the use of RWE for regulatory decision-making. FY 2020-funded projects focused on improving methods for using electronic health records (PI.I.6.b). • FDA announced a funding opportunity in FY 2020 to solicit research on how to improve RWE for regulatory decision-making; 31 proposals were received, and 4 grants were awarded after scientific review. • FDA established an Intra-Departmental Delegation of Authority with the NIH to seek proposals—and funded two supplements in FY 2020 to existing NIH-funded trials—to better understand how current ethical and human subject protection frameworks can be applied to the use of RWE.

Section I.J: Enhancing Regulatory Decision Tools to Support Drug Development and Review

Commitment Title	FY 2020 Accomplishments
I.J.1 Enhancing the Incorporation of the Patient's Voice in Drug Development and Decision-Making	• FDA made progress on hiring goals related to strengthening staff capacity to facilitate development and use of patient-focused methods to inform drug development and regulatory decisions. In addition, FDA held monthly cross-disciplinary meetings to discuss reviews, guidances, and process changes; and staff provided presentations at several internal meetings and public meetings with a high attendance by FDA staff (I.J.1.a). • FDA continued the Standard Core Clinical Outcomes and Endpoints Grant Program that funds the development of core outcome sets in a variety of clinical divisions. The grant program also increases the familiarity and understanding of the Clinicial Outcome Assessment (COA) development within the divisions. As part of this program, 2 public meetings were held. (I.J.1.a). • In June 2020, FDA published a final guidance for industry, FDA staff, and other stakeholders entitled *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input*, describing approaches for collecting comprehensive and representative patient and caregiver input on the burden of disease and current therapy (see www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input) (I.J.1.b.v). • FDA gathered input from patients, patient advocates, academic researchers, expert practitioners, industry, and other stakeholders on COAs and on methods to better incorporate these assessments into endpoints that are considered significantly robust for regulatory decision-making (I.J.1.b.v). • FDA maintained and enhanced its repository of publicly available tools and resources for stakeholders (I.J.1.c).
I.J.2 Enhancing the Benefit-Risk Assessment in Regulatory Decision-Making	• FDA is in the process of developing guidance on the benefit-risk assessment for new drugs and biological products (I.J.2.c). • FDA awarded a contract to a third party to conduct an evaluation of the implementation of the benefit-risk framework in the human drug review program (I.J.2.d). • FDA published a manuscript entitled *FDA's Benefit–Risk Framework for Human Drugs and Biologics: Role in Benefit–Risk Assessment and Analysis of Use for Drug Approvals* (see doi.org/10.1007/s43441-020-00203-6). • FDA is participating in the CIOMS Working Group XII on Benefit-Risk Balance for Medicinal Products (see cioms.ch/working-groups/working-group-xii/).
I.J.3 Advancing Model-Informed Drug Development	• FDA selected proposals on a quarterly basis for which model-informed drug development (MIDD) would be needed to assess uncertainties regarding dosing, duration, and patient selection to help inform decision-making (I.J.3.c.ii). • The Office of Clinical Pharmacology conducted 13 industry meetings from October 2019 to September 2020 related to nine applications.

	• FDA will develop its regulatory science and review expertise and capacity in MIDD approaches. This staff will support the highly specialized evaluation of model-based strategies and development efforts (I.J.3.a).
	• The Office of Clinical Pharmacology launched the inaugural MIDD Education Seminar series designed to provide staff with a foundational understanding of MIDD approaches and their application in drug development and clinical practice (I.J.3.a).
	  ○ Inaugural MIDD Seminar Series, The Role of Model-Informed Drug Discovery and Development in Enhancing Public Health-State of the Art, Innovation or Disruptions, Dr. Stephan Schmidt, University of Florida, March 4, 2020, 163 attendees
	  ○ Pharmacometrics for Clinical Therapeutics: An Opportunity to Democratize the Science and Tooling in Quantitative Pharmacology, Dr. Vijay Ivaturi, University of Maryland, July 20, 2020, 161 attendees
	• The Office of Clinical Pharmacology also provided continuing education (CE) for staff through MIDD Science Rounds, yearly update, September 9, 2020, 117 CE, 772 attendees (I.J.3.a).
	• 20 scientific papers were published by FDA staff on the topic of advancing MIDD.

I.J.4 Enhancing Capacity to Review Complex Innovative Designs	• FDA developed staff capacity to enable processes to facilitate the appropriate use of complex adaptive, Bayesian, and other novel clinical trial designs (I.J.4.a).
	• FDA conducted four CE lectures for the Complex Innovative Design (CID) Seminar Series.
	• FDA reviewed and selected proposals on a quarterly basis that were prioritized based on trial design features and therapeutic areas of unmet need (I.J.4.b.ii):
	  ○ Received five CID meeting requests in FY 2020
	  ○ Reviewed six CID meeting requests in FY 2020
	  ○ Granted two CID meeting requests in FY 2020
	• FDA presented trial designs developed through the program as case studies at four professional meetings (I.J.4.b.iii).
	• FDA published a final guidance for industry entitled *Adaptive Design Clinical Trials for Drugs and Biologics* in December 2019 (I.J.4.d).
	• FDA revised, per public comment, the draft guidance for industry entitled *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products* (published September 2019).
	• FDA completed a draft CID meeting process standard operating procedure (SOP) (I.J.4.e).

I.J.5 Enhancing Capacity to Support Analysis Data Standards for Product Development and Review	• FDA developed an Analysis Data Standards training and resources site to provide statisticians/analysts with guidance, training, and standard processes for an efficient and effective application review (I.J.5.e). • In December 2019, FDA developed a Standard Operating Procedure related to the CID meeting program. The pilot is ongoing, and FDA will continue to revise the SOP accordingly (I.J.5.e). • FDA developed training videos on various topics related to Clinical Data Interchange Standards Consortium data standards (ADaM and SDTM) (I.J.5.a). • FDA participated in the review and development of Therapeutic Area User Guides and technical specification documents. (I.J.5.b).

	• FDA presented at five public workshops and conferences sponsored by standards development organizations. (I.J.5.d).
I.J.6 Enhancing Drug Development Tools Qualification Pathway for Biomarkers	• FDA administers three qualification programs (biomarkers (BQP), clinical outcome assessments, and animal models for use under the animal rule). Although the enhancement focused on biomarkers, the three programs work together in the development of interrelated process and policy. • BQP experienced continued interest and growth, with over 60 projects under development. In FY 2020, the program reviewed 19 submissions (13 Letters of Intent and six Qualification Plans). • BQP continued its extensive public engagement with key stakeholder groups (i.e., the FNIH Biomarkers Consortium, the Critical Path Institute, and the Innovative Medicines Initiative). Staff were invited to speak at over 20 scientific conferences. • FDA published a final guidance for industry and FDA staff on the qualification process for drug development tools, on November 25, 2020 (see www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff) (I.J.6.d). • FDA is developing the Evidentiary Framework guidance and a Biomarker Qualification Analytics guidance (I.J.6.d).

Section I.K: Enhancement and Modernization of the FDA Drug Safety System

Commitment Title	FY 2020 Accomplishments
I.K.1 Advancing Postmarketing Drug Safety Evaluation Through Expansion of the Sentinel System, and Integration into FDA Pharmacovigilance Activities	• Expand sources of data and enhance core capabilities (I.K.1.a) : FDA has been involved in the following actions: ○ Created a 5-year strategic plan to improve access to electronic health records (EHRs) and incorporate advanced analytics. ○ Added the National Patient-Centered Clinical Research Network (see pcornet.org/) and TriNetX (see trinetx.com/) to Sentinel; many other resources are available in the Sentinel Operations Center and the Innovation Center. ○ The Innovation Center is developing a new EHR-based distributed data network. ○ The Biologics Effectiveness and Safety Initiative (BEST) developed and operated by CBER (1) commenced the use of EHRs for post-market surveillance, (2) expanded BEST'saccess to multiple sources covering more than 50 million patients, (3) expanded BEST's access to administrative claims data sources (covering more than 200 million patients) with reduced data lag, (4) expanded BEST's access to on-demand, ad-hoc programming capabilities to accommodate simple and complex studies, (5) commenced the use of linked claims-EHR data sources covering more than 5 million patients to

	provide the capability for phenotype development and other activities. ○ BEST is utilizing new technologies such as machine learning and Natural Language Processing to extract more clinical information from EHR data sources to improve surveillance capabilities. ○ The BEST Initiative has built working relationships with scientific leaders in the field of pharmacoepidemiology and related fields, including participants from academia, industry, and other government agencies, to use their expertise as consultants and to utilize its resources to implement the most advanced and optimal methods and practices for the surveillance of medical products. • Enhance communication with sponsors and the public on methodologies for Sentinel queries (I.K.1.b): FDA completed the following actions: ○ Formalized the existing policies and processes for sponsor notifications in Manual of Policies and Procedures (MAPP) 6701.4 (see www.fda.gov/media/141216/download). ○ Continued to post all results, analytic packages, and analysis tools. ○ Hosted the Sentinel annual meeting with public trainings on tool use. ○ Developed a public website for the BEST Initiative (www.bestinitiative.org/) to post the initiative's work products for public view and access. • Facilitate public and sponsor access to Sentinel (I.K.1.c): FDA completed the following actions: ○ Shared the analytic center with Innovation in Medical Evidence Development and Surveillance (IMEDS). ○ Supported 15 IMEDS queries. (IMEDS benefits from FDA's routinely curated data network and incurs only marginal costs for queries.) ○ Held the annual Sentinel public workshops, with public training on tools (I.K.1.d). ○ Developed and posted sponsor notification MAPP 6701.4 (I.K.1.e) (see www.fda.gov/media/141216/download). • Facilitate integration of Sentinel into the human drug review program (I.K.1.f). FDA has been involved in the following actions: ○ Integrated into the approval letter the Active Risk Identification and Analysis (ARIA) sufficiency process, which is now integral to original and supplemental drug reviews. ○ Developed ARIA templates to improve the consistency of implementation. ○ Revised the postmarketing requirements industry guidance. ○ Developed a six-part, module-based, online training program to ensure that staff have a working knowledge of Sentinel, can identify when Sentinel can inform important regulatory questions, and are able to consistently participate in use of Sentinel to evaluate safety issues (I.K.1.g). ○ CBER revised its standard operating policy and procedure (SOPP) for developing postmarketing requirements and commitments (SOPP 8415) to formalize Sentinel sufficiency assessments in the drug

	review program (see https://www.fda.gov/media/90591/download). ○ CBER prepared a draft SOPP to formalize the manufacturer notification process before the protocol or final report of biologic products' safety and effectiveness studies are posted to the BEST website. This SOPP is in the final stage of being formally approved. • Analyze and report on FDA's use of Sentinel for regulatory purposes (I.K.1.h): FDA did the following: ○ Made ongoing updates to three web pages describing ongoing queries completed queries and regulatory impacts. ○ Made ongoing updates to the "Assessing ARIA's Ability to Evaluate a Safety Concern" web page containing ARIA sufficiency memos. (see www.sentinelinitiative.org/assessments/aria-overview/assessing-arias-ability-evaluate-safety-concern). ○ Reported on FDA's use of ARIA at four different public meetings. ○ Published lessons learned about ARIA sufficiency and next steps for improving distributed data networks in an article entitled *Using and improving distributed data networks to generate actionable evidence: the case of real-world outcomes in the Food and Drug Administration's Sentinel system* (see academic.oup.com/jamia/article/27/5/793/5819225).
I.K.2 Timely and Effective Evaluation and Communication of Postmarketing Safety Findings Related to Human Drugs	• FDA published MAPP 4121.3 *Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)* and launched the Lifecycle Safety Signal Tracker in CDER's Nexus to track NISS in April 2020 (I.K.2.a). • 600-plus CDER staff members have been trained on the NISS MAPP and on the Lifecycle Safety Signal Tracker (I.K.2.a). • FDA analyzed data and found 97.4 percent of application holders were notified, to the extent practicable, not less than 72 hours before the public posting of a safety notice under section 921 of the Food and Drug Administration Amendments Act of 2007 since Q3 (2019) and as described in MAPP 6700.9 and SOP 8420 (I.K.2.b.2).

Section II: Enhancing the Management of User Fee Resources

Commitment Title	FY 2020 Accomplishments
II.A Resource Capacity Planning and Modernized Time Reporting	• FDA published an independent evaluation of the PDUFA resource capacity planning adjustment methodology to assess changes in the resource and capacity needs of the human drug review program (II.A.3). The report was published on April 6, 2020 (see www.fda.gov/media/136606/download).

II.B Financial Transparency and Efficiency	• FDA published the FY 2020 PDUFA Five-Year Financial Plan Update in March 2020 (see www.fda.gov/about-fda/user-fee-reports/user-fee-five-year-financial-plans) (II.B.2). • FDA held a public meeting June 22, 2020, regarding this plan (see FDA's Financial Transparency and Efficiency of the Prescription Drug User Fee Act, Biosimilar User Fee Act, and Generic Drug User Fee Amendments web page at www.fda.gov/drugs/news-events-human-drugs/financial-transparency-and-efficiency-prescription-drug-user-fee-act-biosimilar-user-fee-act-and) (II.B.3).

