Challenges and Opportunities for Complex Generic Products

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Regulatory

GDUFA Funded Research

Why are we here today?

- ✓ To provide public input to help FDA identify science and research priorities that can help ***expand and accelerate patient access to generic drug products***.
- ✓ To find ways to lower generic drug development costs and time ***without sacrificing quality, safety, or efficacy***.
- ✓ In acknowledgement of the importance of increasing the availability of FDA-approved, cGMP-compliant complex generics drugs that can lower healthcare spending (by payors and patients).

Regulatory

GDUFA Funded Research

Why are these science and research priorities important?

- ✓ These priority areas encompass scientific challenges that the generic industry and FDA's generic drug program identify as being significant over the coming years.
- ✓ They also represent opportunities for scientific advancements to ***accelerate access to generic versions of complex products*** and make the development of generic drugs more efficient.

Regulatory

GDUFA Funded Research

Is the GDUFA Science and Research Program helping with accelerating access to generic versions of complex products and making the development of generic drugs more efficient?

- ✓ ***YES, but there is still work to do!***
  - The realizations of this program (PSGs, Guidances, Scientific Articles/Posters, Workshops, Characterization Techniques, Bioequivalence Considerations, etc.) are vital to a generic ecosystem that ***can navigate today's challenges and anticipate and adapt to tomorrow's challenges***.
  - As technology and new drugs continue to advance in complexity, the ***regulatory research program must enable flexible, scientifically sound regulatory approaches***.

Bioequivalence

Long-term Use Complex Products – Extension of Wear

- **Challenge**:
  - Some products, such as hormonal contraceptives, have long-term usage of multiple years. PK studies can be abbreviated/less than duration of wear.
  - However, innovators sometimes will extend their usage duration by several years.
  - Development of generics is very time consuming and expensive. Industry needs assurance the BE requirements are not changed as the innovator extends usage by multiple years.

PSG Snapshots

A. Comparative in vitro drug release
Acceptable comparative in vitro drug release of [redacted] from the test and RS products throughout the intended period of product use (5 years). Any accelerated dissolution method that correlates to the real-time drug release behavior may be submitted for the Agency's consideration through either a controlled correspondence or as part of a pre-ANDA meeting request.

Comparative in vitro drug release:
Acceptable comparative in vitro drug release of [redacted] from the test and RS products (i.e., in water, 37°C) throughout the intended period of product use (3 years).

Additional comments: A real time release study that is shorter than 3 years may be acceptable when an accelerated dissolution method that correlates to the real-time drug release behavior is developed and validated. It is recommended that applicant should submit a proposed accelerated dissolution method for the Agency's consideration through a controlled correspondence or as part of a pre-ANDA meeting request.

Recommended FDA Research:

Evaluate whether the current bioequivalence (BE) recommendations in PSGs account for potential changes in the duration of usage by the innovator, so that our future, ongoing, or completed (costly) bioequivalence studies could support such a change. One potential consideration would be to tighten BE criteria instead of changing the study design / duration of study which could become problematic for those with studies already conducted.

Bioequivalence

Charcoal Block PK Studies for Inhalation Products

- **Challenge**:
  - FDA recently incorporated these studies for inhalation products.
  - There is no standardization of the amount of charcoal needed and the timings of its administration in these studies to ensure sufficient block of the gastrointestinal absorption.

PSG Snapshots

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
   Subjects: Healthy males and non-pregnant, non-lactating females

2. Type of Study: Fasting
   Design: Single-dose, two-way crossover with charcoal block
   Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
   Subjects: Healthy males and non-pregnant, non-lactating females

Recommended FDA Research:

Similar to fed studies where a high-fat breakfast with specific ranges of calories for protein, fat, and carbohydrates are recommended by guidance, and FDA also has a standard high fat breakfast with predetermined foods, it would be beneficial to have a standardized approach to charcoal block PK studies with respect to the amount of charcoal needed and time points to administer the charcoal. Research may include in vitro (charcoal adsorption) studies or in vivo bioavailability studies to standardize this not for single products but possibly for larger groups of products (i.e., IR inhalation products).

Bioequivalence

Uncertainty Regarding Number of Inhalations to Use for Inhalation PK Studies

– **Challenge**:

- PSGs for inhalation products specify to dose a 'Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method' instead of an exact dose like oral products.
- Some oral tablets/capsules PSGs specify the # of units to dose due to low concentrations and some oral suspension PSGs specify the volume of suspension to dose.

