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Using FDASIA to Move Forward with Pediatric Drug Development

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Overview

- Overview of the Pediatric Study Plan (PSP)
- Recommended Sections of the PSP
- PeRC Review of the initial PSP, amended PSP, and agreed initial PSP
- PeRC Review of Written Requests
- Deferral Extension Process
- Non-compliance letters for Overdue PREA Studies

Acronyms

- BPCA – Best Pharmaceuticals for Children Act
- EMA – European Medicines Agency
- EOP2 – End of Phase 2
- FDAAA – Food & Drug Administration Amendments Act (2007)
- FDASIA – Food & Drug Administration Safety and Innovation Act (2012)
- PD – Pharmacodynamics
- PeRC – Pediatric Review Committee
- PK – Pharmacokinetic
- PM – Project Manager or Regulatory Project Manager
- PMR – Post Marketing Requirement
- PPSR – Proposed Pediatric Study Request
- PREA Pediatric Research Equity Act
- PSP – Pediatric Study Plan

Evolution of Pediatric Initiatives

- 1979 - Labeling Requirement
- 1994 - Final Rule: Pediatric labeling-extrapolation of efficacy
- 1997 - FDAMA/Pediatric Exclusivity Provision
- 1998 - Final Rule: Pediatric Studies Required
- 2001 - Subpart D: *Additional Safeguards for Children in Clinical Investigations of FDA-regulated products*

Where Are We Today?

- 2002 - Best Pharmaceuticals for Children Act
- 2003 - Pediatric Research Equity Act
- 2007 - Both Reauthorized under FDAAA
- 2012 - Both Made Permanent under FDASIA

Overview of the PSP

What is a Pediatric Study Plan?

- Outline of the pediatric study or studies the applicant plans to conduct
- Should include to the extent practicable
  - Study objectives and design
  - Age groups to be studied
  - Relevant endpoints
  - Statistical approach
  - Request for deferral, partial waiver, or full waiver
  - Supporting documentation

What is a Pediatric Study Plan?

- The intent of the PSP is to encourage sponsors to identify pediatric studies as early as possible in product development, and when appropriate, to conduct those studies prior to the submission of the NDA or BLA.
- It is understood that in some situations, it may be premature to include detailed pediatric study designs due to the need for additional data (e.g., efficacy, safety, appropriate endpoints, etc.).

Timing of PSP Submission

- EOP2 Meeting occurs on or after 11-6-12
  - PSP must be submitted within 60 days.

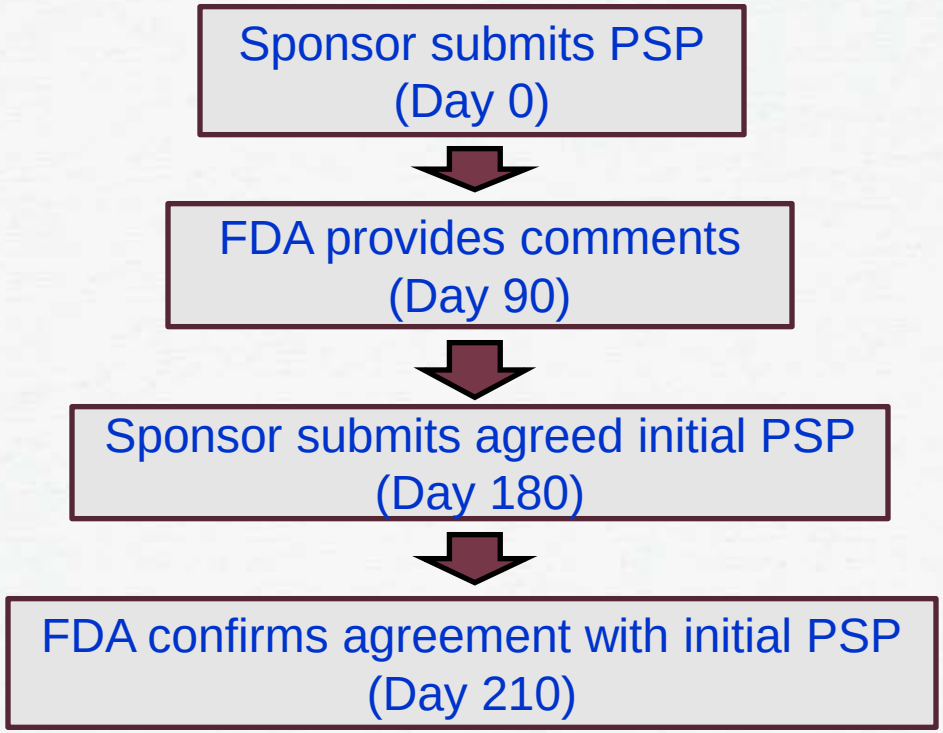
- EOP2 Meeting occurred prior to 11-6-12 or no EOP2 meeting will occur
  - If application expected to be submitted prior to 1-5-14 (one year after PSP process implemented under FDASIA), FDAAA rules apply and pediatric plan must be submitted no later than the application is filed.