Section III: Improving FDA's Hiring and Retention of Review Staff

Commitment Title	FY 2020 Accomplishments
III.A Completion of Modernization of the Hiring System Infrastructure and Augmentation of System Capacity	• The Agency implemented iBAPS as the position management system of record in 2018, and all funded vacancies are now captured and monitored in this central system. eClass was launched in 2018 as a central repository and position description (PD) management system. The Agency currently has over 2800 PDs within the classification tool that allows standardized PDs to be used and provides easy access to classified PDs to reduce the administrative burden.
III.B Augmentation of Hiring Staff Capacity and Capability	• Corporate recruiting has been deployed as an agency best practice by delivering the most qualified candidates for FDA mission-critical positions to the hiring manager. • The human resources contract support staff augmentation was awarded in 2017 and has continued each year thereafter. An additional inter-agency agreement with the Office of Personnel Management was awarded in 2019 to provide an additional human resources support mechanism for staff augmentation for the Agency.
III.C Complete Establishment of a Dedicated Function to Ensure Needed Scientific Staffing for Human Drug Review Program	• The Scientific Staffing Office was established in 2017. A scientist was appointed as the Associate Director for Scientific Staffing, and recruiters provide specialized placement and recruiting in FDA-related scientific fields. The fully staffed team was installed because of its expertise in recruiting in science and related fields. Through the team's affiliations and partnerships with academia and professional organizations, it is able to develop extensive resources to the Centers, as well as to professional job seekers in FDA-related scientific fields.
III.D Set Clear Goals for Human Drug Review Program Hiring	• FDA's FY 2020 hiring goal was for 58 FTEs, and 48 FTEs were onboarded (which was 83 percent of the FY 2020 hiring goal) (III.D.2). • FDA's hiring progress against this goal was posted on FDA's website (see www.fda.gov/industry/prescription-drug-user-fee-amendments/food-and-drug-administration-reauthorization-act-2017-fdara-hiring-data) (III.D.2). • During FY 2020, FDA additionally onboarded 16 FY 2019 FTEs, making progress towards FY 2019's outstanding hiring goal (which is at 93 percent of FY 2019 hiring goals) (III.D.2).

III.E Comprehensive and Continuous Assessment of Hiring and Retention	• FDA published the HR Interim Report on June 5, 2020, and held a public meeting on July 30, 2020 (see www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-interim-hiring-and-retention-assessment-report) (III.E.2).

Section IV: Information Technology Goals

Goal	FY 2020 Accomplishments
IV.B Improve the Predictability and Consistency of PDUFA Electronic Submission Processes	• FDA maintained its targets for and its measure of the Electronic Submissions Gateway's (ESG's) overall availability. • FDA maintained target time frames (1) for the expected submission upload duration(s) and (2) between key milestones and notifications. • FDA maintained its submission upload status (e.g., successfully processed or rejected) to sender/designated contacts. • FDA maintained its ESG operational status on its public website. • FDA maintained its submission instructions to use in the event of an ESG service disruption. • Through quarterly meetings, FDA invited industry to provide feedback and participate in user acceptance testing and provided ample advance notification on systems and process changes. • FDA maintained metrics on its quarterly ESG performance and its monthly volume of submissions on its public website.
IV.C Enhance Transparency and Accountability of FDA Electronic Submission and Data Standards Activities	• FDA held quarterly meetings with industry on both electronic submissions and data standards (IV.C.1). These meetings included discussions of PDUFA milestones and metrics (see www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-information-technology-goals-and-progress) (IV.C.4) • FDA planned a public meeting entitled Electronic Submissions and Data Standards for April 22, 2020; however, the meeting was canceled due to COVID-19 (IV.C.2). • FDA updated the data standards and action plan on a quarterly basis (IV.C.5).

Additional PDUFA VI Review Program Reporting

Hiring and Placement of New PDUFA VI Staff at FDA

FY 2020's hiring and placement of new staff at FDA under PDUFA VI are reported on a quarterly basis and posted on the FDARA hiring performance web page.[11] Starting in FY 2020, FDA will report its progress in hiring new staff to support new initiatives in the annual PDUFA Financial Report, as per the PDUFA VI Commitment Letter.

Rationale for PDUFA Program Changes

FDARA amended the FD&C Act to require the reporting of certain information relating to PDUFA program changes in the annual performance report starting with FY 2020.

Specifically, section 903(a) of FDARA added section 736(b)(4) to the FD&C Act, which requires the annual PDUFA performance report to include the following:

(A) data, analysis, and discussion of the changes in the number of full-time equivalents (FTEs) hired as agreed upon in the letters described in section 101(b) of the Prescription Drug User Fee Amendments of 2017 and the number of FTEs funded by budget authority at FDA by each division within CDER, CBER, the Office of Regulatory Affairs (ORA), and the Office of the Commissioner (OC);

(B) data, analysis, and discussion of the changes in the fee revenue amounts and costs for the process for the review of human drugs, including identifying drivers of such changes; and

(C) for each of the CDER, CBER, ORA, and OC, the number of employees for whom time reporting is required and the number of employees for whom time reporting is not required.

The information below fulfills these reporting requirements.

A. Changes in the number of FTEs hired as agreed in the PDUFA VI Commitment Letter and the number of FTEs funded by budget authority at FDA by division within CDER, CBER, ORA, and OC

This section addresses the requirement to provide data, an analysis, and a discussion of the changes in the number of FTEs hired as agreed upon in the letters described in section 101(b) of the Prescription Drug User Fee Amendments of 2017 and the number of FTEs funded by budget authority at the FDA by each division within CDER, CBER, ORA, and OC.

[11] www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm604305.htm.

Changes in the number of FTEs hired as agreed upon in the PDUFA VI Commitment Letter

FDA is committed to hiring 230 FTEs from FY 2018 to FY 2022 as agreed upon in the PDUFA VI Commitment Letter. FDA has successfuly hired 193 FTEs of the 230 FTEs (84 percent) as of December 19, 2020. The data in the following table shows the total number of FTEs hired towards the FY 2019 and FY 2020 hiring targets as agreed upon in the PDUFA VI Commitment Letter and the change in the number of FTE hires from FY 2019 to FY 2020.

The hiring of FTEs decreased from FY 2019 to FY 2020 due to the hiring goal targets decreasing from 74 FTEs in FY 2019 to 58 FTEs in FY 2020. FDA has successfully fulfilled 96 percent of its hiring target for FY 2019 and 88 percent of its hiring target for FY 2020 as of December 19, 2020. With a total of 37 FTEs remaining to hire through FY 2022, FDA will continue hiring new FTEs to meet its commitments as agreed upon in the PDUFA VI Commitment Letter.

Number of FTEs Hired as Agreed in the PDUFA VI Commitment Letter

Center	FY 2019 Hires*	FY 2020 Hires*	Change in Number of FTE Hires
CDER	57	39	-18
CBER	8	7	-1
ORA	0	0	0
OC/Other	6	5	-1

* A *hire* is defined as someone who has been confirmed as on board by the date indicated in a full-time position at the noted Center. Although some hires are recruited from outside the Center/FDA, a hire can also be a current Center/FDA employee who is changing positions within the Agency.

Number of FTEs funded by budget authority at FDA by division within CDER, CBER, ORA, and OC

The data in the table below show the change from FY 2019 to FY 2020 in the number of FTEs funded by budget authority at FDA by each division within CDER, CBER, ORA, and OC. This table reflects the number of FTEs funded by budget authority for the PDUFA VI program. For this table, *budget authority* refers to FDA's non-user fee annual appropriations. To address the requirement that information on the number of FTEs funded by budget authority be presented "by each division," the information in this table is broken down to the office level for the Centers, ORA, and OC. FDA uses a 2080-hour workload to equate to one FTE, and this calculation is reflected in the table below. Data for FY 2020 and the previous year, FY 2019, are presented and compared to show the change in the number of FTEs over the last 2 fiscal years committed to PDUFA work. The number of FTEs funded by budget authority for FY 2019 are those FTEs as of September 30, 2019. The number of FTEs funded by budget authority for FY 2020 are those FTEs as of September 30, 2020.

FDA reported a decrease in overall FTEs in FY 2020 compared to FY 2019. The decrease in reported FTEs was attributable to the impacts of COVID-19-related efforts. Although FDA saw

a decrease in reported FTEs in FY 2020, FDA will continue to increase staff to address the PDUFA VI program workload.

Center and Office	Number of PDUFA Program FTEs Funded by Budget Authority*		Change in Number of PDUFA Program FTEs Funded by Budget Authority
	FY 2019	FY 2020	
CDER			
Office of Communications	6.7	0.4	-6.3
Office of Compliance	36.9	28.5	-8.4
Office of the Center Director	2.9	0.8	-2.1
Office of Executive Programs	12.8	0.4	-12.4
Office of Generic Drugs	2.2	3.3	1.1
Office of Medical Policy	18.4	10.1	-8.3
Office of Management	5.2	1.3	-3.9
Office of New Drugs	142.1	157.3	15.2
Office of Pharmaceutical Quality	106.1	68.2	-37.9
Office of Regulatory Policy	23.0	6.5	-16.5
Office of Surveillance and Epidemiology	33.0	5.0	-28.0
Office of Strategic Planning	6.6	4.4	-2.2
Office of Information Management and Technology	0.4	0.1	-0.3
Office of Translational Sciences	66.2	55.4	-10.8
Other Offices	3.7	2.7	-1.0
WCF	49.8	43.2	-6.6
CDRH			
Office of Product Evaluation and Quality	7.7	1.6	-6.1
Office of Management	0.0	0.1	0.1
Office of Science and Engineering Laboratories	0.6	0.3	-0.3
WCF	0.7	0.8	0.1
CBER			
Office of Biostatistics and Epidemiology	20.1	17.9	-2.2

Office of Blood Research and Review	4.9	4.6	-0.3
Office of Compliance and Biologics Quality	17.4	19.4	2.0
Office of Tissues and Advanced Therapies	55.7	57.1	1.4
Office of Vaccines Research and Review	85.7	84.8	-0.9
Office of Communication Outreach and Development	13.9	11.1	-2.8
Office of the Center Director	20.7	17.3	-3.4
Office of Management	23.5	19.2	-4.3
Other Offices	1.9	1.8	-0.1
WCF	0.7	33.1	32.4
OC			
OC Immediate Office	6.6	4.4	-2.2
Office of the Chief Counsel	15.1	14.9	-0.2
Office of the Chief Scientist	8.8	9.9	1.1
Office of Clinical Policy and Programs	8.1	22.0	13.9
Office of External Affairs	5.1	5.0	-0.1
Office of Health Informatics	1.3	1.7	0.4
Office of International Programs	3.1	0.1	-3.0
Office of Operations	7.8	8.8	1.0
Office of Policy Legislation and International Affairs	11.0	11.5	0.5
Office of Special Medical Programs	22.4	0.2	-22.2
WCF	18.3	17.1	-1.2
ORA			
Office of Pharmaceutical Quality Operations	89.1	89.9	0.8
WCF	8.8	8.6	-0.2

* This table includes PDUFA program FTE calculated through working capital fund (WCF) assessments for certain centrally administered services provided to CDER, CBER, ORA, and OC. Because many employees under OC and WCF do not report time, an average cost per OC and WCF FTE was applied to derive the number of PDUFA program FTEs funded by budget authority.

B. Changes in the fee revenue amounts and costs for the review process

Section 903(a) of FDARA amended the FD&C Act to require FDA to provide data, an analysis, and a discussion of the changes in the fee revenue amounts and costs for the process for the review of human drugs, including identifying drivers of such changes. Accordingly, the table below provides data for the PDUFA fee revenue amounts and process costs for FY 2019 and FY 2020, as well as the changes in these amounts from FY 2019 to FY 2020. Relevant information about the data provided is as follows:

- *Fee Revenue Amounts* represent FDA's net collection of human drug user fees.
- *Review Process Costs* represents FDA's total expenditure of the PDUFA program.
- Numbers are provided for both the most recent fiscal year (FY 2020) and the prior fiscal year (FY 2019). Although FDARA does not explicitly require this data, they do provide relevant context necessary to interpret the required information.

In FY 2020, FDA had net collections of $1.020 billion in prescription drug user fees, spent $1.075 billion in user fees for the human drug review process, and carried a cumulative balance of $194 million forward for future fiscal years. Detailed financial information for the PDUFA user fee program can be found in the FY 2020 PDUFA Financial Report.

The process for setting the annual target revenue is set forth in the statute. For FY 2020, the base revenue amount is $1,001,479,592. The FY 2020 base revenue amount is adjusted for inflation and for the resource capacity needs for the process for the review of human drug applications (the capacity palnning adjustment). An additional dollar amount specified in the statute (see section 736(b)(1)(F) of the FD&C Act) is then added to provide for additional FTE positions to support PDUFA VI initiatives. The revenue amount may be adjusted further, if necessary, to provide for sufficient operating reserves of carryover user fees. Finally, the FY 2020 amount is adjusted to provide for additional direct costs yielding a total adjusted fee revenue amount of $1,074,714,059, which funds PDUFA VI initiatives.

