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Complex Drug Products

FDA Regulatory Science Workshop
Association for Accessible Medicines
May 24, 2018

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.*
  - *Conclusiuons*

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) **method**s, (3) **characterization of PLA/PLGA**, and (4) **modeling and simulation of PLA/PLGA-based drug products.**

Projects Running

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

Research category	Project title	Awardee	Year started
Development of IVIVC	In vitro-in vivo correlations of parenteral microsphere drug products	University of Connecticut	2013
	In vitro-in vivo correlations of parenteral microsphere drug products	University of Michigan	2013
	In vitro-in vivo correlations of ocular implants	University of Colorado	2013
Development of IVRT methods	Dissolution methods for parenteral sustained release implant drug products	University of Connecticut	2014
	Development of hydrogel-based in vitro dissolution apparatus for microparticle formulations	Akina, Inc.	2014
	A biorelevant dissolution methods for particulate dosage forms in the periodontal pocket	Magee-Womens Research Institute & Foundation	2015
Characterization of PLA/PLGA	Influence of raw materials, manufacturing variables, and storage conditions on release performance of LAI (long-acting injectable) microsphere products	University of Michigan	2015
Modeling and simulation of PLA/PLGA-based LAI drug products	Computational drug delivery: leveraging predictive models to develop bioequivalent generic LAI products	Qrono, Inc.	2015
	Development of PBPK simulation for long-acting injectable microspheres	Simulations Plus	2015
	Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products	University of Massachusetts Lowell	2015
	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Utah	2015

The Outcome

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Development of *in vitro-in vivo* correlation of parenteral naltrexone loaded polymeric microspheres

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ABSTRACT

Establishment of *in vitro-in vivo* correlations (IVIVCs) for parenteral polymeric microspheres has been very challenging, due to their complex multiphase release characteristics (which is affected by the nature of the drug) as well as the lack of compendial *in vitro* release testing methods. Previously, a Level A correlation has been established and validated for polymeric microspheres containing risperidone (a practically water insoluble small molecule drug). The objectives of the present study were: 1) to investigate whether a Level A IVIVC can be established for polymeric microspheres containing another small molecule drug with different solubility profiles compared to risperidone; and 2) to determine whether release characteristic differences (bi-phasic vs tri-phasic) between microspheres can affect the development and predictability of IVIVCs. Naltrexone was chosen as the model drug. Three compositionally equivalent formulations of naltrexone microspheres with different release characteristics were prepared using different manufacturing processes. The critical physicochemical properties (such as drug loading, particle size, porosity, and morphology) as well as the *in vitro* release characteristics of the prepared naltrexone microspheres and the reference-listed drug (Vivitrol®) were determined. The pharmacokinetics of the naltrexone microspheres were investigated using a rabbit model. The obtained pharmacokinetic profiles were deconvoluted using the Loo-Riegelman method, and compared with the *in vitro* release profiles of the naltrexone microspheres obtained using USP apparatus 4. Level A IVIVCs were established and validated for predictability. The results demonstrated that the developed USP 4 method was capable of detecting manufacturing process related performance changes, and most importantly, predicting the *in vivo* performance of naltrexone microspheres in the investigated animal model. A critical difference between naltrexone and risperidone loaded microspheres is their respective bi-phasic and tri-phasic release profiles with varying burst release and lag phase. These variations in release profiles affect the development of IVIVCs. Nevertheless, IVIVCs have been established and validated for polymeric microspheres with different release characteristics.