Timing of PSP Submission (cont.)

- EOP2 Meeting Occurred prior to 11-6-12 or no EOP2 meeting will occur (cont.)
  - If application will be submitted on or after 1-5-14, PSP should be submitted as early as possible and at a time agreed upon by FDA and sponsor.
    - FDA strongly encourages PSP to be submitted prior to the initiation of Phase 3 studies.
    - PSP must be submitted no later than 210 days prior to submission of application.

Timing of PSP Submission

How did we arrive at 210 days for the process?



Recommended Sections of the PSP

Overview of Disease in Pediatric Population

- Pathophysiology of the disease
- Methods of diagnosis
- Currently available treatments and/or prevention strategies in pediatric patients, including neonates
- Incidence and prevalence in both the overall population and the pediatric population
- 1-5 pages

Overview of the Drug Or Biological Product

- Proposed mechanism of action of the product
- Description of the potential therapeutic benefits or fulfillment of therapeutic needs in the pediatric population, including neonates
- May include any other possible therapeutic uses of the product in children beyond the disease or indication being sought
- 1-5 pages

Overview of Extrapolation to Specific Pediatric Populations

- Plans to extrapolate efficacy from adults to children or from one pediatric age group to another
- Clear justification and available supporting data for extrapolation in all age groups
- Information on the similarities (and differences) between adults and children (or between one pediatric population and another) in disease pathogenesis

Overview of Extrapolation to Specific Pediatric Populations (cont.)

- Criteria for disease definition, clinical classification, and measures of disease progression
- Pathophysiologic, histopathologic, and pathobiological characteristics of the disease
- 1-5 pages

Request for Product Specific Waivers

- Plans to request either full or partial waiver
- Clear justification with supporting data to support waiver
- Data from all available sources, including sponsor data, published literature, expert panels and workshops, consensus documents

Request for Product Specific Waivers (cont.)

- Information on other products in the same class that have been previously granted a waiver
- 1-3 pages
- Waivers not officially granted until product is approved

Summary of Planned Nonclinical Studies

- Necessary if existing nonclinical data are not sufficient to support proposed clinical trials
- Include species to be studied
- Include type of study
- Should be in table format

Summary of Planned Clinical Studies

- Include age group for each study
- Include type of study
- Include comments about the study
- Indicate whether a deferral request is planned
- Should be in table format

Pediatric Formulation Development

- Potential use of formulation currently being developed in all pediatric populations
- Details of any pediatric-specific formulation development plans
- Information regarding all planned excipients, to the extent practicable
- Details about the size of all planned capsules or tablets to be used in pediatric studies
- 1-3 pages

Nonclinical Studies

- Brief description of the data from relevant nonclinical studies
- Information that supports the maximum dose and duration of treatment
- Rationale for not including any additional nonclinical studies if none are planned

Nonclinical Studies (cont.)