In FY 2020, PDUFA costs increased by approximately $41 million from FY 2019. The increase in PDUFA costs was attributed to growth in payroll and operating costs. The payroll cost increase is attributable to payroll cost inflation and salary increases due to Centers and Offices converting employees under CURES Authority pay bands.

Changes in the Fee Revenue Amounts and Review Process Costs

Fiscal Year	FY 2019	FY 2020	Change from FY 2019 to FY 2020
Net Fiscal Year Collections	$1,015,152,012	$1,020,229,037	1%
Review Process Costs	$1,430,338,888	$1,471,144,928	3%

C. Number of Employees for Whom Time Reporting Is Required

Section 903(a) of FDARA amended the FD&C Act to require FDA to provide—for CDER, CBER, ORA, and OC—the number of employees for whom time reporting is required and the number of employees for whom time reporting is not required. Accordingly, the table below provides the number of employees within CDER, CBER, ORA, and OC who are required to report their time and those who are not required to report their time as of September 30, 2020.

These data reflect time reporting across all employees in each entity, rather than only those engaged in PDUFA program activities.

Time Reporting Requirements for FY 2020

Center	FTEs for Whom Time Reporting Is Required	FTEs for Whom Time Reporting Is Not Required
CDER	5,256	15
CBER	1,119	8
ORA	3,106	1,682
OC	483	1,479

Appendices

Appendix A: List of Approved Applications

This appendix includes detailed review histories of the NDA and BLA submissions approved under PDUFA VI in FY 2020. Approvals are grouped by priority designation and submission year and listed in order of total approval time. *Approval time* is presented in months and includes each review cycle's time with FDA, time with the sponsor, and the total time on that application.

Review histories of the NDA and BLA submissions approved prior to FY 2020 can be found in the appendices of the earlier PDUFA performance reports.[12]

Please note: When determining total time, FDA calculates the number of months and rounds to the nearest tenth. Therefore, when cycle times are added, rounding discrepancies may occur.

Because months consist of varying numbers of days, FDA uses the average number of days in a month to calculate review time in months. Therefore, a submission may appear overdue even though it was approved on the goal date. For example, the submission *tazemetostat* on page A-3 was received on May 23, 2019, and had an 8-month review goal date of January 23, 2020, as it was reviewed under the program and had priority review. FDA approved the submission on the goal date, but because FDA uses the average number of days in a month to calculate months, the time taken to review the submission is reported as 8.1 months, and the review appears overdue.

Terms and Coding Used in Tables in This Appendix

Action Codes:

AE = Approvable
AP = Approved
CR = Complete Response
NA = Not Approvable
TA = Tentative Approval
WD = Withdrawn

▲ Denotes Class 1 Resubmission (2-month review-time goal)

△ Denotes Class 2 Resubmission (6-month review-time goal)

◊ Expedited review and TA of an NDA by FDA for fixed dose combinations and co-packaged antiretroviral medications as part of the President's Emergency Plan for AIDS Relief

♦ Application reviewed under the program with review goals starting from the 60-day filing date, rather than the submission date

♯ Major amendment was received, which extended the action goal date by 3 months[13]

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[12] www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm2007449.htm.

[13] Under PDUFA VI, a major amendment can be received any time during the review cycle and extend the goal date by 3 months. If the review cycle occurred prior to FY 2013, the major amendment must have been received within 3 months of the action due date to extend the action goal date by 3 months.

FY 2020 Priority NDA and BLA Approvals (by Fiscal Year of Receipt)

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
Submitted in FY 2020							
TUKYSA (tucatinib)	SEATTLE GENETICS Inc.	Y	First	3.9	AP	3.9	Y♦
TABRECTA (capmatinib)	NOVARTIS PHARMACEUTICAL Corp.	Y	First	4.9	AP	4.9	Y♦
QINLOCK (ripretinib)	DECIPHERA PHARMACEUTICALS LLC	Y	First	5.1	AP	5.1	Y♦
RETEVMO (selpercatinib)	LOXO ONCOLOGY Inc.	Y	First	5.2	AP	5.2	Y♦
GAVRETO (pralsetinib)	BLUEPRINT MEDICINES Corp.	Y	First	5.4	AP	5.4	Y♦
JELMYTO (mitomycin)	UROGEN PHARMA Ltd.	N	First	5.9	AP	5.9	Y
XYWAV (calcium, magnesium, potassium, and sodium oxybates)	JAZZ PHARMACEUTICALS Inc.	N	First	6.0	AP	6.0	Y
TAZVERIK (tazemetostat)	EPIZYME Inc.	N	First	6.0	AP	6.0	Y
ZEPZELCA (lurbinectedin)	JAZZ PHARMACEUTICALS IRELAND Ltd.	Y	First	6.0	AP	6.0	Y♦
TIVICAY PD (dolutegravir)	VIIV HEALTHCARE Co.	N	First	6.0	AP	6.0	Y
XELJANZ (tofacitinib)	PFIZER Inc.	N	First	6.0	AP	6.0	Y
ONUREG (azacitidine)	CELGENE Corp.	N	First	6.0	AP	6.0	Y
TEPEZZA (teprotumumab-TRBW)	HORIZON THERAPEUTICS IRELAND DAC	Y	First	6.5	AP	6.5	Y♦
INQOVI (decitabine and cedazuridine)	OTSUKA PHARMACEUTICAL Co. Ltd.	Y	First	6.9	AP	6.9	Y♦
RUKOBIA (fostemsavir)	VIIV HEALTHCARE Co.	Y	First	7.0	AP	7.0	Y♦
MONJUVI (tafasitamab-CXIX)	MORPHOSYS US Inc.	Y	First	7.0	AP	7.0	Y♦
TECARTUS (brexucabtagene autoleucel)	KITE PHARMA Inc.	Y	First	7.4	AP	7.4	Y♦
VILTEPSO (viltolarsen)	NIPPON SHINYAKU Co. Ltd.	Y	First	8.0	AP	8.0	Y♦
LAMPIT (nifurtimox)	BAYER HEALTHCARE PHARMACEUTICALS Inc.	Y	First	8.0	AP	8.0	Y♦
DETECTNET (copper cu 64 dotatate injection)	RADIOMEDIX Inc.	Y	First	8.0	AP	8.0	Y♦
BLENREP (belantamab mafodotin-BLMF)	GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT Ltd. ENGLAND	Y	First	8.0	AP	8.0	Y♦
Submitted in FY 2019							
TRIKAFTA (elexacaftor/tezacaftor/ivacaftor)	VERTEX PHARMACEUTICALS Inc.	Y	First	3.1	AP	3.1	Y♦
ENHERTU (fam-trastuzumab deruxtecan-NXKI)	DAIICHI SANKYO Inc.	Y	First	3.7	AP	3.7	Y♦
BRUKINSA (zanubrutinib)	BEIGENE USA Inc.	Y	First	4.6	AP	4.6	Y♦

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
OXBRYTA (voxelotor)	GLOBAL BLOOD THERAPEUTICS Inc.	Y	First	5.0	AP	5.0	Y♦
PADCEV (enfortumab vedotin)	ASTELLAS PHARMA US Inc.	Y	First	5.1	AP	5.1	Y♦
ERVEBO (Ebola Zaire Vaccine, Live)	MERCK SHARP & DOHME Corp.	Y	First	5.1	AP	5.1	Y♦
GIVLAARI (givosiran)	ALNYLAM PHARMACEUTICALS Inc.	Y	First	5.6	AP	5.6	Y♦
potassium phosphates	FRESENIUS KABI USA LLC	N	First	6.0	AP	6.0	Y
TALICIA (omeprazole magnesium, amoxicillin and rifabutin)	REDHILL BIOPHARMA Ltd.	N	First	6.0	AP	6.0	Y
ADAKVEO (crizanlizumab-TMCA)	NOVARTIS PHARMACEUTICALS CORPORATION	Y	First	6.0	AP	6.0	Y♦
DIFICID (fidaxomicin)	CUBIST PHARMACEUTICALS LLC	N	First	6.1	AP	6.1	Y
PEMAZYRE (pemigatinib)	INCYTE Corp.	Y	First	6.6	AP	6.6	Y♦
AYVAKIT (avapritinib)	BLUEPRINT MEDICINES Corp.	Y	First	6.9	AP	6.9	Y♦
KOSELUGO (selumetinib)	ASTRAZENECA PHARMACEUTICALS LP.	Y	First	6.9	AP	6.9	Y♦
REBLOZYL (luspatercept – AAMT)	CELGENE CORPORATION	Y	First	7.2	AP	7.2	Y♦
TISSUEBLUE (brilliant blue g ophthalmic solution)	DUTCH OPHTHALMIC RESEARCH CENTER INTERNATIONAL BV	Y	First	7.7	AP	7.7	Y♦
TAUVID (flortaucipir f18 injection)	AVID RADIOPHARMACEUTICALS Inc.	Y	First	7.9	AP	7.9	Y♦
BEOVU (brolucizumab-DBLL)	NOVARTIS PHARMACEUTICALS CORPORATION	Y	First	8.0	AP	8.0	Y♦
Artesunate	AMIVAS LLC	Y	First	8.0	AP	8.0	Y♦
Artesunate	LA JOLLA PHARMACEUTICAL Co.	N[14]	First	8.0	TA	8.0	Y♦
Tazemetostat	EPIZYME Inc.	Y	First	8.1	AP	8.1	Y♦
NURTEC ODT (rimegepant)	BIOHAVEN PHARMACEUTICAL HOLDING Co. Ltd.	Y	First	8.1	AP	8.1	Y♦
ZX008 (fenfluramine)	ZOGENIX Inc.	N	First	9.0	AP	9.0	Y♯
NOURESS (cysteine hydrochloride injection)	EXELA PHARMA SCIENCES LLC	N	First	9.0	AP	9.0	Y♯
EVRYSDI (risdiplam)	GENENTECH Inc.	Y	First	10.5	AP	10.5	Y♯♦
FETROJA (cefiderocol)	SHIONOGI Inc.	Y	First	11.0	AP	11.0	Y♯♦

[14] Non-NME NDA reviewed under the NME program. At time of receipt, the active ingredient artesunate had never been approved in the United States, allowing for NME designation; however, at time of approval, artesunate had already been approved for marketing in another application, causing this application to lose its NME designation.

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
SCENESSE (afamelanotide)	CLINUVEL Inc.	Y	First	11.0	AP	11.0	Y♯♦
VYONDYS 53 (golodirsen)	SAREPTA THERAPEUTICS Inc.	Y	First	8.0	CR	8.0	Y♦
			Sponsor	3.3		11.3	
			Second	0.5	AP	11.8	Y▲
TRODELVY (sacituzumab govitecan-HZIY)	IMMUNOMEDICS Inc.	Y	First	8.0	CR	8.0	Y♦
			Sponsor	10.5		18.5	
			Second	4.7	AP	23.2	YΔ
Submitted in FY 2017							
VESICARE LS (solifenacin succinate)	ASTELLAS PHARMA US Inc.	N	First	6.0	CR	6.0	Y
			Sponsor	27.0		33.0	
			Second	6.0	AP	39.0	YΔ

FY 2020 Standard NDA and BLA Approvals (by Fiscal Year of Receipt)

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
Submitted in FY 2020							
atropine sulfate	ACCORD HEALTHCARE Inc.	N	First	6.0	AP	6.0	Y
PHESGO (pertuzumab, trastuzumab, and hyaluronidase-ZZXF)	GENENTECH Inc.	N	First	6.4	AP	6.4	Y
XTANDI (enzalutamide)	ASTELLAS PHARMA US Inc.	N	First	9.2	AP	9.2	Y
PULMOTECH MAA (kit for the preparation of technetium tc99m albumin aggregated injection)	CIS BIO INTERNATIONAL	N	First	9.3	AP	9.3	Y
DARZALEX FASPRO (daratumumab and hyaluronidase-FIHJ)	JANSSEN BIOTECH Inc.	N	First	9.7	AP	9.7	Y
ALKINDI SPRINKLE (hydrocortisone)	DIURNAL Ltd.	N	First	10.0	AP	10.0	Y
LYUMJEV (insulin lispro-AABC)	ELI LILLY AND COMPANY	N	First	10.0	AP	10.0	Y
Methotrexate	ACCORD HEALTHCARE Inc.	N	First	10.0	AP	10.0	Y
QWO (collagenase clostridium histolyticum-AAES)	ENDO GLOBAL AESTHETICS Ltd.	N	First	10.0	AP	10.0	Y
QDOLO (tramadol hydrochloride)	ATHENA BIOSCIENCE LLC	N	First	10.1	AP	10.1	Y
SARCLISA (isatuximab-IRFC)	SANOFI-AVENTIS US LLC	Y	First	10.1	AP	10.1	Y♦
ENSPRYNG (satralizumab-MWGE)	GENENTECH Inc.	Y	First	12.0	AP	12.0	Y♦
SOGROYA (somapacitan-BECO)	NOVO NORDISK Inc.	Y	First	12.0	AP	12.0	Y♦
UPLIZNA (inebilizumab-CDON)	VIELA BIO	Y	First	12.0	AP	12.0	Y♦
VYEPTI (eptinezumab-JJMR)	LUNDBECK SEATTLE BIOPHARMACEUTICALS Inc.	Y	First	12.0	AP	12.0	Y♦
SEMGLEE (insulin glargine injection)	MYLAN PHARMACEUTICALS Inc.	N	First	10.0	CR	10.0	Y
			Sponsor	9.4		19.4	
			Second	6.0	CR	25.4	Y△
			Sponsor	3.6		29.0	
			Third	5.9	AP	34.8	Y△
Submitted in FY 2019							
IBRANCE (palbociclib)	PFIZER Inc.	N	First	9.0	AP	9.0	Y
PROCYSBI (cysteamine bitartrate)	HORIZON PHARMA USA Inc.	N	First	9.0	AP	9.0	Y
dolutegravir, lamivudine, and tenofovir disoproxil fumarate	CELLTRION Inc.	N	First	9.6	TA	9.6	Y◊
EXSERVAN (riluzole)	AQUESTIVE THERAPEUTICS	N	First	9.7	AP	9.7	Y