PSG Snapshots

1. Type of study: Fasting
Design: Single-dose, two-way crossover
Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
Subjects: Healthy males and non-pregnant, non-lactating females

2. Type of Study: Fasting
Design: Single-dose, two-way crossover with charcoal block
Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
Subjects: Healthy males and non-pregnant, non-lactating females

Recommended FDA Research:

When creating or revising PSGs FDA should specifically indicate the recommended dose to support inhalation PK studies to alleviate residual uncertainties with these complex products.

Bioequivalence

Product Specific Guidances for Oncology and/or Pediatric Patients

– **Challenge**:

- There are PSGs for oncology and/or pediatric patients where dosing and administration according to the prescribing information must be followed.
- Recruiting very sick patients or children which need to adhere to multiple dosing cycles and extensive PK sampling is very difficult to achieve. Orphan drugs, including cytotoxic injectables and implant products, having a low incidence rate of the underlying condition are also particularly challenging.
- There are very high dropout rates for these types of studies and in general low motivation for patients to enroll in these generic PK studies.

PSG Snapshots

4. Given that the dosing frequency is every two weeks, two consecutive treatment cycles should be used for the two treatment periods.

4. A full course of [redacted] injection consists of 1-2 cycles of induction and up to 2 cycles of consolidation at the dose and schedule recommended on the RLD label.

7. Collect PK samples on days 1 and 5 of the first cycle of induction.

Recommended FDA Research:

PSGs for oncologic and/or pediatric drugs should anticipate the different circumstances and challenges that these specific patient populations introduce to alleviate the difficulties and residual risk of conducting these studies. In vitro and/or model-based research approaches should be clearly defined in the PSGs instead of proposing a general concept without specific details.

Characterization & Demonstration of Sameness

Analytical Methodology

- **Challenge**:
  - Several advanced analytical techniques are required to demonstrate API sameness and comparable physicochemical attributes as recommended in PSGs for complex products.
  - FDA has broad discretion to determine whether an ANDA applicant has submitted information sufficient for the Agency to reasonably conclude that the proposed generic drug product's active ingredient is the same as the active ingredient of the RLD.[1]
  - FDA has specific preferences on sample preparation, study design, etc., but these preferences are not documented in guidance and are only learned through deficiency letters.

PSG Snapshots

1. Secondary structure.
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RS.
3. Biological activities[5].
4. Active ingredient-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RS and impurities found at a significantly higher level in the proposed generic drug product than in the RS, should be identified and characterized. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be recommended.
5. Comparative study demonstrating comparable innate immune response risk of the test and RS products.

a. Iron core characterization: core size and morphology, crystalline structure, iron environment, magnetic properties, Fe(III) to Fe(II) reduction potential, reduction kinetic and Fe(II) content.
b. Carbohydrate shell characterization: composition of carbohydrate shell.
c. Physicochemical properties of the drug product: particle size and morphology, surface properties, colloid molecular size,[5] interactions between iron core and the carbohydrate shell, stoichiometric ratios of iron, derisomaltose, citrate, and other relevant components.

a. Mass spectrometry (MS), including tandem mass spectrometry (MS/MS)
b. Nuclear magnetic resonance (NMR) spectroscopy
c. Liquid chromatography (LC)
d. Duplex melting temperature (Tm) to a complementary strand

a. Circular dichroism (CD) spectroscopy
b. Differential scanning calorimetry (DSC)
c. Size exclusion chromatography (SEC)
d. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

Recommended FDA Research:

Conduct research to develop a guidance or position with recommended sample preparation, study design, etc. for the more common advanced analytical techniques based on product type (e.g., peptide, iron complex, oligonucleotide).

[1] FDA Draft Guidance for Industry, Sameness Evaluations in an ANDA – Active Ingredients (November 2022)

Characterization & Demonstration of Sameness

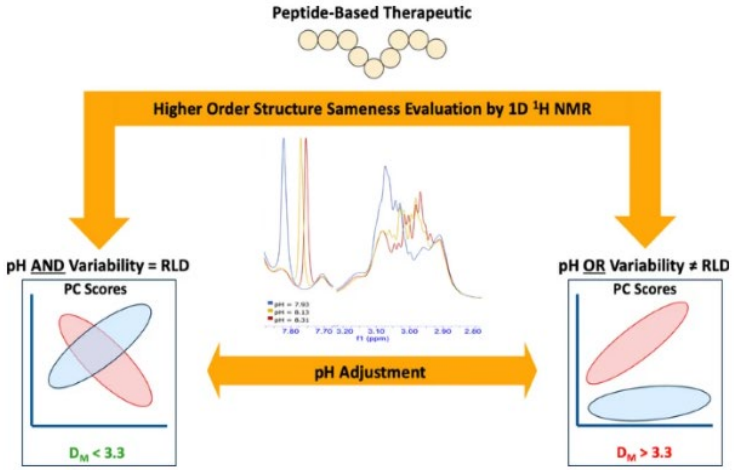
Statistical Analyses

- **Challenge**:
  - Statistical analyses are sometimes employed in data evaluation to demonstrate sameness.
  - There are no FDA guidances for the preferred statistical techniques, creating residual uncertainty in whether the results will be considered acceptable.
  - Often, Industry defaults to the population bioequivalence approach because this is most commonly accepted by FDA.

