Recommendations from the Generic Industry Working Group for Comments on the Draft Guidance on General Principles for Development of Generic of Abuse-Deterrent Opioid Formulations

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The remarks in this presentation do not necessarily represent the views of that individual, or that individual's company, or individual working group participant companies, but represent only the best available consensus views of the working group as a whole

Day 1

Overview

- Background
- FDA Questions
  - FDA Q1: Based on any testing you have attempted to perform or performed in accordance with the March 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement? (Slides 7-10)
  - FDAQ2:Are there any characteristics of currently approved ADF RLDs for which issuance of product-specific guidance, beyond what is in the March 2016 draft guidance, can facilitate development of abuse-deterrent generic opioid drug products? (Slides 12,13)
  - FDAQ3:Are there any approaches or technologies for evaluating the abuse deterrence of generic opioid drug products that were not included in the March 2016 draft guidance that should be? (Slide 14)
  - FDAQ4: What additional actions could FDA take to encourage the submission of ANDAs that reference an opioid drug product whose labeling describes abuse-deterrent properties? (Slide 15,16)
  - FDA Q5:Are there potential consequences of the development and introduction of abuse-deterrent opioid drug products that warrant further consideration? (Slide 17)
- Case Study
- Summary

Background

- Generic products now account for 89% of US prescriptions
- As new abuse deterrent formulations are approved for brand products, there should be appropriate FDA guidance available for the development of the generic product
- 2014 FDA held public meeting about the then draft guidance '*Abuse Deterrent Opioids- Evaluation and Labeling*' and asked input from generic industry
- 2015 FDA issued final guidance '*Abuse Deterrent Opioids – Evaluation and Labeling'*
- 2016 FDA issued draft guidance '*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*'

Background Cont..

- Currently, there are no FDA approved ADF opioid generics
- The current draft guidance requires further clarity on FDA's requirements for a generic to develop the data for submission of an ANDA
- The draft guidance must be revised, reissued for public comment, and then finalized expeditiously
- FDA issuance of Product Specific Guidance should be in close proximity to the RLD approval

Question 1: General Comments Draft Guidance Warranting Clarity

FDA QUESTION: Based on any testing you have attempted to perform or performed in accordance with the March 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement?

REGULATORY

- Provision of **consistent guidance** across ANDAs to ensure homogeneity of generic ADF products
- **Need regulatory pathway** for pending ANDAs (until GDUFA 2 – Complex Product)
- Need **additional communication venues** to discuss program with FDA beyond traditional controlled correspondence (until GDUFA 2)
- **As long as an ANDA contains appropriate studies for ADF, it should be accepted for filing**
- **Priority review** potential for generic ADF sponsors (until GDUFA 2)
- **Classification of ADF generics** as a Complex Product per GDUFA 2 alongside program provisions associated
- Refine Draft Guidance such that **nomenclature is analogous** and ordered to that of the brand Final Guidance

Question 1: General Comments Draft Guidance Warranting Clarity (2)

FDA QUESTION: Based on any testing you have attempted to perform or performed in accordance with the March 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement?

LEGAL POLICY

- Need clarity on conditions of approval of brand & incremental improvement to ensure 'ever greening' does not occur preventing approval of generic ADF options

STUDIES/TECHNOLOGIES/ANALYSES

- Need guidance on immediate release (IR) products & current/newer technologies that do not rely on excessive hardness (resistance to crush)
- Need to address number of test units testing or statistical power to detect specified difference should be performed on and, ideally this should be standardized
- Need statistical principles described to ensure inherent analytical variability within a method is properly accounted for

Question 1: General Comments Draft Guidance Warranting Clarity (3)

FDA QUESTION: Based on any testing you have attempted to perform or performed in accordance with the March 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement?

STUDIES/TECHNOLOGIES/ANALYSES (cont.)

- Need dedicated sections on the **required in-vitro studies** included in **product-specific guidance**
- Need **clarity on when a PK or PD studies may be re**quired and include in general guidance and details of the required study (ies) in **product-specific guidance**
- When possible the **Control should be same as used for RLD**. When not, details should be included in product specific guidance
- Need **FDA to develop acceptance criteria** for the in-vitro and the PK studies
  - Expect one-sided (e.g., no worse than)

Question 1: General Comments Draft Guidance Warranting Clarity (4)

FDA QUESTION: Based on any testing you have attempted to perform or performed in accordance with the March 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement?

STUDIES/TECHNOLOGIES/ANALYSES (cont.)

- Demonstration of AD properties would only **be performed against the RLD**
  - In vitro methods are used to verify that the suitability of non-dosing strengths
- Evaluation of the drug product's AD performance would **not be part of routine QC testing**
  - Sponsor demonstrates significant formulation/process understanding during product development
  - Requires appropriate release testing of key AD excipients prior to manufacture

GIWG Assumptions

- Category 1 (in vitro) mandatory, category 2 (pk) and category 3 (HAL) studies based on the science of the RLD:

  Examples

  - When the Category 1 and Category 2 testing are predictive (correlation exists or can be established) of Category 3, then only Category 1/Category 2 testing would be needed
  - If the Category 1 and Category 2 are not predictive (correlation does not exist or cannot be established) of Category 3, then Category 3 would be required
  - This would be explained in a product specific guidance.
  - Platform approach which leverages multiple drug products over a range of strengths
- Generic ADF opioids will not be subject to post marketing commitments (PMC) or requirements (PMR)
- Section 9 labeling to be comparable to brand (no carve-outs)
- Generic ADF opioids will be recognized as therapeutically equivalent in the Orange Book

Question 2: The Value of Product Specific Guidance

FDA QUESTION: Are there any characteristics of currently approved ADF RLDs for which issuance of product-specific guidance, beyond what is in the March 2016 draft guidance, can facilitate development of abuse-deterrent generic opioid drug products?