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
CONJUPRI (levamlodipine)	CSPC OUYI PHARMACEUTICAL CO Ltd.	N	First	9.7	AP	9.7	Y
UPNEEQ (oxymetazoline hydrochloride)	RVL PHARMACEUTICALS Inc.	N	First	9.8	AP	9.8	Y
MONOFERRIC (ferric derisomaltose)	PHARMACOSMOS AS	N	First	9.9	AP	9.9	Y
Tralement	AMERICAN REGENT Inc.	N	First	9.9	AP	9.9	Y
QUZYTTIR (cetirizine)	JDP THERAPEUTICS LLC	N	First	9.9	AP	9.9	Y
ARALZO (tazarotene)	BAUSCH HEALTH AMERICAS Inc.	N	First	9.9	AP	9.9	Y
BONSITY (teriparatide)	ALVOGEN MALTA OPERATIONS Ltd.	N	First	9.9	AP	9.9	Y
SECUADO (asenapine)	HISAMITSU PHARMACEUTICAL Co. Inc.	N	First	9.9	AP	9.9	Y
AMZEEQ (minocycline)	FOAMIX PHARMACEUTICALS Inc.	N	First	9.9	AP	9.9	Y
ZILXI (minocycline)	FOAMIX PHARMACEUTICALS Inc.	N	First	9.9	AP	9.9	Y
DURYSTA (bimatoprost)	ALLERGAN Inc.	N	First	10.0	AP	10.0	Y
ELYXYB (celecoxib)	DR REDDYS LABORATORIES Ltd.	N	First	10.0	AP	10.0	Y
FERRIPROX (deferiprone)	CHIESI USA Inc.	N	First	10.0	AP	10.0	Y
AVNU (ferric pyrophosphate citrate)	ROCKWELL MEDICAL Inc.	N	First	10.0	AP	10.0	Y
BIORPHEN (phenylephrine hydrochloride)	ETON PHARMACEUTICALS	N	First	10.0	AP	10.0	Y
FENSOLVI (leuprolide acetate)	TOLMAR INTERNATIONAL Ltd.	N	First	10.0	AP	10.0	Y
ORIAHNN (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules)	ABBVIE Inc.	N	First	10.0	AP	10.0	Y
WYNZORA (calcipotriene and betamethasone dipropionate)	MC2 THERAPEUTICS Ltd.	N	First	10.0	AP	10.0	Y
IMPEKLO (clobetasol propionate)	MYLAN PHARMACEUTICALS Inc.	N	First	10.0	AP	10.0	Y
EMERPHED (ephedrine sulfate)	NEXUS PHARMACEUTICALS Inc.	N	First	10.0	AP	10.0	Y
levonorgestrel/ethinyl estradiol	EXELTIS USA Inc.	N	First	10.1	AP	10.1	Y
TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release tablets)	BOEHRINGER INGELHEIM PHARMACEUTICALS Inc.	N	First	10.1	AP	10.1	Y
BYNEFEZIA PEN (octreotide acetate)	SUN PHARMACEUTICAL INDUSTRIES Ltd.	N	First	10.1	AP	10.1	Y
VUMERITY (diroximel fumarate)	BIOGEN	N	First	9.9	TA	9.9	Y
			Sponsor	0.0		9.9	
			Second	0.6	AP	10.5	Y▲

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
DOJOLVI (triheptanoin)	ULTRAGENYX PHARMACEUTICAL Inc.	Y	First	11.0	AP	11.0	Y♦
DAYVIGO (lemborexant)	EISAI Inc.	Y	First	11.8	AP	11.8	Y♦
UBRELVY (ubrogepant)	ALLERGAN SALES LLC	Y	First	11.9	AP	11.9	Y♦
MENQUADFI(Meningococcal (Groups A, C, Y, W) Conjugate Vaccine)	SANOFI PASTEUR Inc.	Y	First	11.9	AP	11.9	Y♦
REYVOW (lasmiditan)	ELI LILLY AND Co.	Y	First	12.0	AP	12.0	Y♦
AKLIEF (trifarotene)	GALDERMA LABORATORIES LP.	Y	First	12.0	AP	12.0	Y♦
NEXLETOL (bempedoic acid)	ESPERION THERAPEUTICS Inc.	Y	First	12.0	AP	12.0	Y♦
NEXLIZET (bempedoic acid/ezetimibe)	ESPERION THERAPEUTICS Inc.	N[15]	First	12.0	AP	12.0	Y♦
ONGENTYS (opicapone)	NEUROCRINE BIOSCIENCES Inc.	Y	First	12.0	AP	12.0	Y♦
ISTURISA (osilodrostat)	RECORDATI RARE DISEASES Inc.	Y	First	12.0	AP	12.0	Y♦
XCOPRI (cenobamate)	SK LIFE SCIENCE Inc.	Y	First	12.0	AP	12.0	Y♦
WINLEVI (clascoterone)	CASSIOPEA SPA	Y	First	12.0	AP	12.0	Y♦
AUDENZ (Influenza A (H5N1) Monovalent Vaccine, Adjuvanted)	SEQIRUS Inc.	Y	First	12.0	AP	12.0	Y♦
ZEPOSIA (ozanimod)	CELGENE INTERNATIONAL II SARL	Y	First	12.1	AP	12.1	Y♦
REDITREX (methotrexate)	CUMBERLAND PHARMACEUTICALS Inc.	N	First	12.7	AP	12.7	Y♯
ADVIL DUAL ACTION WITH ACETAMINOPHEN (ibuprofen/acetaminophen)	GLAXOSMITHKLINE CONSUMER HEALTHCARE HOLDINGS US LLC	N	First	12.9	AP	12.9	Y♯
VALTOCO (diazepam)	NEURELIS Inc.	N	First	13.0	AP	13.0	Y♯
EXEM FOAM (air polymer-type A)	GISKIT BV	Y	First	13.0	AP	13.0	Y♯♦
CERIANNA (fluoroestradiol f18)	ZIONEXA US Corp.	Y	First	14.7	AP	14.7	Y♯♦
BYFAVO (remimazolam)	ACACIA PHARMA Ltd.	Y	First	14.9	AP	14.9	Y♯♦
vasopressin	AMERICAN REGENT Inc.	N	First	10.0	TA	10.0	Y
			Sponsor	4.2		14.2	
			Second	2.0	AP	16.2	Y▲
CYSTADROPS (cysteamine)	RECORDATI RARE DISEASES Inc.	N	First	10.1	CR	10.1	Y
			Sponsor	1.0		11.1	

[15] The applicant submitted two NDAs for the same new moiety (bempedoic acid), but one of the NDAs is in combination with a currently marketed drug (bempedoic acid vs. bempedoic acid and ezetimibe). Only one NDA retains the NME designation upon approval; in this case, the NDA for the bempedoic acid alone retained the NME designation.

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
			Second	5.7	AP	16.8	Y∆
BREZTRI AEROSPHERE (budesonide, glycopyrrolate, and formoterol fumarate)	ASTRAZENECA AB	N	First	10.0	CR	10.0	Y
			Sponsor	3.8		13.8	
			Second	6.0	AP	19.8	Y∆
Submitted in FY 2018							
HEMADY (dexamethasone)	DEXCEL PHARMA TECHNOLOGIES Ltd.	N	First	12.9	AP	12.9	Y♯
ABSORICA LD (isotretinoin)	SUN PHARMACEUTICAL INDUSTRIES Ltd.	N	First	14.6	AP	14.6	N♯
PIZENSY (lactitol)	BRAINTREE LABORATORIES Inc.	Y	First	14.7	AP	14.7	Y♯♦
CAPLYTA (lumateperone)	INTRA-CELLULAR THERAPIES Inc.	Y	First	14.8	AP	14.8	Y♯♦
fluorescein sodium and benoxinate hydrochloride	BAUSCH HEALTH IRELAND Ltd.	N	First	9.8	CR	9.8	Y
			Sponsor	4.9		14.7	
			Second	2.8	AP	17.5	Y∆
bendamustine hydrochloride	SLAYBACK PHARMA LLC	N	First	9.5	CR	9.5	Y
			Sponsor	0.5		10.0	
			Second	2.5	CR	12.5	Y∆
			Sponsor	5.0		17.4	
			Third	4.6	TA	22.0	Y∆
cyclophosphamide	INGENUS PHARMACEUTICALS LLC	N	First	9.7	CR	9.7	Y
			Sponsor	0.2		9.9	
			Second	5.7	CR	15.6	Y∆
			Sponsor	0.7		16.3	
			Third	5.8	AP	22.1	Y∆
GIMOTI (metoclopramide)	EVOKE PHARMA Inc.	N	First	10.0	CR	10.0	Y
			Sponsor	8.6		18.6	
			Second	6.0	AP	24.6	Y∆
KYNMOBI (apomorphine)	SUNOVION PHARMACEUTICALS Inc.	N	First	10.1	CR	10.1	Y
			Sponsor	9.7		19.8	
			Second	6.0	AP	25.8	Y∆
BAFIERTAM (monomethyl fumarate)	BANNER LIFE SCIENCES LLC	N	First	9.9	TA	9.9	Y
			Sponsor	13.8		23.7	
			Second	3.6	AP	27.3	Y∆
BARHEMSYS (amisulpride)	ACACIA PHARMA Ltd.	Y	First	12.0	CR	12.0	Y♦
			Sponsor	1.0		13.0	
			Second	5.9	CR	18.9	Y∆
			Sponsor	3.8		22.7	
			Third	6.1	AP	28.8	Y∆
XARACOLL (bupivacaine HCl)	INNOCOLL PHARMACEUTICALS	N	First	9.9	CR	9.9	Y
			Sponsor	14.9		24.8	
			Second	6.1	AP	30.9	N∆

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
OLINVYK (oliceridine)	TREVENA Inc.	Y	First	12.0	CR	12.0	Y♦
			Sponsor	15.2		27.2	
			Second	6.0	AP	33.2	Y△
Submitted in FY 2017							
NUMBRINO (cocaine hydrochloride)	CODY LABORATORIES Inc. A WHOLLY OWNED SUBSIDIARY OF LANNETT Co. Inc.	N	First	9.9	CR	9.9	Y
			Sponsor	11.0		20.9	
			Second	6.7	AP	27.6	N△
ANJESO (meloxicam)	BAUDAX BIO Inc.	N	First	9.9	CR	9.9	Y
			Sponsor	4.1		14.0	
			Second	5.9	CR	19.9	Y△
			Sponsor	9.0		28.9	
			Third	2.1	AP	31.0	Y▲
ABBOJECT SYRINGE (epinephrine)	HOSPIRA Inc.	N	First	9.9	TA	9.9	Y
			Sponsor	21.2		31.1	
			Second	2.0	AP	33.1	Y▲
PEMFEXY (pemetrexed)	EAGLE PHARMACEUTICALS Inc.	N	First	9.9	TA	9.9	Y
			Sponsor	21.4		31.3	
			Second	2.0	TA	33.3	Y▲
			Sponsor	2.0		35.3	
			Third	2.0	AP	37.3	Y▲
SEVENFACT (Coagulation Factor VIIa (Recombinant))	LABORATOIRE FRANCAIS DU FRACTIONNEMENT ET DES BIOTECHNOLOGIES S.A.	Y	First	12.0	CR	12.0	Y♦
			Sponsor	23.9		35.9	
			Second	5.7	AP	41.6	Y△
Pemetrexed	ACTAVIS LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA Inc.	N	First	9.1	CR	9.1	Y
			Sponsor	3.9		13.0	
			Second	5.0	CR	18.0	Y△
			Sponsor	19.9		37.9	
			Third	6.0	AP	43.9	Y△
Submitted in FY 2016							
Pemetrexed	DR REDDYS LABORATORIES Ltd.	N	First	10.0	CR	10.0	Y
			Sponsor	9.4		19.4	
			Second	5.8	CR	25.2	Y△
			Sponsor	6.8		32.0	
			Third	6.0	CR	38.0	Y△
			Sponsor	2.0		40.0	
			Fourth	5.8	CR	45.8	Y△
			Sponsor	3.3		49.1	
			Fifth	6.0	TA	55.1	Y△
Submitted in FY 2015							
romidepsin		N	First	9.5	CR	9.5	Y

