Developing Complex Generics- How to Ensure Success-Industry Perspective

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Disclaimer:

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the opinions of Teva

LOST???

I wish we had good directions?!?!

Pre-GDUFA roadmap for Complex Generics

How has the roadmap improved? Are we better off now?

It helps if you follow the directions

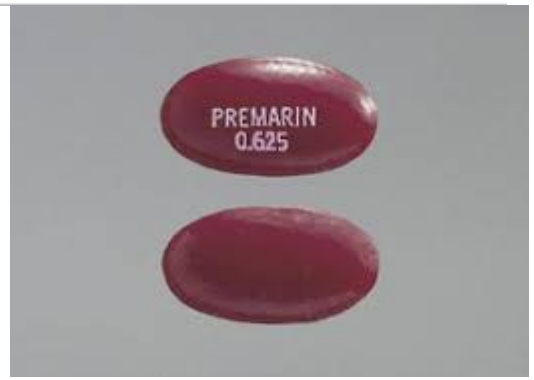
History and Progress

GDUFA has ushered in major progress

- Since 2012 close to 900 product specific guidances have been issued
  - Almost 40% of those are for complex products
- As part of GDUFA II more interaction with FDA can occur through the Pre-ANDA program
  - Product Development meetings
  - Pre-submission meetings
  - Mid cycle review meetings
  - MAAP 5220.8 issued in September 2019, outlining the policies and procedures for such meetings
- Overall, this leads to more guidance and interaction with the agency than ever before

What are Complex Generic Drug Products?

- Complex products include:
  - Complex routes of delivery
  - Complex formulations
  - Complex API
  - Complex Drug-Device combinations
  - Complex Dosage Forms
  - Other products- where approval pathway is uncertain or an alternative approach may be warranted with early scientific input from FDA



What are the “goals” for FDA in meetings with industry

- Product Development Meetings
  - FDA can meet the Goal by either
    - conducting a meeting or
    - providing a meaningful written response that will inform development and/or regulatory decision making to the applicant, within the applicable goal date
- Pre-Submission Meetings
  - Grant/Deny
    - 1st 2 years of GII – within 30 days
    - last 3 years GII within 14 days
- Meetings to be held within 120 days of being granted.

You are about to develop a complex generic

What are your options?

- #1 - If there is a PSG- follow it to the letter
- #2 - If there is no PSG- approach FDA through a predevelopment meeting
- #3 - Alternate approach to the PSG- approach FDA - predevelopment meeting
- #4 - Proceed at your own peril
- #5 - Go back to developing simple products

Other FDA interaction opportunities- Controlled correspondence

- Controlled Correspondence (CC)
  - FDA will review and respond to standard CC's and to complex CC's with meaningful responses that can more consistently inform development and/or regulatory decision making
    - Review & respond to Standard CC's w/in 60 days of submission
    - Review & respond to Complex CC's w/in 120 days of submission
  - FDA will review and respond to 90% of requests to clarify ambiguities in the CC response w/in 14 days of receipt of such request.

How to ensure success

- If you are unsure, utilize the pre-ANDA meeting as well as other avenues, throughout the development process
- Take advantage of pre-ANDA and post CRL meetings to get FDA concurrence
- Do not expect FDA to do your work for you!! Non specific questions or seeking solutions from the agency will lead to a denial of the meeting
- All meeting requests should be supported with data, and suggestions from the sponsor on how to solve the problem/issue
- Make the interaction with FDA be a normal routine. Incorporate this behavior in your development process and timelines

How to ensure success (continued)

- Understand your product! Based on the target product profile, have well defined critical quality attributes (CQA's)
- Understand the Critical process parameters (CPP) in your manufacturing process and how changes can affect the product
- Ensure your critical materials are secured and available throughout development and submission process (API, critical excipients etc.)
- Continual testing of RLD throughout the development and submission process, so potential RLD changes can be identified early and included in the development plan
- Specifically for products with complex API, ensure you are using the most modern, quantitative analytical techniques to characterize and establish API sameness

How to ensure success (continued)

- For implants and IUD's, develop discriminatory, accelerated and predictive (if possible) drug release methods
- For drug-device combinations:
  - Conduct your pivotal BE study on the to be marketed device
  - Consider the overall presentation and the user interface during development
  - To support design differences between generic drug-device and RLD, three point threshold analysis along with comparative use human factor studies should be conducted
  - Device should be shown to be compatible with the formulation through appropriate studies (extractable/leachable studies etc.)

Teva's experience

- Teva has had numerous opportunities to interact with the agency for pre-ANDA, post-CRL and pre-submission meetings
- In general:
  - The products included in our experience examples were drug-device combinations, complex formulation, complex dosage form and complex API
  - When we submitted a complete package with clear and concise questions, we received detailed, thoughtful and scientific responses that were extremely helpful to our development process
  - When we submitted a less robust package or unclear questions, the responses were less than optimal
  - In the end, the more robust the package, the better the feedback

Teva's experience (continued)

- One recent glaring example of a very poor interaction with FDA that Teva recently experienced
  - The product is a complex API
  - PSG is available since 2015
  - Teva followed the PSG and submitted the product
  - Teva received a major CRL stating the BE was inadequate
  - We were puzzled because we followed the recommendations in the PSG
  - FDA informed us another study was needed
  - We asked for clarification at a post-CRL meeting and were told another study is needed but FDA could not give us any detail on what they expected and suggested we submit a protocol.
  - We now have no clear regulatory pathway to approval and no idea how to proceed, because we believe the current PSG is adequate

Some final thoughts and suggestions

- For sponsors:
  - Take advantage of the opportunities to interact with FDA
  - Don’t think FDA will do your job for you, the interactions are only meaningful if you put the effort and thought into them
- For FDA:
  - Please post a timeline on when the PSG’s you are working on will be available
  - When updating guidances, could we get a “track changes” version, so we can clearly see what has changed?
  - When asking for additional studies in a CRL (in vitro or in vivo) is there any other more substantive mechanism to interact other than a post-CRL meeting?
  - While you are working on alternatives to CE studies, is there an opportunity to simplify the current designs, not just a copy of what the innovator did?

Before and After GDUFA for Complex Products

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