1. Introduction

Owing to their advantages such as improved patient compliance and longer duration of action, extended release drug delivery systems have attracted great attention in the past several decades, resulting in the successful commercialization of various types of extended release drug products [1]. Parenteral polymeric microspheres, particularly poly (lactic-*co*-glycolic acid) (PLGA) and poly(lactic acid) (PLA) based microspheres have been one of the most effective non-oral extended release drug products on the market [2]. This is due to the fact that the PLGA/PLA-based microsphere drug products are biodegradable and biocompatible with the ability to sustain the delivery of various therapeutics (e.g. small molecules and biologics) over long periods of time [3–6]. These microsphere drug products often contain a substantial amount of potent therapeutics, which makes them "high-risk" drug products since any unexpected change in bioavailability may result in severe side effects or toxicity [7]. Moreover, the critical physicochemical properties of polymeric microspheres (such as drug loading, particle size and porosity) are sensitive to minor changes in the manufacturing processes, which in turn may affect drug release characteristics and hence product performance [8]. Accordingly, it is crucial to assure the performance and safety of such drug products.

In vitro drug release testing can provide extensive insight into the release rate as well as drug release mechanism(s) [9,10]. Therefore, it is an important tool to not only ensure consistent product performance and safety, but also assist in product development. When a correlation

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Accelerated *in vitro* release testing method for naltrexone loaded PLGA microspheres

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ABSTRACT

The objective of the present study was to develop a discriminatory and reproducible accelerated release testing method for naltrexone loaded parenteral polymeric microspheres. The commercially available naltrexone microsphere product (Vivitrol®) was used as the testing formulation in the *in vitro* release method development, and both sample-and-separate and USP apparatus 4 methods were investigated. Following an *in vitro* drug stability study, frequent media replacement and addition of anti-oxidant in the release medium were used to prevent degradation of naltrexone during release testing at "real-time" (37 °C) and "accelerated" (45 °C), respectively. The USP apparatus 4 method was more reproducible than the sample-and-separate method. In addition, the accelerated release profile obtained using USP apparatus 4 had a shortened release duration (within seven days), and good correlation with the "real-time" release profile. Lastly, the discriminatory ability of the developed accelerated release method was assessed using compositionally equivalent naltrexone microspheres with different release characteristics. The developed accelerated USP apparatus 4 release method was able to detect differences in the release characteristics of the prepared naltrexone microspheres. Moreover, a linear correlation was observed between the "real-time" and accelerated release profiles of all the formulations investigated, suggesting that the release mechanism(s) may be similar under both conditions. These results indicate that the developed accelerated USP apparatus 4 method has the potential to be an appropriate fast quality control tool for long-acting naltrexone PLGA microspheres.

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1. Introduction

Biodegradable polymeric microsphere based parenteral controlled release drug products have been widely used for long-term controlled delivery of small molecule therapeutics as well as biologics such as peptides and proteins owing to their various clinical advantages such as low dosing frequency and hence improved patient compliance, as well as their ability to maintain effective therapeutic concentrations over extended periods of time, thus enhancing product safety and efficacy (FDA Guidance for Industry, 1997; Burgess et al., 2004a). As the improved therapy of these controlled release drug products is rooted in the optimum drug concentration/time profiles at the site of action in the body, it is essential to understand drug release characteristics of these types of drug products to ensure product performance and safety.

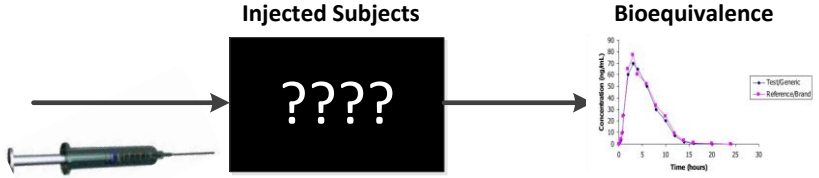
"Real-time" *in vitro* release testing is typically conducted to characterize drug release characteristics under physiological conditions (Burgess et al., 2002; Mitra and Wu, 2010). However, "real-time" *in vitro* release testing of controlled release formulations often runs over a long period of time ranging from weeks to months, or even years (Hoffman, 2008; Mao et al., 2012; Wang and Burgess, 2012; Miragotri et al., 2014), which if applied to batch release testing would result in reduced effective product shelf-life. Consequently, there is a need to develop fast and reliable quality control tool(s) to assure product performance as well as batch-to-batch reproducibility for consistent pharmacological effect. An accelerated *in vitro* release testing method, which increases drug

- **In principal perfect iniative 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.