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
	TEVA PHARMACEUTICALS USA Inc.		Sponsor	6.9		16.4	
			Second	5.1	CR	21.5	Y△
			Sponsor	23.9		45.4	
			Third	5.2	CR	50.6	Y△
			Sponsor	0.6		51.2	
			Fourth	3.7	AP	54.9	Y△
XEGLYZE (abametapir)	DR REDDYS LABORATORIES SA	Y	First	11.6	CR	11.6	Y♦
			Sponsor	38.4		50.0	
			Second	8.4	AP	58.4	Y♯△
PHEXXI (lactic acid, citric acid, and potassium bitartrate)	EVOFEM Inc.	N	First	9.9	CR	9.9	Y
			Sponsor	42.9		52.8	
			Second	5.9	AP	58.7	Y△
MYCAPSSA (octreotide)	CHIASMA Inc.	N	First	10.1	CR	10.1	Y
			Sponsor	44.4		54.5	
			Second	6.0	AP	60.5	Y△
Submitted in FY 2014							
Cabazitaxel	FRESENIUS KABI USA LLC	N	First	10.0	CR	10.0	Y
			Sponsor	46.8		56.8	
			Second	6.0	TA	62.8	Y△
Bortezomib	DR REDDYS LABORATORIES Ltd.	N	First	9.5	CR	9.5	Y
			Sponsor	11.2		20.7	
			Second	5.4	CR	26.0	Y△
			Sponsor	36.0		62.0	
			Third	5.1	AP	67.1	Y△
Submitted in FY 2013							
[F-18] FLUORODOPA (fdopa)	FEINSTEIN INSTITUTE MEDICAL RESEARCH	Y	First	12.0	CR	12.0	Y♦
			Sponsor	25.8		37.8	
			Second	9.1	CR	46.9	Y♯△
			Sponsor	30.8		77.7	
			Third	6.0	AP	83.7	Y△
Submitted in FY 2012							
GENOSYL (nitric oxide)	VERO BIOTECH	N	First	9.9	CR	9.9	Y
			Sponsor	60.9		70.8	
			Second	6.1	CR	76.9	Y△
			Sponsor	4.9		81.8	
			Third	6.0	AP	87.8	Y△
TWIRLA (levonorgestrel and ethinyl estradiol)	AGILE THERAPEUTICS Inc.	N	First	10.1	CR	10.1	Y
			Sponsor	52.4		62.5	
			Second	5.9	CR	68.4	Y△
			Sponsor	16.8		85.2	

Proprietary Name (Established Name)	Applicant	NME (Y/N)	Review Cycle	Cycle Time (Mos.)	Cycle Result	Total Time (Mos.)	Goal Met
			Third	9.0	AP	94.2	Y♯Δ
Submitted in FY 2010							
MILPROSA (progesterone)	FERRING PHARMACEUTICALS Inc.	N	First	10.0	CR	10.0	Y
			Sponsor	59.9		59.9	
			Second	9.0	CR	68.9	Y♯Δ
			Sponsor	35.2		104.1	
			Third	6.0	AP	110.0	YΔ

Appendix B: Filed Application Numbers by Review Division

The tables below and on the pages that follow show the number of applications filed in FY 2020 for various application types and review designations broken out by review division. This reporting for PDUFA VI is required under section 736B(a) of the FD&C Act.

Original Applications Filed in FY 2020 by Review Division/Office

Review Division/Office	Priority NDAs	Standard NDAs	Priority BLAs	Standard BLAs	Undesignated Original Applications
CDER Review Divisions					
Division of Anesthesiology, Addiction Medicine, and Pain Medicine	0	7	0	1	1
Division of Anti-Infectives	3	3	0	0	1
Division of Antivirals	6	6	2	0	0
Division of Cardiology and Nephrology	2	9	0	0	1
Division of Dermatology and Dentistry	2	2	0	4	1
Division of Diabetes, Lipid Disorders, and Obesity	1	3	1	0	0
Division of Gastroenterology	0	1	0	0	0
Division of General Endocrinology	0	3	0	1	1
Division of Hematologic Malignancies I	2	1	0	0	1
Division of Hematologic Malignancies II	2	2	2	0	1
Division of Hepatology and Nutrition	0	0	0	0	0
Division of Imaging and Radiation Medicine	1	1	0	0	2
Division of Neurology I	3	0	1	0	1
Division of Neurology II	0	4	0	0	0
Division of Non-Malignant Hematology	3	1	1	2	1
Division of Non-Prescription Drugs I	0	2	0	0	0
Division of Non-Prescription Drugs II	0	0	0	0	0
Division of Non-Prescription Drugs III	0	0	0	0	0

Review Division/Office	Priority NDAs	Standard NDAs	Priority BLAs	Standard BLAs	Undesignated Original Applications
Division of Oncology I	4	4	1	2	0
Division of Oncology II	6	4	2	0	1
Division of Oncology III	1	1	0	0	1
Division of Ophthalmology	0	1	0	1	0
Division of Psychiatry	1	7	0	0	0
Division of Pulmonology, Allergy, and Critical Care	0	1	0	0	0
Division of Rare Diseases and Medical Genetics	3	1	1	0	1
Division of Rheumatology and Transplant Medicine	3	2	0	1	0
Division of Urology, Obstetrics, and Gynecology	0	4	0	0	1
CDER Totals	*43*	*70*	*11*	*12*	*15*
CBER Review Offices					
Office of Blood Research and Review	0	0	0	0	0
Office of Tissues and Advanced Therapies	0	0	6	1	0
Office of Vaccines Research and Review	0	0	0	0	0
CBER Totals	*0*	*0*	*6*	*1*	*0*
FDA Totals	**43**	**70**	**17**	**13**	**15**

Efficacy Supplements Filed in FY 2020 by Review Division/Office

Review Division/Office	Priority Efficacy Supplements	Standard Efficacy Supplements	Undesignated Efficacy Supplements
CDER Review Divisions			
Division of Anesthesiology, Addiction Medicine, and Pain Medicine	0	8	1
Division of Anti-Infectives	3	11	1
Division of Antivirals	4	18	0
Division of Cardiology and Nephrology	2	7	2
Division of Dermatology and Dentistry	1	8	0
Division of Diabetes, Lipid Disorders, and Obesity	3	7	0

Review Division/Office	Priority Efficacy Supplements	Standard Efficacy Supplements	Undesignated Efficacy Supplements
Division of Gastroenterology	0	2	0
Division of General Endocrinology	1	2	0
Division of Hematologic Malignancies I	7	0	0
Division of Hematologic Malignancies II	6	7	1
Division of Hepatology and Nutrition	0	1	0
Division of Imaging and Radiation Medicine	1	3	0
Division of Neurology I	1	7	1
Division of Neurology II	3	11	1
Division of Non-Malignant Hematology	3	6	0
Division of Non-Prescription Drugs I	0	2	0
Division of Non-Prescription Drugs II	0	2	0
Division of Non-Prescription Drugs III	0	0	0
Division of Oncology I	16	10	1
Division of Oncology II	10	7	2
Division of Oncology III	25	7	0
Division of Ophthalmology	0	0	0
Division of Psychiatry	2	7	0
Division of Pulmonology, Allergy, and Critical Care	6	1	1
Division of Rare Diseases and Medical Genetics	0	6	0
Division of Rheumatology and Transplant Medicine	7	10	0
Division of Urology, Obstetrics, and Gynecology	0	5	0
CDER Totals	*101*	*155*	*11*
CBER Review Offices			
Office of Blood Research and Review	0	0	0
Office of Tissues and Advanced Therapies	2	14	0
Office of Vaccines Research and Review	2	11	0

Review Division/Office	Priority Efficacy Supplements	Standard Efficacy Supplements	Undesignated Efficacy Supplements
CBER Totals	*4*	*25*	*0*
FDA Totals	**105**	**180**	**11**

Submissions with Special Designations Filed in FY 2020 by Review Division/Office

Review Division/Office	Accelerated Approval	Fast Track Products	Orphan Designations	Breakthrough Designations*
CDER Review Divisions				
Division of Anesthesiology, Addiction Medicine, and Pain Medicine	0	1	1	0
Division of Anti-Infectives	0	2	3	2
Division of Antivirals	0	7	2	1
Division of Cardiology and Nephrology	0	1	2	6
Division of Dermatology and Dentistry	1	1	2	4
Division of Diabetes, Lipid Disorders, and Obesity	0	0	2	0
Division of Gastroenterology	0	0	0	1
Division of General Endocrinology	0	0	3	1
Division of Hematologic Malignancies I	0	0	4	6
Division of Hematologic Malignancies II	4	1	6	1
Division of Hepatology and Nutrition	0	0	0	2
Division of Imaging and Radiation Medicine	0	1	1	1
Division of Neurology I	2	3	4	0
Division of Neurology II	0	1	1	0
Division of Non-Malignant Hematology	0	0	3	4
Division of Non-Prescription Drugs I	0	0	0	0
Division of Non-Prescription Drugs II	0	0	0	0
Division of Non-Prescription Drugs III	0	0	0	0
Division of Oncology I	2	3	3	7
Division of Oncology II	4	1	7	10

Review Division/Office	Accelerated Approval	Fast Track Products	Orphan Designations	Breakthrough Designations*
Division of Oncology III	1	2	2	6
Division of Ophthalmology	0	0	1	0
Division of Psychiatry	0	0	1	3
Division of Pulmonology, Allergy, and Critical Care	0	1	1	4
Division of Rare Diseases and Medical Genetics	1	3	4	2
Division of Rheumatology and Transplant Medicine	0	1	1	3
Division of Urology, Obstetrics, and Gynecology	0	0	0	0
CDER Totals	*15*	*29*	*54*	*64*
CBER Review Offices				
Office of Blood Research and Review	0	0	0	0
Office of Tissues and Advanced Therapies	0	1	6	4
Office of Vaccines Research and Review	0	0	0	0
CBER Totals	*0*	*1*	*6*	*4*
FDA Totals	**15**	**30**	**60**	**68**

* This column does not represent filed figures; rather it shows the number of BT designations granted on INDs, NDAs, and BLAs during FY 2020. BT designation is granted based on indication, and, therefore, one submission may have more than one BT designation granted.

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Appendix C: Analysis of Use of Funds

On August 18, 2017, FDARA was signed into law. FDARA amended the FD&C Act to revise and extend the user fee programs for human drugs, biologics, generic drugs, medical devices, and biosimilar biological products.

FDARA requires, in the annual performance reports of each of the human medical product user fee programs, specified analyses of the use of funds to include information such as the differences between aggregate numbers of applications and approvals, an analysis of performance enhancement goals, and the most common causes and trends affecting the ability to meet goals. In addition, FDARA (specifically, section 904) requires the issuance of corrective action reports.

A. Original Application Approval Cycle Summary

The following table addresses section 904(a)(1) of FDARA (section 736B(a)(5)(A) of the FD&C Act), pertaining to PDUFA, which requires FDA to include data showing the aggregate number of approvals that occurred during FY 2020. Data represent all the original NDA and BLA approvals that occurred during FY 2020, regardless of when the application was received. Data are presented by the type of application and performance goal, as well as whether the approval occurred on time or was overdue on the performance goal.

This table captures not only first cycle approvals, but also multiple cycle approvals. For applications that were approved after multiple cycles, the performance metric is counted for the last cycle when the approval was given. Approval counts also include applications that were given a tentative approval.

Figures provided in the table below are indicated in detail in Appendix A of this report, which provides a detailed review history of the NDAs and BLAs approved under PDUFA during FY 2020.[16]

[16] Performance is calculated only on the first cycle in which the application received an approval or tentative approval. Any subsequent tentative or full approvals, after the first tentative approval action, will not affect the performance metric regardless of the fiscal year of the first tentative approval.

Approval Cycle Type	Performance Goal: Act on 90 Percent Within	Approval Count	On Time	Overdue	Percent On Time
First Cycle Priority NMEs & BLAs	6 months of filing date	36	36	0	**100%**
First Cycle Standard NMEs & BLAs	10 months of filing date	28	28	0	**100%**
First Cycle Priority non-NME NDAs	6 months	12	12	0	**100%**
First Cycle Standard non-NME NDAs	10 months	43	42	1	**98%**
Class 1 Resubmissions	2 months	2	2	0	**100%**
Class 2 Resubmissions	6 months	27	25	2	**93%**
Total		**148**	**145**	**3**	**--***

* Performance is not calculated on combined goals.