- Brief description of any studies to be performed including
  - Species to be studied
  - Age of animals at start of dosing
  - Duration of dosing and target organ systems of concern
  - Key developmental endpoints to be evaluated
- 1-5 pages

Additional Data to Support Studies in Children

- Details of any additional data to support the design and/or initiation of pediatric studies
- Available data in adults or children who have received treatment with the product for any condition in earlier studies
- 1-5 pages

Clinical Studies

- Pediatric Pharmacokinetic studies (1-10 pages)
- Include the following to the extent possible:
  - Outline of each pediatric PK/PD study(ies) planned
  - Type of Study/Study Design
  - Objectives of Study
  - Age Group and population to be studied
  - Pediatric formulations to be used

Clinical Studies

- Include the following to the extent possible (cont.):
  - Dose ranges to be used in PK studies
  - Endpoints and justification (PK parameters, PD biomarkers)
  - Existing or planned modeling and simulation of doses to be used

Clinical Studies

- Clinical Effectiveness and Safety Studies Planned (1-10 pages)
- Include the following to the extent possible:
  - Outline of each pediatric study planned
  - Type of Study/Study Design
  - Objectives of Study
  - Age Group and population to be studied

Clinical Studies

- Include the following to the extent possible (cont.):
  - Inclusion and Exclusion criteria
  - Endpoints (primary and key secondary) to be used
  - Timing of endpoint assessments
  - Safety assessments
  - Statistical approach

Timeline of the Pediatric Development Plan

- Provide general timeline for the completion of the specific components in the PSP template outline.
- Estimate dates based on current projections for the development program.
- Amend initial PSP if dates change.
- Provide justification for amending dates.
- Include dates for estimated protocol submission, estimated study initiation, and estimated final study submission and list as, “No later than _____.”

Plan to Request Deferral of Pediatric Studies

- Include plans to defer pediatric studies in some or all pediatric groups until after approval of future application.
- Deferred assessments should include data from the following:
  - Studies that will be completed, but are not included in application

Plan to Request Deferral of Pediatric Studies (cont.)

- Deferred assessments should include data from the following (cont.):
  - Studies that are ongoing
  - Studies that will not have started at the time of approval of future application
- Include adequate justification for deferring studies.
- 1-2 pages

Agreements for Pediatric Studies with Other Regulatory Authorities

- Summary of agreed-upon pediatric investigation plan with EMA or other regulatory authority
- Summary of draft plan if negotiations are in progress
- 1-5 pages

PeRC Review of the Initial PSP, Amended PSP, and Agreed Initial PSP

Timeline for Review of Initial PSP

- Review division and PeRC must review initial PSP within 90 days.
  - Sponsor should submit both a PDF and Word version of the PSP to facilitate PeRC review.
- Review division must either provide written comments to the sponsor or meet with the sponsor by day 90 to provide feedback on the initial PSP.

PeRC Review of Initial PSP

- Ideally, PeRC review should occur before Day 75.
- Review Division PM should contact the PeRC PM as soon as the PSP arrives in order to schedule PeRC review.
- PeRC review will include tracked changes to the initial PSP submitted by the sponsor. PeRC will provide any recommended tracked changes to the review division.
- The review division will finalize their comments and provide recommended changes to the PSP to the sponsor in tracked changes for ease of review.

Timeline for Review of Agreed Initial PSP

- The sponsor should review and negotiate any further edits to the PSP with the review division within 90 days of the meeting or receipt of written comments.
- The sponsor must submit an “Agreed Initial PSP” within 90 days of the meeting or receipt of written comments.

Timeline for Review of Agreed Initial PSP (cont.)

- Prior to the review division responding to the “Agreed Initial PSP,” they must consult PeRC and PeRC must review.
- The review division must confirm agreement with “Agreed Initial PSP” within 30 days of submission of Agreed Initial PSP.

PeRC Review of Agreed Initial PSP

- Ideally, PeRC review should occur before Day 25.
- Review Division PM should contact PeRC PM as soon as Agreed Initial PSP arrives in order to schedule PeRC review.
- PeRC will review the materials provided by the sponsor and the review division to make a final recommendation of agreement or no agreement with the Agreed Initial PSP.

Timeline for Review of Amended PSP

- Review division must review amended PSP.
- If the proposed changes are significant, PeRC must also review during that timeframe.
  - Examples of significant changes to a PSP include, but are not limited to
    - Removal or addition of one or more entire study(ies)
    - A change in the nonclinical program
    - A change in plans for formulation development

Timeline for Review of Amended PSP (cont.)