- FDA categorize ADF generic as Complex Product and provide GDUFA 2 provisions associated with it
  - Product development meetings associated with Complex Products
  - Pre-submission meeting should be vehicle to facilitate sponsor – FDA discussion and agreement on development plan including deviations from guidance when appropriate
- With advances in technology product might not be comparable in size, shape, and other attributes (per FDA guidance June 2015)

Question 2: The Value of Product Specific Guidance (cont.)

FDA QUESTION: Are there any characteristics of currently approved ADF RLDs for which issuance of product-specific guidance, beyond what is in the March 2016 draft guidance, can facilitate development of abuse-deterrent generic opioid drug products?

- Product Specific Guidance for generic ADF product should be issued within 30 days of approval of innovator
  - Via private meeting with generic manufacturers or other mechanism to ensure safety of public
- Consistent with the abuse deterrent attributes described for the RLD in the label
- Referring to the studies in both the general and product specific guidance in an analogous manner to that of the brand guidance (i.e., category 1, category 2, category 3) would be helpful

Question 3: Approaches or Technologies for Evaluating ADF Missing from Draft Guidance

FDA QUESTION: Are there any approaches or technologies for evaluating the abuse deterrence of generic opioid drug products that were not included in the March 2016 draft guidance that should be?

- Clarity around "totality of evidence" in terms of ADF context
- Very little information about PK or PD (HAL; Liking) and no details as to when they would be required and what combination
- Statistical acceptance criteria

Question 4: What FDA Could do to Foster Generic ADF ANDAs

FDA Question: **What additional actions could FDA take to encourage the submission of ANDAs that reference an opioid drug product whose labeling describes abuse-deterrent properties?**

- Timely product specific guidance
- The generic ADF product must have same label as innovator to mitigate potential safety events
- Similar to pediatric development, provide incentives for the generic manufacturer to address this public health crisis
  - Automatic priority review of generic ADF opioids ANDAs
  - Reduce fees for submission of such ANDAs

Question 4: What FDA Could do to Foster Generic ADF ANDAs (cont.)

What additional actions could FDA take to encourage the submission of ANDAs that reference an opioid drug product whose labeling describes abuse-deterrent properties? (cont.)

- Depending on route of abuse, FDA establish specific standard tests and then give confidence to manufacturers that products meet acceptable level of rigor
  - Collaborative endeavor between FDA and Industry to develop standards
- Design a Human Abuse Liability study (HAL) or other surrogate that is more reliable than the current design

Question 5: Further Consideration…

- ***FDA Question*: Are there potential consequences of the development and introduction of abuse-deterrent opioid drug products that warrant further consideration?**

  - The generic ADF opioid will be testing in accordance with the requirements associated with the RLD. Hence, the approved generic ADF opioid will demonstrate it is no less abuse deterrent than the RLD

  - If incremental improvement is not clarified on the innovator side and ever greening is not prevented, the American public may not be able to benefit from a generic ADF product

Case Study: Remoxy ER Capsules: CRL (09-26-16)

- **Third attempt by Innovator to obtain AD Labeling**
  - ** To support a potential drug label claim against abuse by injection: Repeat an injectability/syringeability study using thin films of drug, smaller volumes of solvents, additional mixed solvents and alternative extraction methods and syringe filter.*
  - ** To support a potential drug label claim against abuse by inhalation: Repeat a volatilization study using the same thickness for each drug to increase surface area.*
  - ** To support a potential drug label claim against abuse by snorting: Conduct an intranasal abuse potential study in human volunteers (i.e., not the animal data we had submitted) with drug applied directly inside the human nasal cavity.*
- **GWIG Concerns:**
  - Effectiveness of Pre-ANDA discussions with FDA
  - Subjective interpretation of study designs, test conditions and corresponding data can result in additional studies.
  - Additional studies are resource intensive and time consuming.

Source: Pain Therapeutics, Inc. Website

Summary

Summary

The Generics Industry Working Group Recommendations are:

- Generic ADF opioids will be considered Complex Products and included in the pre-ANDA program
  - Enhanced pathway for Complex Products benefits including product development meetings, pre-submission meetings, and mid-review cycle meetings
- Category 1 mandatory, Category 2 and Category 3 required as needed for generic ADF opioids
  - Category 2 and Category 3 will be required based on the scientific properties of the RLD
- FDA develop policy to ensure no “ever greening” will occur blocking generic ADF
- FDA revise Draft Guidance reflecting recommendations identified by GIWG and issue Product Specific Guidance timely