Complex Drug Products

FDA Regulatory Science Workshop
Association for Accessible Medicines
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Overview

- Complex Drug Products
- Bioequivalence waiver consideration for complex drug products
  - Current Status
  - Why to reduce BE studies?
  - How to reduce BE studies? – The way out
  - A glance to the future.
  - Conclusions
Complex Drug Products

- Complex drug substances and formulations present challenges for demonstrating sameness and bioequivalence to RLD. Some of the complex drug products include:

  - Products with complex active ingredients (e.g., Peptides - Highly Purified Synthetic Peptides, polymeric compounds).

  - Complex modified release formulations: suspensions, emulsions, in situ forming gels, liposomal drugs, polymeric microparticles, etc.
Current Status

**Current Regulation:**

21 CFR 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

**Current Regulation:**

(§ d) For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:

1. [Reserved]
2. The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:
   (i) The bioavailability of this other drug product has been measured;
   (ii) Both drug products meet an appropriate in vitro test approved by FDA; and
   (iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

   **(iv) Paragraph (d) of this section does not apply to delayed release or extended release products.**

3. The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.
4. The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met: ….
Very Good Approach from Authorities

FDA’s Approach for PLA/PLGA based Products:

Since the enactment of GDUFA in July 2012, OGD has awarded grants and contracts for multiple research projects involving PLA/PLGA based drug products in various dosage forms, such as microspheres, implants, and in situ gelling systems. Broadly, these projects can be categorized into four areas: (1) development of in vitro-in vivo correlations (IVIVC), (2) development of in vitro release testing (IVRT) methods, (3) characterization of PLA/PLGA, and (4) modeling and simulation of PLA/PLGA-based drug products.

### Table 2. Research projects involving PLA/PLGA-based drug products

<table>
<thead>
<tr>
<th>Research category</th>
<th>Project title</th>
<th>Awardee</th>
<th>Year started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of IVIVC</td>
<td>In vitro-in vivo correlations of parenteral microsphere drug products</td>
<td>University of Connecticut</td>
<td>2013</td>
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<tr>
<td>Development of IVIVC</td>
<td>In vitro-in vivo correlations of parenteral microsphere drug products</td>
<td>University of Michigan</td>
<td>2013</td>
</tr>
<tr>
<td>Development of IVRT methods</td>
<td>Dissolution methods for parenteral sustained release implant drug products</td>
<td>University of Colorado</td>
<td>2014</td>
</tr>
<tr>
<td>Development of IVRT methods</td>
<td>Development of Hytrel-Based in vitro dissolution apparatus for microparticle formulations</td>
<td>Airea, Inc.</td>
<td>2014</td>
</tr>
<tr>
<td>Characterization of PLA/PLGA</td>
<td>A biocompatible dissolution methods for particulate dosage forms in the peritoneal pocket</td>
<td>Magen-Warner Research Institute &amp; Foundation</td>
<td>2015</td>
</tr>
<tr>
<td>Characterization of PLA/PLGA</td>
<td>Influence of raw materials, manufacturing variables, and storage conditions on release performance of LAI (long-acting injectable) microsphere products</td>
<td>University of Michigan</td>
<td>2015</td>
</tr>
<tr>
<td>Modelling and simulation of PLA/PLGA-based LAI drug products</td>
<td>Computational drug delivery leveraging predictive models to develop bioequivalent generic LAI products</td>
<td>Genteq, Inc.</td>
<td>2015</td>
</tr>
<tr>
<td>Modelling and simulation of PLA/PLGA-based LAI drug products</td>
<td>Development of 3D format for long-acting injectable microspheres</td>
<td>Simulations Plus</td>
<td>2015</td>
</tr>
<tr>
<td>Modelling and simulation of PLA/PLGA-based LAI drug products</td>
<td>Data-driven bioequivalence assessment of long-acting injectable products</td>
<td>University of Massachusetts Lowell</td>
<td>2015</td>
</tr>
<tr>
<td>Modelling and simulation of PLA/PLGA-based LAI drug products</td>
<td>Pharmacokinetic modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection</td>
<td>University of Utah</td>
<td>2015</td>
</tr>
</tbody>
</table>

• **In principal perfect initiative with many benefits:**
  • Authorities understand the complexity of certain products.
  • Have a better insight of what is feasible and what is not.
  • Evaluate better the submitted files by the generic companies.
Bioequivalence Biowaver

**Need to Reduce Reliance on *In Vivo* BE Studies**

- Ethical reasons
  - 21 CFR 320.25(a) “... no unnecessary human research should be done.”
  - Especially when it comes to the cases where no healthy volunteers can be used for BE studies.
- Sometimes act against sufficient understanding of the drug product – Black Box Thinking.
  - Release mechanism (understanding, control, etc).
  - Critical process parameters.
  - Sufficient physico-chemical characterization.
- Time and cost of drug development and review.
  - Especially when multi-dose studies for extended release products, are required.
- No repetition of BE studies for PASs linked to minor or moderate manufacturing changes.
- Batch to Batch Variability of the Reference product.
Why to Reduce BE studies ???