B. Performance Enhancement Goals

The following table addresses section 904(a)(1) of FDARA (section 736B(a)(5)(B) of the FD&C Act), pertaining to PDUFA, which requires FDA to include relevant data to determine whether CDER and CBER have met performance enhancement goals identified in the letters described in section 101(b) of the Prescription Drug User Fee Amendments of 2017 for the applicable fiscal year. A link to each performance enhancement goal completed under PDUFA VI can be found on FDA's website.[17]

For purposes of this report, *performance enhancement goals* are defined as any non-review performance goal described in PDUFA with a specified goal date that falls within the applicable fiscal year.

[17] www.fda.gov/industry/prescription-drug-user-fee-amendments/completed-pdufa-vi-deliverables.

The table below represents FDA's FY 2019 updated performance.

Performance Enhancement Goal	Target Goal Date	On Time (Y/N)	Actual Completion Date	Comments
PDUFA FY 2019 Hiring Web Posting Quarter 4	10/14/2019	N	10/18/2019	FDARA Hiring Data (see https://www.fda.gov/industry/prescription-drug-user-fee-amendments/food-and-drug-administration-reauthorization-act-2017-fdara-hiring-data)

The table below represents FDA's FY 2020 performance.

Performance Enhancement Goal	Target Goal Date	On Time (Y/N)	Actual Completion Date	Comments
FY 2020 PDUFA Hiring Goals	10/15/2019	N	N/A	FDA's FY 2020 hiring goal was for 58 FTEs, and 48 FTEs were onboarded (83 percent of the FY 2020 hiring goal)
CY 2019 FDA Data Standards Action Plan - Quarter 4	12/31/2019	Y	11/6/2019	Data Standards Program Strategic Plan and Board (see www.fda.gov/drugs/electronic-regulatory-submission-and-review/data-standards-program-strategic-plan-and-board) FDA Resources for Data Standards (see www.fda.gov/industry/fda-resources-data-standards)
PDUFA FY 2020 Hiring Web Posting - Quarter 1	1/14/2020	N	1/17/2020	FDARA Hiring Data (see www.fda.gov/industry/prescription-drug-user-fee-amendments/food-and-drug-administration-reauthorization-act-2017-fdara-hiring-data)
Innovative Drug Approval Report on Rare Diseases Program	1/30/2020	Y	1/6/2020	Innovation in New Drug Approvals of 2019 Advances Patient Care Across a Broad Range of Diseases (see www.fda.gov/news-events/fda-voices/innovation-new-drug-approvals-2019-advances-patient-care-across-broad-range-diseases)
CY 2020 FDA Data Standards Action Plan - Quarter 1	3/30/2020	Y	2/12/2020	Data Standards Program Strategic Plan and Board (see www.fda.gov/drugs/electronic-regulatory-submission-and-review/data-standards-program-strategic-plan-and-board) FDA Resources for Data Standards (see www.fda.gov/industry/fda-resources-data-standards)
2020 Annual Update to 5-Year Plan	3/31/2020	Y	3/31/2020	User Fee Five-Year Financial Plans (see www.fda.gov/about-fda/user-fee-reports/user-fee-five-year-financial-plans)
Interim Assessment for Hiring and Retention	3/31/2020	N	6/5/2020	FDA Interim Hiring and Retention Assessment Report (see www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-interim-hiring-and-retention-assessment-report)
PDUFA FY 2020 Hiring Web Posting - Quarter 3	4/14/2020	Y	4/13/2020	FDARA Hiring Data (see www.fda.gov/industry/prescription-drug-user-fee-amendments/food-and-drug-administration-reauthorization-act-2017-fdara-hiring-data)
FY 2020 Financial Public Meetings	6/30/2020	Y	6/22/2020	Financial Transparency and Efficiency of the Prescription Drug User Fee Act, Biosimilar User Fee Act, and Generic

Performance Enhancement Goal	Target Goal Date	On Time (Y/N)	Actual Completion Date	Comments
				Drug User Fee Amendments (see www.fda.gov/drugs/news-events-human-drugs/financial-transparency-and-efficiency-prescription-drug-user-fee-act-biosimilar-user-fee-act-and)
Interim Public Meeting for Hiring and Retention	6/30/2020	N	7/30/2020	FDA PDUFA Hiring and Retention Interim Assessment Public Meeting (see www.fda.gov/drugs/news-events-human-drugs/fda-pdufa-hiring-and-retention-interim-assessment-public-meeting-07302020-07302020)
CY 2020 FDA Data Standards Action Plan - Quarter 2	6/30/2020	Y	4/26/2020	Data Standards Program Strategic Plan and Board (see www.fda.gov/drugs/electronic-regulatory-submission-and-review/data-standards-program-strategic-plan-and-board) FDA Resources for Data Standards (see www.fda.gov/industry/fda-resources-data-standards)
PDUFA FY 2020 Hiring Web Posting - Quarter 4	7/14/2020	Y	7/6/2020	FDARA Hiring Data (see www.fda.gov/industry/prescription-drug-user-fee-amendments/food-and-drug-administration-reauthorization-act-2017-fdara-hiring-data)
Communication During Drug Development Independent Assessment	9/30/2020	Y	6/17/2020	Assessment of FDA-Sponsor Communication Practices During the IND Stage of Drug/Biologic Development (see www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-assessment-fda-sponsor-communication-practices-during-ind-stage-drugbiologic-development)
Combination Products Independent Assessment	9/30/2020	Y	8/28/2020	Assessment of Combination Product Review Practices in PDUFA VI (see www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-assessment-combination-product-review-practices-pdufa-vi)
Drafting PFDD Guidance - Fit-for-Purpose COAs	9/30/2020	N	N/A	
Report on Enhancing Patient Engagement in Trials	9/30/2020	Y	3/18/2019	Enhancing the Incorporation of Patient Perspectives in Clinical Trials: Meeting Summary (see www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/meeting_summary_-_enhancing_incorporation_of_patient_perspectives_-_final.pdf)
BRA Draft Guidance	9/30/2020	N	N/A	FDA aims to publish the guidance in the near future.
FY 2020 MIDD Selections and Meetings - Quarter 1	9/30/2020	Y	10/4/2019	
FY 2020 MIDD Selections and Meetings - Quarter 2	9/30/2020	Y	1/6/2020	
FY 2020 MIDD Selections and Meetings - Quarter 3	9/30/2020	Y	4/3/2020	
FY 2020 MIDD Selections and Meetings - Quarter 4	9/30/2020	Y	7/6/2020	
Innovative Trial Design Pilot Program FY 2020 Meetings - Quarter 1	9/30/2020	Y	10/31/2019	

Performance Enhancement Goal	Target Goal Date	On Time (Y/N)	Actual Completion Date	Comments
Innovative Trial Design Pilot Program FY 2020 Meetings - Quarter 2	9/30/2020	Y	3/31/2020	
Innovative Trial Design Pilot Program FY 2020 Meetings - Quarter 3	9/30/2020	Y	5/7/2020	
Innovative Trial Design Pilot Program FY 2020 Meetings - Quarter 4	9/30/2020	Y	7/30/2020	
MAPP and SOP Templates for Evaluating Complex Clinical Trial Design	9/30/2020	Y	12/31/2019	
Revising or Developing MAPPs and SOPs on Biomarker Qualification Process	9/30/2020	Y	9/30/2020	
Guidance on Evidentiary Standards (Draft Guidance)	9/30/2020	N	N/A	FDA aims to publish this guidance in the near future.
Develop Sentinel Sponsor Notification MAPPs (MAPP 6701.4)	9/30/2020	Y	8/17/2020	MAPP 6701.4 *Notifying Applicants of Sentinel Analyses and Results* (see www.fda.gov/media/141216/download)
Integrating Sentinel into Pharmacovigilance Activities (ARIA Templates)	9/30/2020	Y	8/16/2019	
Integrating Sentinel into Pharmacovigilance Activities (Training)	9/30/2020	Y	9/24/2020	
Electronic Submissions and Data Standards FY 2020 Meeting - Quarter 1	9/30/2020	Y	12/3/2019	
Electronic Submissions and Data Standards FY 2020 Meeting - Quarter 2	9/30/2020	Y	3/4/2020	
Electronic Submissions and Data Standards FY 2020 Meeting - Quarter 3	9/30/2020	Y	6/2/2020	
Electronic Submissions and Data Standards FY 2020 Meeting - Quarter 4	9/30/2020	N	N/A	
Annual Public Meeting FY 2020 for IT Strategic Plan	9/30/2020	N	N/A	This meeting was jointly canceled by FDA and industry.
Annual ESG and Standard Metrics - Submission Statistics FY 2020	9/30/2020	Y	12/31/2019	Electronic Submissions Gateway: About ESG Submission Statistics (see www.fda.gov/industry/about-esg/submission-statistics)
FY 2020 Annual Discussion of IT Strategic Plan	9/30/2020	Y	12/3/2019	

Performance Enhancement Goal	Target Goal Date	On Time (Y/N)	Actual Completion Date	Comments
CY 2020 FDA Data Standards Action Plan - Quarter 3	9/30/2020	Y	7/29/2020	Data Standards Program Strategic Plan and Board (see www.fda.gov/drugs/electronic-regulatory-submission-and-review/data-standards-program-strategic-plan-and-board) FDA Resources for Data Standards (see www.fda.gov/industry/fda-resources-data-standards)
New Adjustment Report	9/30/2020	Y	4/6/2020	Resource Capacity Planning and Modernized Time Reporting (see www.fda.gov/industry/fda-user-fee-programs/resource-capacity-planning-and-modernized-time-reporting) Independent Evaluation of the PDUFA and BsUFA Resource Capacity Planning Adjustment Methodology (see www.fda.gov/media/136606/download)

C. Common Causes and Trends Impacting Ability to Meet Goals

The following table addresses section 904(a)(1) of FDARA (section 736B(a)(5)(C) of the FD&C Act), pertaining to PDUFA, which requires FDA to identify the most common causes and trends of external or other circumstances affecting the ability of FDA, including CDER, CBER, and ORA, to meet the review time and performance enhancement goals identified in the letters described in section 101(b) of the Prescription Drug User Fee Amendments of 2017.

Cause or Trend	Impact on FDA's Ability to Meet Goals
COVID-19 health pandemic	• The COVID-19 health pandemic required FDA to shift resources towards addressing the health emergency, which impacted the goals that were eventually missed. The volume of COVID-19-related meeting requests also substantially increased FDA's meeting-related workload. Additionally, circumstances surrounding the COVID-19 health pandemic led some new FDA hires to extend their start dates, thereby contributing to missing the hiring goal.
Federal government shutdown	• The FY 2019 federal government shutdown delayed the start of the contract for the Interim Assessment of Hiring and Retention, contributing to the delay in the publication of the report.
Change in hiring web posting methodology	• A change in the methodology used to calculate metrics for the hiring web posting was made in FY 2019 and took some time to be established, which contributed to the short delay in posting two quarterly hiring web postings.
Loss of points of contact for hiring data	• The loss of several Agency points of contact also contributed to short delays in clearing hiring data for two quarterly web postings.
Security clearance for new hires	• The federal hiring process requires clearances (e.g., security and ethics) to finalize the onboarding process, which led to some delays in onboarding and subsequent declinations, requiring the reinitiation of the recruitment process.
Cross-cutting topics in major dispute	• Multiple cross-cutting topics that raised complex policy and scientific issues took time to address, causing FDA to miss the Major Dispute Resolution goal.

Appendix D: FY 2020 Corrective Action Report

On August 18, 2017, FDARA (Public Law 115-52) was signed into law. FDARA amended the FD&C Act to revise and extend the user fee programs for drugs, biologics, medical devices, and biosimilar biological products, as well as to perform other purposes. Among the provisions of Title IX, section 904 of FDARA, FDA is required to publicly issue an analysis of its use of funds, which includes a corrective action report that details FDA's progress in meeting the review and performance enhancement goals identified in PDUFA VI for the applicable fiscal year.

If each of the review and performance enhancement goals for the applicable fiscal year have been met, the corrective action report shall include recommendations on ways in which the Secretary can improve and streamline the human drug application process.

For any of the review and performance enhancement goals during the applicable fiscal year that were not met, the corrective action report shall include a justification, as applicable, for the types of circumstances and trends that contributed to missed review goal times; and with respect to performance enhancement goals that were not met, a description of the efforts that FDA has put in place to improve the ability of the Agency to meet each goal in the coming fiscal year. Such a description of corrective efforts is not required by statute for review time goals, but FDA is providing this information regardless in an effort to be complete.

This report satisfies this reporting requirement.