Specific Example

Statistical Evaluation of Similarity for Peptide and Oligonucleotide Drug Products using NMR Spectroscopy

- Peptide Drug Products:
  - Principal Component Analysis (PCA):
  - Used to assess structural similarity.
  - Recommended by FDA for synthetic peptides.
  - Combined with NMR spectroscopy.
- Oligonucleotide Drug Products:
  - NMR Spectroscopy:
  - Required test in draft guidances.
  - Specific statistical methods are not always mentioned.



Recommended FDA Research:

Conduct research to develop a guidance or position with recommended statistical approaches for various physicochemical comparisons based on product type (e.g., peptide, iron complex, oligonucleotide).

Immunogenicity

Adaptive Immunogenicity Research

- **Challenge**:
  - Two initiatives are happening in parallel.
    - ✓ FDA granted a contract to create an immunogenicity standard for adaptive immunogenicity (which surely will work well on their specific assay platform).
    - ✓ A separate initiative by AAPS/HESI examined adaptive immunogenicity assays across multiple innovator labs and their results suggest that adaptive immunogenicity assays can vary widely in their results by format.

Specific Example

In the research presented by Laurent Malherbe at the 2024 Immunogenicity Summit, bocacizumab (known to be immunogenic in clinical testing) was observed to be immunogenic in many platforms, but not all. Additional work is ongoing to determine if this is a limitation of certain assay platforms, or could it be that different platforms provide different information? And how might this information impact the in vitro approaches for generic peptide assessment?

Recommended FDA Research:

FDA should organize a consortium for testing of any standards produced to ensure compatibility with multiple adaptive immunogenicity assay formats, and to better understand the differences between the formats.

Immunogenicity

The Missing Link

- **Challenge**:
  - In vitro immunogenicity assays are used to support ANDAs for generic peptides and oligonucleotides, as clinical trial testing for safety or efficacy are not suitable for the 505(j) pathway.
  - However, the in vitro testing performed provides a risk assessment that may or may not be relevant to the clinical experience, as the clinical relevance of these in vitro assays has not been established.

Specific Example

While an impurity in a proposed drug candidate may exhibit a statistically significant increase in immunogenicity compared to the reference product, it is not clear if the same increase is in any way biologically relevant.

Without further research, generic developers are limited in their options if they observe any type of statistically significant increase in in vitro immunogenicity.

Recommended FDA Research:

A grant sample testing in a Ph1 or Ph2 clinical study could potentially compare immunogenicity observed from in vitro samples collected prior to dosing patients with IMP to the clinically relevant observations for safety, efficacy, and immunogenicity (i.e., anti-drug antibody) observed in those same patients after dosing to establish a correlation.

Drug-Device Combination Products

Propellant Transition

- **Challenge**:
  - Through the Kigali Amendment to the Montreal Protocol there is a global phase down of the 2nd generation metered dose inhaler (MDI) propellants - HFC-134a and HFC-227ea.
  - Propellants are critical drivers of MDI performance as they release the drug from the actuator, facilitate the atomization of the formulation into aerosolized droplets and maturation of the droplets to their depositing forms, and constitute the bulk of an MDI's formulation.
  - In response to the global phase down, companies are in the process of transitioning to 3rd generation propellants - HFC-152a and HFO-1234ze.

There is a lack of clarity on the regulatory requirements to transition to a new propellant. Research is needed to facilitate a smooth transition and more importantly uninterrupted access to patients of these critical medicines.

Drug-Device Combination Products

Propellant Transition

– **A Lesson from History**:

- The 1st generation propellants (Chlorofluorocarbons; CFCs) were phased out in response to the Montreal Protocol.
- The removal of CFC propellants was a complex, multi-faceted, multi-year process that negatively impacted the availability of generic MDIs.
- Surely, we can learn from the first transition and minimize or eliminate the impact that this propellant transition will have on patients who rely on these important life-saving and disease-treating medications.