- If the proposed changes are significant, PeRC must also review during that timeframe. (cont.)
  - The sponsor should submit both a PDF and Word version of the amended PSP to facilitate PeRC review.
- Review division must provide written comments to the Sponsor or meet with the Sponsor by day 90 to provide feedback on the amended PSP.

PeRC Review of Amended PSP

- Ideally, PeRC review, if needed, should occur before Day 75.
- Review Division PM should contact the PeRC PM as soon as the amended PSP arrives to schedule PeRC review.

PeRC Review of Amended PSP (cont.)

- PeRC review will include tracked changes in the actual sponsor-amended PSP (provided to PeRC by the review division). PeRC will provide any recommended tracked changes to the review division.
- The review division will finalize their comments and provide recommended changes to the amended PSP to the sponsor in tracked changes for ease of review.

Timeline for Review of Agreed Amended PSP

- The sponsor must incorporate recommendations and submit “Agreed Amended PSP” within 90 days of the meeting or receipt of written comments
- Prior to the review division responding to the “Agreed Amended PSP,” they must consult PeRC and PeRC must review if the changes are significant.
- The review division must confirm agreement with “Agreed Amended PSP” within 30 days of submission of Agreed Amended PSP

PeRC Review of Agreed Amended PSP

- Ideally, PeRC review, if required, should occur before Day 25.
- Review Division PM should contact PeRC PM as soon as Agreed Amended PSP arrives in order to arrange PeRC review.
- PeRC will review the materials provided by the sponsor and the review division to make a final recommendation of agreement or no agreement with the Agreed Amended PSP.

Timeline for Pediatric Study Plan Review

Day 0

End of Phase 2 Meeting

60 days

Day 60

Sponsor must submit initial PSP

90 days

PeRC review and concurrence with initial PSP

Division review of initial PSP

Day 150

Sponsor meeting to discuss initial PSP (or written responses in lieu of meeting)

90 days

Division and sponsor negotiate PSP

Day 240

Sponsor must submit Agreed Initial PSP

30 days

PeRC review and concurrence with Agreed Initial PSP

Day 270

Letter to confirm agreement with plan must be sent

PeRC Review of Written Requests

Timeline for Review of Written Requests

- Internal FDA goal is to respond to the Proposed Pediatric Study Request (PPSR) from sponsor within 120 days.
- Response to a PPSR may be either a Written Request or an Inadequate Letter.
- PeRC must review all Written Requests before issued.

PeRC Review of Written Requests

- As soon as the Review Division has decided that they will issue a Written Request, the Review Division PM should contact the PeRC PM to schedule PeRC review of the Written Request.
- The PeRC will review the Written Request and make recommendations.
- PeRC considers the public health benefit of the studies when making recommendations.

Deferral Extension Process

Deferral Extensions

- Phase 1: PREA PMRs due on or before April 5, 2013
  - This provision also applies to all PREA PMRs and studies that were deferred under the Pediatric Rule that also triggered PREA.
  - Sponsors must submit Deferral Extension Requests by January 5, 2013.
  - PeRC must review and make a recommendation to the review division.
  - Review division must either grant or deny deferral extension by July 9, 2013.

Deferral Extensions (cont.)

- Phase 2: PREA PMRs due after April 5, 2013
  - Sponsor must request Deferral Extension at least 90 days prior to the due date.
  - FDA must respond within 45 days of request.
  - Ideally, PeRC review will take place by Day 40.