Executive Summary

FY 2020 Review Goal Performance

Goal Type	Circumstances and Trends Impacting FDA's Ability to Meet Goal Dates	Corrective Action Plan
Procedural and Processing Goals	• **Meeting management goals**: ○ 4,678 meeting requests in FY 2020 ○ 24% increase in meeting requests from FY 2019 ○ Large increase in COVID-19 related submissions adding to overall workload ○ Limited resources • **Major Dispute Resolution goal**: ○ Multiple cross-cutting topics that raised complex policy and scientific issues ○ Increased COVID-19 workload and appropriate prioritization on addressing the public health emergency	• FDA anticipates that once the pandemic ends, formal PDUFA meeting volume may return to pre-COVID levels and we anticipate that our limited resources will be able to address other important issues such as formal disputes in a more timely manner.

FY 2020 Performance Enhancement Goal Performance

Goal Type	Circumstances and Trends Impacting Ability to Meet Goal Date	Corrective Action Plan
Guidances	• Three guidances were missed this year due to the COVID-19 health pandemic. Resources needed to expedite the development and clearance of these guidances were instead directed to the pandemic.	• The draft guidances related to patient input, benefit-risk, and biomarker qualification. These will be published when complete.
Website Publishing	• A change in the methodology used to calculate metrics for posting was made in FY 2019 and took some time to be established, which contributed to the short delay in posting. • The loss of several agency POCs also contributed to the delay.	• The new methodology has been fully established, as well as new primary and secondary POCs for the hiring data.
Human Capital/Hiring	• Delays in clearing selected candidates led to subsequent delays in onboarding as well as some declinations. • Circumstances surrounding the COVID-19 health pandemic led some candidates to extend their start dates.	• Expanded use of the hiring authority granted under the 21st Century Cures Act should leave more time for the clearance process and to make alternative selections should selected candidates decline.
Reporting	• The start of the contract for the Interim Assessment of Hiring and Retention was delayed by the FY 2019 government shutdown. • The assessment was also delayed by COVID-19 pandemic, which prevented timely report review by key staff.	• The Interim Assessment of Hiring and Retention was published on June 5, 2020.
Public Meetings	• Two public meetings were delayed due to the COVID-19 health pandemic. • Industry and FDA jointly agreed to cancel the FY 2020 Annual Public Meeting for the IT Strategic Plan to focus on addressing the COVID-19 health pandemic.	• The public meeting for the Interim Assessment of Hiring and Retention was held on July 30, 2020. • The fourth quarter 2020 meeting on enhancing transparency and accountability of FDA electronic submission and data standards activities is slated to be held in the first quarter of 2021.

PDUFA Review Goals

The following section addresses section 904(a)(2)(B) of FDARA (section 736B(c)(2)(A) of the FD&C Act), which requires FDA to provide a justification for the determination of review goals missed during FY 2020, and a description of the circumstances and any trends related to missed review goals.

This section presents PDUFA performance and workload information for two different types of goals: (1) review of applications and other submissions pertaining to human drugs and biologics and (2) meeting management and other procedural goals related to responses and notifications in the human drug review process.

This section includes all PDUFA VI goals as they pertain to receipts/filed submissions in FY 2020.

I. FY 2020 Procedural and Processing Performance

A. *Summary of Performance*

FDA missed the following procedural goals related to formal meeting management:

- Meeting request response for Type A, B (EOP) and C
- Meeting scheduling for Type A, B, B (EOP), and C
- Final written response for Type A, B, B (EOP), and C
- Meeting preliminary response for Type B (EOP)
- Major dispute resolutions

B. *Justification*

Meeting management goals:

In FY 2020, FDA received 4,678 formal PDUFA meeting requests, compared to 3,771 in FY 2019. That represents a 24 percent increase from FY 2019, whereas in previous years the trend has been an average increase of 6 percent per year. Many meeting requests were for COVID-19 treatments, including new indications for approved drugs and new drug development. Unfortunately, the Agency did not receive a correlating number of new resources to address this significant increase in meeting volume. In addition, the onset of the COVID-19 pandemic (which contributed to the dramatic increase in workload), required the Agency to prioritize COVID-19 related submissions, utilizing our limited resources in order to appropriately address the public health emergency. The increased workload, pandemic focus, and limited resources resulted in difficulty achieving the meeting management goals.

Major Dispute Resolution goals:

There were a number of New Drug-related formal disputes this year that involved cross-cutting topics raising complex policy and scientific issues that took extra time to resolve.

In addition, with the increased COVID-19 workload and appropriate prioritization on addressing the public health emergency, some of the timelines for disputes were missed.

C. *FY 2021 Corrective Actions*

As we continue to appropriately prioritize and address the COVID-19 pandemic, we anticipate that once the pandemic ends, formal PDUFA meeting volume may return to pre-COVID levels and we anticipate that our limited resources will be able to address other important issues such as formal disputes in a more timely manner.

PDUFA Performance Enhancement Goals

The following section addresses section 904(a)(2) of FDARA (section 736B(c)(2) of the FD&C Act), which requires FDA to provide a justification for missed performance enhancement goals and a description of the efforts FDA has put in place to improve the ability of the Agency to meet each goal in the coming fiscal year (included here under the heading "FY 2021 Corrective Actions").

This section presents non-review performance goals cited in the PDUFA VI Commitment Letter with required completion dates in FY 2020. For the purposes of this report, *performance enhancement goals* are defined as any non-review performance goal with a specified deadline as named in the PDUFA Commitment Letter. Performance enhancement goals with specified completion dates in FY 2021 through FY 2022 will be covered in subsequent corrective action reports.

I. Guidances

A. *Summary of Performance*

The PDUFA goal dates for the following guidances were missed:

- Draft guidance describing approaches to identifying and developing measures for an identified set of impacts to facilitate collection of meaningful patient input in clinical trials.
- Draft guidance on FDA's benefit-risk assessment for new drugs and biologics.
- Draft guidance on general evidentiary standards for biomarker qualification to be supplemented with focused guidance on specific biomarker uses and contexts.

B. *Justification*

- Approaches to impact metrics draft guidance: The guidance describing approaches to identifying and developing measures for an identified set of impacts to facilitate collection of meaningful patient input in clinical trials was delayed due to departure of senior staff and then the shifting of agency priorities related to COVID-19. The pandemic utilized the reviewers working on the Patient Focused Drug Development (PFDD) guidance to consult on trial changes, to review submissions, and to help draft COVID-19 specific guidances. These guidances included the Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment (see www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs), which was published in September, and the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (see www.fda.gov/regulatory-information/search-fda-guidance-

documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency), which was published in March 2020. The latter guidance has been updated multiple times, with the most recent update being January 27, 2021.

- Benefit-risk draft guidance: A significant contributing factor for the delay in issuing a draft guidance on FDA's benefit-risk assessment for new drugs and biologics has been the COVID-19 pandemic, which began early in the document clearance process. The increased workload and critical priorities introduced by the pandemic resulted in delays in engaging in the comprehensive review and discussions that are a necessary part of development of a guidance on such a complex, multi-disciplinary topic.

- Biomarker qualification draft guidance: The draft guidance on general evidentiary standards for biomarker qualification was delayed because the working group developing the guidance included expertise from review divisions heavily impacted by the COVID-19 pandemic; pandemic work was prioritized over the guidance.

C. *FY 2021 Corrective Actions*

- Approaches to impact metrics draft guidance: The draft guidance for describing approaches to identifying and developing measures for an identified set of impacts to facilitate collection of meaningful patient input in clinical trials will be published as soon as it is completed.

- Benefit-risk draft guidance: The completion of the draft guidance on FDA's benefit-risk assessment for new drugs and biologics remains a strong priority for FDA. The document is being finalized for issuance.

- Biomarker qualification draft guidance: The draft guidance on general evidentiary standards for biomarker qualification will be published as soon as it is completed.

II. Website Publishing

A. *Summary of Performance*

FDA missed the PDUFA goal date for posting on the web the FY 2019 fourth and FY 2020 first quarter hiring data.

B. *Justification*

In 2019, FDA implemented a new methodology for the purpose of these postings that defines a "hire" as "someone who has been confirmed as on board by the date indicated in a full-time position at the noted Center." Using this new methodology, FDA can provide clearer and more precise data that are easier to obtain and report and are more closely aligned with what the commitment intended. This led to some confusion with compiling the correct quarterly hiring data, which contributed to delays in FDA's data

reporting. In addition, several POCs for hiring data left the Agency, which also contributed to continuing delays in receiving and aggregating the data.

C. *FY 2021 Corrective Actions*

The methodology for the calculations is now well established, as is the new process for obtaining and posting the data. Additionally, primary and secondary POCs for the data have been established.

III. Human Capital/Hiring

A. *Summary of Performance*

FDA missed the PDUFA goal for hiring in FY 2020. Specifically, 48 out of 58 (83%) employees were hired.

B. *Justification*

The FDA FY 2020 PDUFA hiring goals were not met; however, candidates were identified and selected for all positions. The federal hiring process requires clearances (e.g., security and ethics) to finalize the onboarding process which led to some delays in onboarding and subsequent declinations, requiring the reinitiation of the recruitment process. The time-to-hire has been further impacted by the COVID-19 pandemic by requiring FDA to maximize candidate flexibilities to include extended start dates to accommodate candidates' individual circumstances.

C. *FY 2021 Corrective Actions*

As FDA continues to use the hiring authority granted under the 21st Century Cures Act to advance hiring, hiring managers continue to focus on prioritizing the completion of the recruitment and selection process by the third quarter of the fiscal year. By doing so, this will increase FDA's ability to identify alternative selections should a candidate decide to decline the offer as well as allow additional time for the various clearance processes.

Due to the COVID-19 pandemic, FDA had to quickly transition its recruitment process to incorporate virtual platforms as an essential outreach strategy to build external candidate talent pools. Thus, hiring managers will continue to increase their use of social media and other innovative recruitment tools to enhance recruitment and outreach in support of user fee hiring goals.

IV. Reporting

A. Summary of Performance:

FDA missed the PDUFA goal date for publishing the Interim Assessment of Hiring and Retention.

B. Justification:

The government shutdown delayed by several months the award for the contract under which this assessment was performed. Additionally, the onset of the COVID-19 pandemic prevented timely report review by key staff from Office of Operations, CDER and CBER.

C. FY 2021 Corrective Actions:

The assessment was published on June 5, 2020.

V. Public Meetings

A. Summary of Performance:

- FDA missed the PDUFA goal date for holding a public meeting on the Interim Assessment of Hiring and Retention.
- FDA did not hold a quarterly meeting in the fourth quarter of 2020 on enhancing transparency and accountability of FDA electronic submission and data standards activities.
- The FY 2020 Annual Public Meeting for the IT Strategic Plan was not held.

B. Justification:

- The COVID-19 pandemic made it difficult to find a date for the public meeting on the Interim Assessment of Hiring and Retention prior to the goal date on which key senior leadership could attend. Likewise, COVID-19 priorities delayed the fourth quarter 2020 meeting with industry related to electronic submission and data standards.
- The FY 2020 Annual Public Meeting for the IT Strategic Plan was initially scheduled within goal, but industry and FDA jointly agreed to cancel it to focus on addressing the COVID-19 pandemic.

C. FY 2021 Corrective Actions:

- The public meeting on the Interim Assessment of Hiring and Retention was held on July 30, 2020.
- The fourth quarter 2020 meeting on enhancing transparency and accountability of FDA electronic submission and data standards activities is slated to be held in the first quarter of 2021.

Appendix E: Definitions of Key Terms

A. The phrase *review and act on* means the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

B. Review Performance Goal Extensions

1. Major Amendments

   a. A major amendment to an original application, efficacy supplement, or Class 2 resubmission of any of these applications, submitted at any time during the review cycle, may extend the goal date by 3 months. [Note: If the review cycle occurred prior to FY 2013, the major amendment must have been received within 3 months of the action due date to extend the action goal date by 3 months.]

   b. A major amendment may include, for example, a major new clinical safety/efficacy study report; major re-analysis of previously submitted study (studies); submission of a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) not included in the original application; or significant amendment to a previously submitted REMS with ETASU. Generally, changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.

   c. A major amendment to a manufacturing supplement submitted at any time during the review cycle may extend the goal date by 2 months. [Note: If the review cycle occurred prior to FY 2013, the major amendment must have been received within 2 months of the action due date to extend the action goal date by 2 months.]

   d. Only one extension can be given per review cycle.

   e. Consistent with the underlying principles articulated in the Good Review Management Principles and Practices for PDUFA Products guidance,[18] FDA's decision to extend the review clock should, except in rare circumstances, be limited to occasions where review of the new information could address outstanding deficiencies in the application and lead to approval in the current review cycle.

2. Inspection of Facilities Not Adequately Identified in an Original Application or Supplement

   a. All original applications, including those in the "Program," and supplements are expected to include a comprehensive and readily located list of all manufacturing facilities included or referenced in the application or supplement. This list provides FDA with information needed to schedule inspections of manufacturing facilities that may be necessary before approval of the original application or supplement.

   b. If, during FDA's review of an original application or supplement, the Agency identifies a manufacturing facility that was not included in the comprehensive and readily located list, the goal date may be extended.

[18] https://www.fda.gov/media/99140/download

i. If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in an original application or efficacy supplement, the goal date may be extended by 3 months.
ii. If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in a manufacturing supplement, the goal date may be extended by 2 months.

