Industry Perspective: Regulatory Challenges in Development of Generic Long-Acting Injectables

November 2021 CRGC Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products

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Background

- Long Acting Injectable (LAI) Formulations are formulated to achieve an extended drug release action (from days to months)

- FY2016 Regulatory Science Report: **“***LAI formulations include biodegradable injectable microspheres and in-situ gelling implants. Compendial in vitro release methods for these complex formulations are not well developed, and demonstration of BE for these products can be challenging”*.

- Published Product Specific Guidance (PSG) for LAI formulations need *in-vitro* and *in-vivo* studies
  - Challenges in BE studies
  - Challenges in development of *in-vitro* methods

Challenges in BE studies

- Some products need studies in patients
  - Difficulty in recruiting patients
  - Typically require multiple clinical centers
  - Rare or orphan drug indications can make recruitment much more challenging or not feasible at all
- Longer duration of studies
  - Impact on submissions timelines
- More complex dosing procedures
  - Reconstitution, infusion devices, following the IFU
  - Risk of protocol violations

Challenges in development of *in-vitro* methods

- Developing real time dissolution method
  - Product release only after dosage regime (28 days/ 42 days, etc.)
  - Extensive degradation during the dissolution run

- Demonstrating Discrimination
  - Multiple critical process parameters (CPPs) and/or Critical Material attributes (CMAs) may need to be changed simultaneously
  - Change in parameters may need to be more than the Agency recommended ± 20% of the target

- Establishing an *in-vivo in-vitro correlation* (IVIVC)
  - 1:1 co-relation is difficult to establish

Next Steps

- Understanding FDA expectations for Model Integrated Evidence (MIE) in an ANDA
  - Beneficial to both industry and FDA if there was a mutual understanding of the information to be submitted in Pre-ANDA meetings to make the most of the meetings
  - Validation requirements
- Inclusion of MIEs in PSGs
  - Paliperidone Palmitate published in August 2021
- Generic manufacturers need to understand if there's a roadmap to potential approvals following MIE approach

Summary

- There are several challenges when developing LAIs
- BE studies and Dissolution method development are time consuming and expensive
- MIEs may help accelerate availability of generic LAIs
- Currently no standard expectations on the data needed to be included in pre-ANDA meetings
- Would be very beneficial if available recommendations are included in the PSG

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