PLENARY 2

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"Bioequivalence of new formulations of approved antiretroviral LAI drugs: What are the regulatory considerations?"

"FDA has sought ways to minimize study duration and investigate alternative approaches to bring [generic LAIs] to market"

Complicating factors of in vivo BE study design and conduct for LAIs

General considerations for study design.

- Crossover vs parallel design.
  - ◊ SD study: parallel design helps avoid washout concerns due to long half-life.
    - * Medroxyprogesterone acetate 50d washout; Naltrexone 5 to 10d washout.
  - ◊ Multi-dose/Steady-state study: either design.
- Strength to be studied.
  - ◊ Highest strength is recommended unless safety is a concern.
  - ◊ Multiple strengths may be recommended.
  - ◊ Any strength may be used for certain products with multiple approved strengths (e.g., risperidone LAI).
- PK metrics to be evaluated.
  - ◊ SD study: Cmax; AUCt; AUCinf; and Tmax.
  - ◊ Multi-dose study: Cmax; AUCtau; Tmax; Cmin; and Fluctuation/variability.
  - ◊ Partial AUC based on clinical relevance and formulation characteristics.
    - * Naltrexone ER injectable suspension: AUC1-10 and AUC10-28 were included to account for the multi-phasic release profile and therapeutic threshold.
  - ◊ 90% CI for Cmax and AUC must be within 80 –125%.
- Injection site included.
  - ◊ Gluteal or deltoid sites based on RLD information.
    - * If both included, ensure proportions of patients are similar among test and reference product groups.
- Steady state (SS).
  - ◊ Administer sufficient doses to achieve ss.
    - * For some LA ARV products, it could take nine months to achieve ss.

Challenges in study conduct.

- Recruitment difficulty.
  - ◊ Large sample size and long study duration with high dropout rate.
- High variability for parallel studies.
  - ◊ Multiple contributing factors (e.g., Demographics, across clinical centers, etc.).
- Steady-state determination.
  - ◊ Ensure steady state is captured.
  - ◊ Safety concerns with long duration studies.
  - ◊ Ensure reserve sample retention.

Key takeaways

- Study design should account for the formulation (release-controlling mechanism), dosing frequency, and study population.
- Determine the appropriate number of doses to achieve SS and balance this with the need to minimize study duration.
- Consider the drop-out rate in the sample size estimate.
- Use an appropriate sampling scheme to accurately capture PK parameters.
- Conduct sufficient pre-study method validation examining the interference of concomitant medications (i.e., To avoid introducing confounding factors).
- Incorporate appropriate safety monitoring.
- Use an appropriate statistical approach to evaluate demographics and clinical center effect, as needed.

Next steps

New approaches to streamline in vivo BE studies.

- 2021 workshop (FDA & Center for Research on Complex Generics): Establishing the suitability of model-integrated evidence (MIE) to demonstrate BE for LAIs.
  - ◊ MIE may reduce study duration and/or sample size and justify the use of alternative study designs and/or BE metrics through a model-based BE analysis framework.
  - ◊ Important considerations of using MIE for BE.
    - * Demonstrate sensitivity to detect the formulation difference with confidence.
    - * Sufficient model verification and validation.
  - ◊ MIE has been used in new drug development.
    - * Totality of evidence approach.
    - * Optimize dosing regimens, define dosing windows, select re-initiation plans, and adjust dose in subgroups.
- Model-informed vs model-integrated approaches.
  - ◊ Model-informed: M&S informs study design and analysis methods.
    - * Increase efficiency of in vivo BE studies.
    - * Assist product development and decision-making.
    - * Design/justify an appropriate sampling scheme strategy.
  - ◊ Model-integrated: M&S informs pivotal study plan and serves as pivotal evidence to support product approval.
    - * Pre-specified model-based analysis of an in vivo BE study.
    - * Virtual BE study based on M&S.
    - * Used in combination with relevant in vitro BE tests to support an alternative approach to FDA-recommended in vivo BE studies, including PK, PD, or comparative clinical endpoint BE studies.
  - ◊ Both approaches can help reduce study duration and/or sample size (i.e., Help design a more feasible BE study for an LAI product).
  - ◊ **FDA has awarded 39 research contracts and 50 grants for model-related research relevant to establishing BE for various products.**

Opportunities for MIE in generic LAI development.

- 2024 FDA workshop.
  - ◊ Strategies for alternative BE approaches supported by MIE.
    - * Enhance efficiency of in vivo PK BE studies via population PK modeling.
    - * BE decision based on in vitro studies, in lieu of PK BE study, mediated via mechanistic PBPK modeling.
  - ◊ Leverage MIE to generate pivotal evidence for BE decision (see above).
- FDA is seeing a clear demand for modeling approaches.
  - ◊ Increased use of modeling in pre-ANDA meeting requests and ANDA submissions.
- Frequent and constant communication with FDA is critical.
  - ◊ Pre-ANDA meetings are offered by the Office of Generic Drugs.
  - ◊ New MIE pilot program.
- FDA is enthusiastic about working with this group and developers in the field.
  - ◊ To bring products to the US.
  - ◊ To help others design products for use in other countries.

Resources

- Lenacapavir draft PSG (Feb 2024).
  - ◊ Recommended study: Request waiver for in vivo BE study requirement.
  - ◊ Waiver qualification: Test product qualitatively (Q1) and quantitatively (Q2) the same as the RLD.
  - ◊ Rationale: Dosage form is a solution; Composition does not contain any release-controlling excipients; and LA properties are not related to the formulation.
- Draft guidance for industry population PK (2019).
- Guidance for industry exposure-response relationships – study design, data analysis, and regulatory applications (2003).
- Draft guidance for industry adaptive designs for clinical trials of drugs and biologics (Nov 2019).
- Leveraging quantitative methods in reviewing complex/locally acting products (Oct 2-3, 2017).
- Contacts.
  - ◊ Pre-ANDA Meetings Program for complex generic products. For questions about submitting a meeting request, contact PreANDAHelp@fda.hhs.gov.
  - ◊ MIE Pilot Program. For questions about the program, contact MIE@fda.hhs.gov.