C. A *resubmitted original application* is an applicant's complete response to an action letter addressing all identified deficiencies.

D. *Class 1 resubmitted applications* are applications resubmitted after a complete response letter (or a not approvable or approvable letter) that include the following items only (or combinations of these items):

1. Final printed labeling
2. Draft labeling
3. Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information, including important new adverse experiences not previously reported with the product, are presented in the resubmission)
4. Stability updates to support provisional or final dating periods
5. Commitments to perform postmarketing studies, including proposals for such studies
6. Assay validation data
7. Final release testing on the last 1-2 lots used to support approval
8. A minor reanalysis of data previously submitted to the application (determined by the Agency as fitting the Class 1 category)
9. Other minor clarifying information (determined by the Agency as fitting the Class 1 category)
10. Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry

E. *Class 2 resubmissions* are resubmissions that include any other items, including any item that would require presentation to an advisory committee.

F. Meeting requests commit FDA to notify the requestor of a formal meeting in writing within 14 days of request for Type A and Type B (EOP) meetings or within 21 days of request for Type B and Type C meetings.

G. Scheduled meetings should be made within 30 days of receipt of request for Type A meetings, 60 days for Type B meetings, 70 days for Type B (EOP) meetings, and 75 days for Type C meetings. If the requested date for any of these types of meetings is greater than 30, 60, or 75 days, as appropriate, from the date the request is received by FDA, the meeting date should be within 14 days of the requested date.

H. Preliminary responses to sponsor questions contained in the background package for Type B (EOP) meetings should be sent to the sponsor no later than 5 calendar days prior to the meeting date.

I. Meeting minutes are to be prepared by FDA clearly outlining agreements, disagreements, issues for further discussion, and action items. They will be available to the sponsor within 30 days of the meeting.

J. *A Type A Meeting* is a meeting that is necessary for an otherwise stalled drug development program to proceed (a "critical path" meeting) or to address an important safety issue.

K. Type B meetings include pre-IND meetings and pre-NDA/BLA meetings, while Type B(EOP) meetings are reserved for certain End-of-Phase 1 meetings (i.e., for 21 CFR part 312 subpart E or 21 CFR part 314 subpart H or similar products) and End-of-Phase 2/pre-Phase 3 meetings. Meetings regarding REMS or postmarketing requirements that occur outside the context of the review of a marketing application will also generally be considered Type B meetings.

L. A *Type C Meeting* is any other type of meeting.

M. The performance goals and procedures also apply to original applications and supplements for human drugs initially marketed on an over-the-counter (OTC) basis through an NDA or switched from prescription to OTC status through an NDA or supplement.

N. IT-specific definitions:

1. *Program* refers to the organizational resources, procedures, and activities assigned to conduct "the process for the review of human drug applications," as defined in PDUFA.
2. *Standards-base* means compliant with published specifications that address terminology or information exchange between FDA and regulated parties or external stakeholders, as adopted by FDA or other agencies of the federal government, and often based on the publications of national or international Standards Development Organizations.
3. *FDA Standards* means technical specifications that have been adopted and published by FDA through the appropriate governance process. FDA standards may apply to terminology, information exchange, engineering or technology specifications, or other technical matters related to information systems. FDA standards often are based on the publications of other federal agencies or the publications of national or international Standards Development Organizations.
4. *Product life cycle* means the sequential stages of human drug development, regulatory review and approval, postmarket surveillance and risk management, and where applicable, withdrawal of an approved drug from the market. In the context of the process for the review of human drug applications, the product life cycle begins with the earliest regulatory submissions in the IND phase, continues through the NDA or BLA review phase, and includes postmarket surveillance and risk management activities as covered under the process for the review of human drug applications.

O. Special Protocol Assessments: Upon specific request by a sponsor, FDA will evaluate certain protocols and issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

P. The Application Integrity Policy focuses on the integrity of data and information in applications submitted to FDA for review and approval. It describes FDA's approach regarding the review of applications that may be affected by wrongful acts that raise significant questions regarding data reliability. More information on the policy is available at www.fda.gov/downloads/ICECI/EnforcementActions/ApplicationIntegrityPolicy/UCM072631.pdf.

Department of Health and Human Services
Food and Drug Administration

This report was prepared by FDA's Office of Planning in collaboration with the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). For information on obtaining additional copies, contact:

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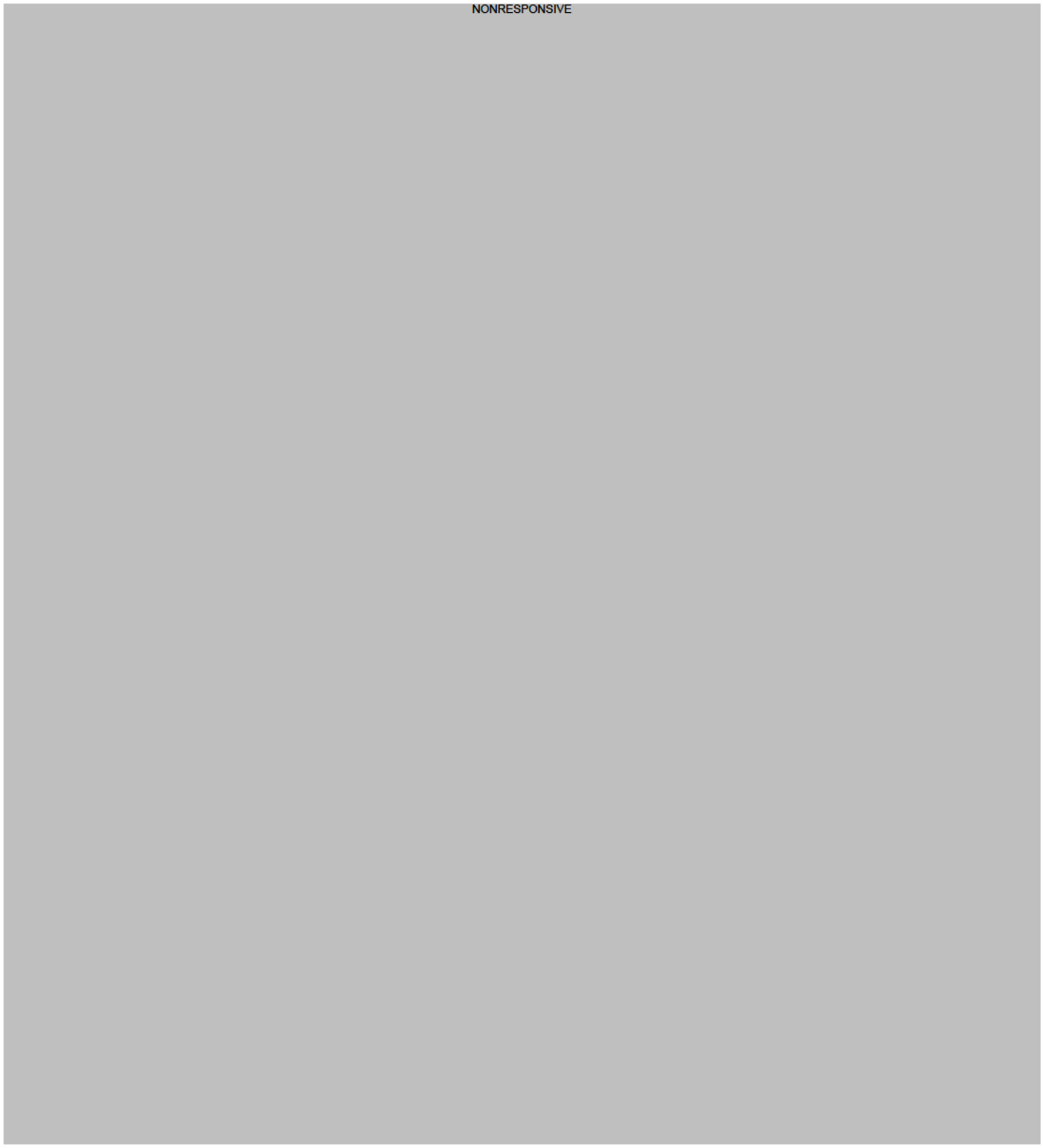
This report is available on the FDA home page at www.fda.gov.

Office of New Drugs Biweekly Report

October 15, 2021

Reporting Period: October 4th to November 12th

NONRESPONSIVE


NONRESPONSIVE

Recent and Upcoming NDA/BLA Actions

New Molecular Entities (NDA/BLA)						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Molecular Entities (NDA/BLA)

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

[PAGE * MERGEFORMAT]

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

505(b)(2) Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Biosimilar Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Efficacy Supplements						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

Other Applications						
Drug Name	App. No./ Filing Status	Division	Notable Issue	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE						

New Applications Received

Notable IND Applications

Drug Name	App. No./	Division	Notable Issue	Received Date	Goal Date	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

New Molecular Entities (NDA/BLA)

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

New Molecular Entities (NDA/BLA)							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

[PAGE * MERGEFORMAT]

New Molecular Entities (NDA/BLA)

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

505(b)(2) Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action

NONRESPONSIVE

[PAGE * MERGEFORMAT]

505(b)(2) Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Biosimilar Applications

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements

Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	**App. No./ Filing Status**	**Division**	**Notable Issue**	**Received Date**	**Goal Date (PDUFA/ BsUFA)**	**Planned Action Date**	**Application Information Planned Action**
NONRESPONSIVE							
Lupron Depot 7.5 mg; 3M 22.5 mg, 4M 30 mg, and 6M 45 mg	NDA 019732/ S-045 NDA 020517/ S-043 Filed	DO 1		8/6/2021	6/6/2022	5/6/2022	AbbVie; palliative treatment of advanced prostatic cancer; supplement is requesting to remove "palliative" from palliative treatment of advanced prostatic cancer. Filing date: 10/5/2021.
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Efficacy Supplements							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA/ BsUFA)	Planned Action Date	Application Information Planned Action
NONRESPONSIVE							

Other Applications							
Drug Name	App. No./ Filing Status	Division	Notable Issue	Received Date	Goal Date (PDUFA)	Planned Action Date	Application Information (Applicant/Sponsor name, indication) Planned Action
NONRESPONSIVE							

Notable End-of-Phase 2 Meetings

Notable Type A/Type B						
Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

[PAGE * MERGEFORMAT]

Notable Type A/Type B

Meeting Type	Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE						

Other Notable End-of-Phase Meetings

Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information
NONRESPONSIVE					

Other Notable End-of-Phase Meetings					
Drug Name	**App. No.**	**Division**	**Notable Issue**	**Meeting Dates (Internal/Sponsor)**	**Application Information**
NONRESPONSIVE					

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Other Notable End-of-Phase Meetings					
Drug Name	App. No.	Division	Notable Issue	Meeting Dates (Internal/Sponsor)	Application Information

NONRESPONSIVE

Clinical Holds					
Drug Name	App. No.	Division	Notable Issue	Date Issued	Application Information

NONRESPONSIVE

Advisory Committee Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Other Public Meetings

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Office or Division	Date	Summary
NONRESPONSIVE			

Other Meetings

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Drug Name or Meeting Title	Division	Date	Summary
NONRESPONSIVE			

Breakthrough Therapy Designations

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Drug Name/ App. No./	Sponsor	Division	Indication	Decision (Grant/Deny/Pending)
NONRESPONSIVE				

Formal Dispute Resolution Requests

Office/ Division	Deciding Authority/ Appeal level	Sponsor	Drug Name/ Application No.	Description	Status or Outcome
NONRESPONSIVE					

CDER Biosimilar Review Committee, CDER/CBER Biosimilar Policy Council, and CDER/CBER Biologicals Product Classification Subcommittee (to be completed by OTBB Operations)

Meeting Type	App. No.	Date	Office/Division	Topic
NONRESPONSIVE				

Safety Issues

Newly Identified Safety Signals				
Drug Name	**SSID No.**	**Division**	**Planned or Actual Date of Action**	**Description**
NONRESPONSIVE				

Newly Identified Safety Signals				
Drug Name	SSID No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Drug Safety Communications				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Safety Labeling Change				
Drug Name	App. No.	Division	Planned or Actual Date of Action	Description
NONRESPONSIVE				

Publications and External Presentations

Publications			
Office/ Division	FDA Authors	Citation with Link	Publication Date
NONRESPONSIVE			

External Presentations					
Office/ Division	FDA Presenters	Conference/Workshop/Mtg	Title/Topic	Location	Date and Time

NONRESPONSIVE

Leave and Coverage

NONRESPONSIVE

Guidances and Noteworthy Policy Documents Recently Published or In Clearance

In Clearance, OND-Authored			
Authoring Div. or Office	Title of Guidance/Document	Status (Draft, Final or Revision)	OND Clearance Due Date
NONRESPONSIVE			

In Clearance, Authored Outside of OND
NONRESPONSIVE

Recently Published, OND-Authored			
Authoring Div. or Office	Title of Guidance/Document	Status (Draft, Final or Revision)	Publication Date
NONRESPONSIVE			