Recommended FDA Research

- ✓ FDA should evaluate whether abbreviated in vitro and/or in vivo bioequivalence packages could be utilized to support a transition to a 3rd generation propellant. The research should focus on the extension of the 'Option 1' bioequivalence approach as per recently updated locally acting drug PSGs (i.e., Breztri), to include the new propellant product so long as a weight of evidence is provided indicating that the product performs comparably both in vitro and during systemic absorption studies.

Parting Thoughts

The GDUFA Science and Research Program is a critical factor in the generic ecosystem and the outputs represent opportunities for scientific advancements to accelerate access to generic versions of complex products and make the development of generic drugs more efficient.

A continuous feedback loop and meaningful Industry-Agency collaboration will streamline the utility of the research performed.

Focus should be put on ensuring the research performed is compatible, useful, and reproducible for generic applicants to incorporate into development programs in a timely manner!

"Coming together is a beginning; keeping together is progress; working together is success"

– Henry Ford

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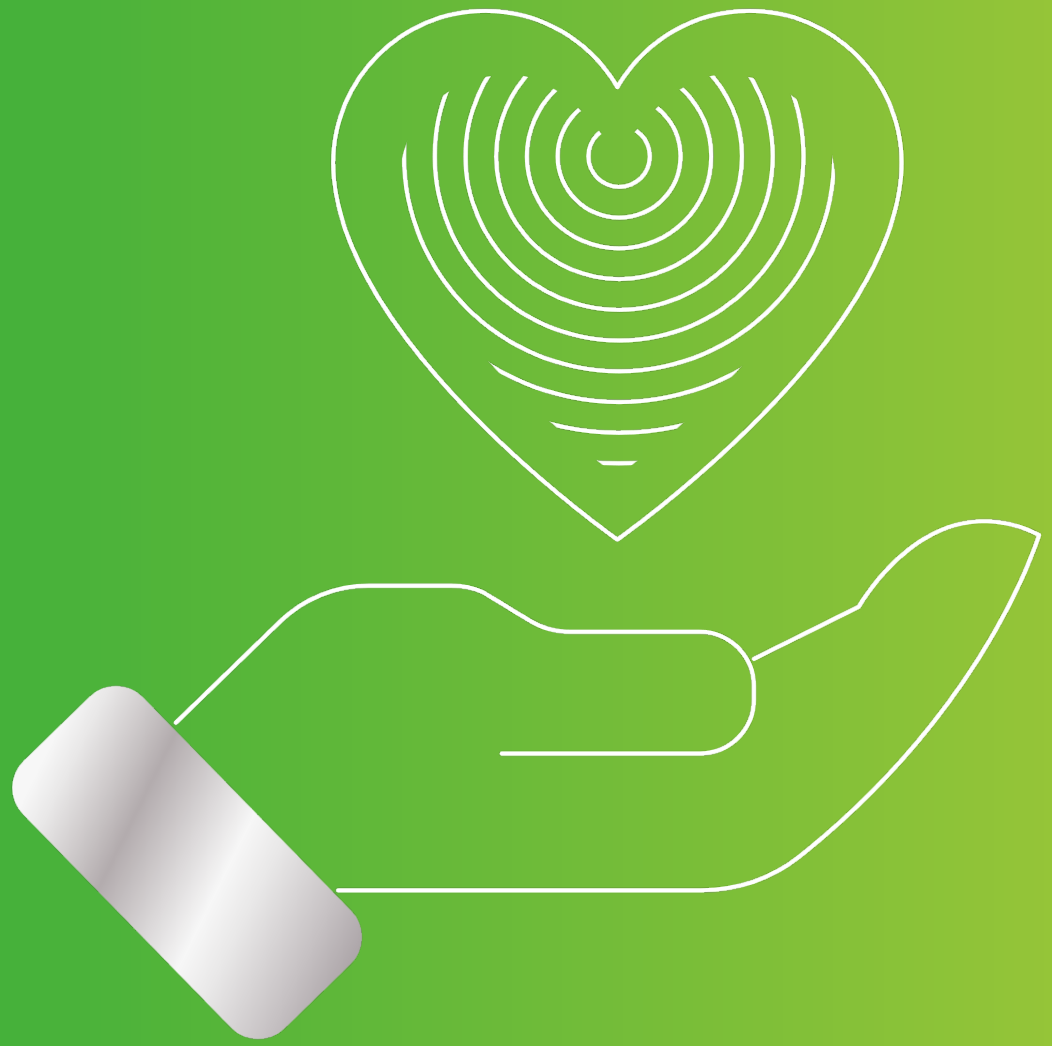
THANK YOU

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