Need to Reduce Reliance on *In Vivo* BE Studies

- Batch to Batch Variability of the Reference products (e.g. case study based on published data).

![Suspension graphs]

**Same product & same strength**

**Generic 1 & 2 or RLD 1 & 2 = Bioequivalent ??**

**$C_{\text{max}}$ ??**
How to Reduce BE Studies ??

The Way Forward....

• **RLD In depth Reverse Engineering**
  
  □ **API Characterization**: Crystallinity (%), polymorphs, drug loading, particle size distribution, specific surface area, morphology, impurity profile, etc.

  □ **Drug product**: Viscosity, release surface area (particle size distr. & porosity), residual solvents, quality of excipients, stability during shelf life, lot to lot variability, glass transition temperature, in-vitro dissolution profile, flowability, injectability, etc.

  □ **Manufacturing process**: identification of the manufacturing technique and manufacturing equipment, sterilization or aseptic process, filling process.

• **Base the Development on the QbD Approach**

  □ **Identification of CQAs & Linkage to CPPs**: Proper identification of the CQAs and correlation to the CPPs by utilization of DOE tools.

  □ **In Depth Characterization**: Utilization of state-of the art analytical techniques and equipment in order to characterize the API, excipients and final product. Application of more than one analytical techniques for the CQAs (e.g. PSD).
How to Reduce BE Studies ??

• **Appropriate In Vitro Dissolution Method and IVIVC**
  - *In-vitro dissolution method*: Development of an appropriate dissolution method utilizing state-of-the-art equipment with high discriminating power on CMAs and CPPs – Understanding the release mechanism.
  - *IVIVC*: Initial correlation of the in-vitro method with published in vivo data.

• **PK Animal Studies**
  - *Performance of PK animal studies*: Identification of appropriate animal model and perform in-vivo studies at key development phases and different manufacturing scales (lab, pilot, commercial).
  - *IVIVC*: Establishment of IVIVC on the generated animal in-vivo data.

• **Engineering Driven Scale up Approach**
  - Equipment Scale up: Identification of the scale-up factors based on designing equations for the critical manufacturing equipment.
  - Bridging the commercial and lab scale by utilization of intermediate/pilot scale.
  - Simulation the whole or part of the manufacturing process (critical manufacturing steps).
  - Increase the number of In Process Controls.
A Glance to the Future

What if we could test drugs on virtual organisms? – In Silico Trials

- **Benefits**
  - 1st Step is reducing the size and duration of clinical trials due to better design.
  - Predicting interactions and long term or rare effects that clinical trials are not able to predict.
  - Final aim will be the complete substitution of the clinical trials especially in cases where the release mechanism is fully understandable and can be mathematically modeled.

- **Do such tools exist??**
  HumMod is one of the most advanced simulations in this respect. It provides a top–down model of human physiology from whole organs to individual molecules. It features more than 1,500 equations and 6,500 variables such as body fluids, circulation, electrolytes, hormones, metabolism, and skin temperature. HumMod aims to simulate how human physiology works, and claims to be the most sophisticated mathematical model of human physiology ever created.

Will in the future Pharmacogenomics be more important than Bioequivalence?

- Medications do not have the same effect on people and....
- ... increasing the number of subjects in a clinical study to gain bioequivalence is statistics but not the solution.
Conclusions (Biowaiver Vs BE)

- Many complex drug formulations like suspensions, polymeric microspheres, extended release formulations are excluded in 21 CFR 320.22 (Criteria for waiver of evidence of *in vivo* bioavailability or bioequivalence)

- Biowaiver **option** should be considered for complex modified release formulations to avoid clinical trials and reduce reliance on in vivo Bioequivalence studies

- FDA Guidance document should be created on *in vitro* characterization of the complex drug product based on the clinical application. A **correlation of physico-chemical characteristics** of the drug with the *in vivo* performance should be established to put together this guidance document.

- New and improved analytical methods as well as *in-silico* clinical trials should be utilized to demonstrate similarity to RLD in lieu of clinical trials.