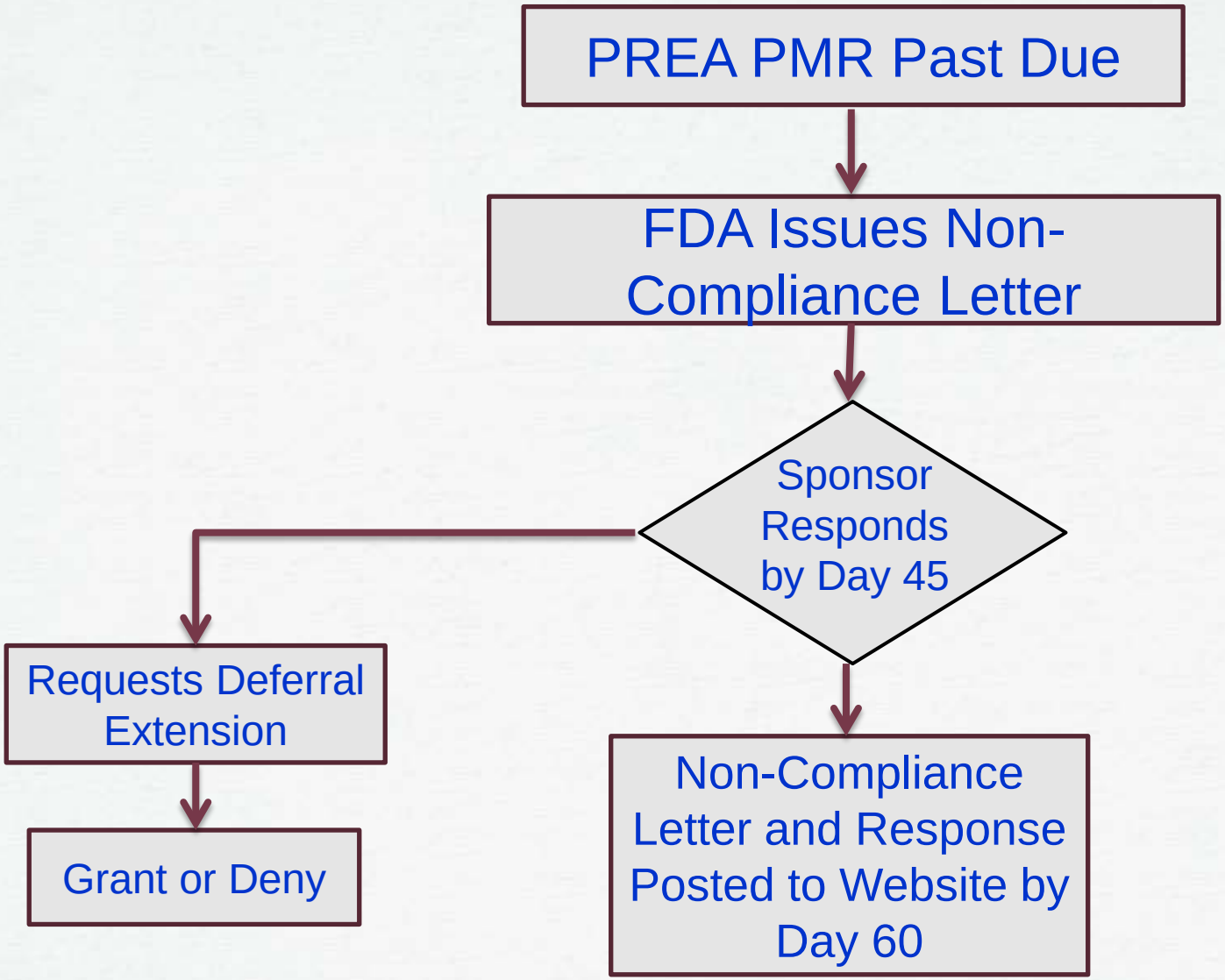
Deferral Extensions

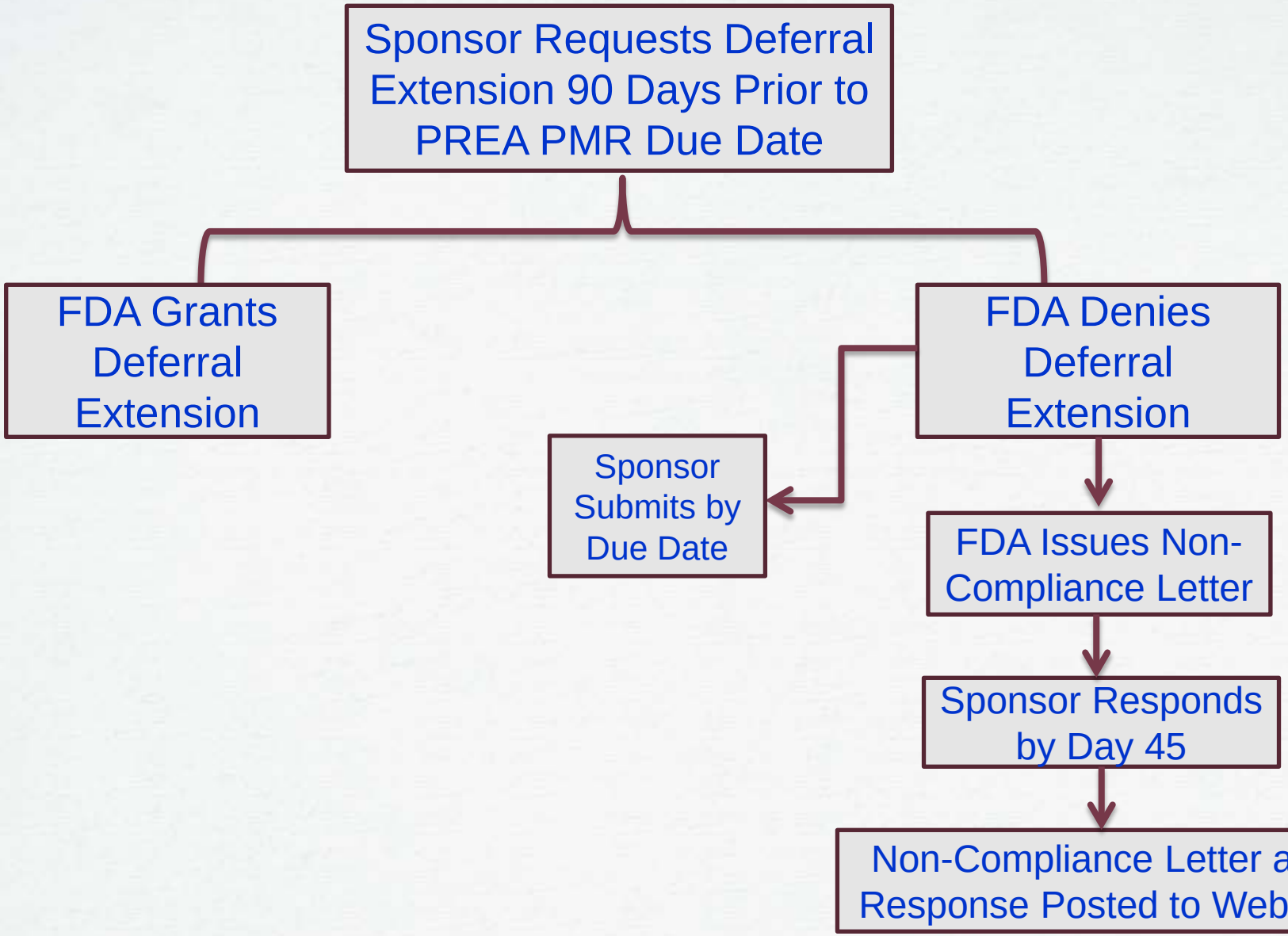
- General criteria for acceptance of deferral extension requests
  - Sponsor can show that delay in development could not have been prevented or could not have been foreseen.
  - Sponsor will still be able to complete the studies.
  - Provide general consistency with reasons for delayed FDAAA PMRs.

Non-compliance letters for Overdue PREA Studies

Overview of Non-Compliance Letters

- If sponsors have not submitted PREA studies by the due date and have not received a deferral extension, FDA will issue a non-compliance letter.
- Sponsor must respond to non-compliance letter within 45 days.
- FDA will post on the FDA website both the non-compliance letter and the sponsor's response 60 days after the letter is issued.


PREA PMR Past Due
FDA Issues Non-Compliance Letter
Sponsor Responds by Day 45
Requests Deferral Extension
Grant or Deny
Non-Compliance Letter and Response Posted to Website by Day 60


Sponsor Requests Deferral Extension 90 Days Prior to PREA PMR Due Date
FDA Grants Deferral Extension
FDA Denies Deferral Extension
Sponsor Submits by Due Date
FDA Issues Non-Compliance Letter
Sponsor Responds by Day 45
Non-Compliance Letter and Response Posted to Website

Questions?


THE
END