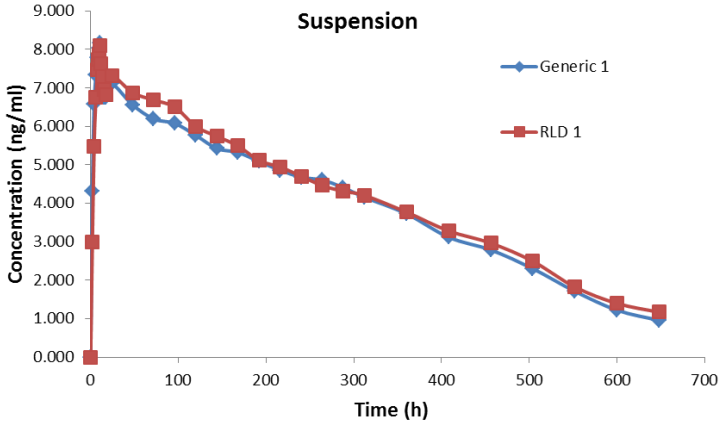


- Time and cost of drug development and review.
  - Especially when multi-dose studies for extended release products, are required.
- No repetition of BE studies for PASs linked to minor or moderate manufacturing changes.
- Batch to Batch Variability of the Reference product.

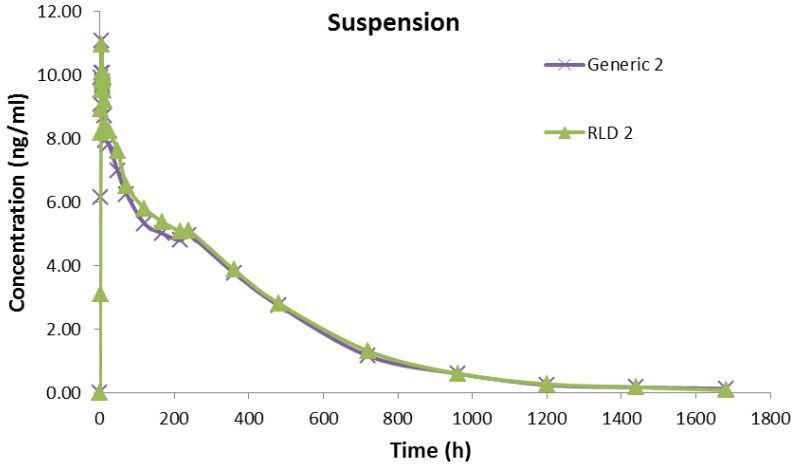
Why to Reduce BE studies ???

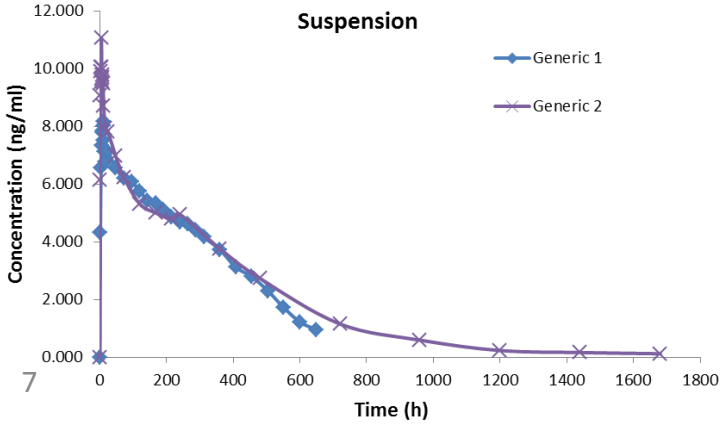
Need to Reduce Reliance on *In Vivo* BE Studies

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

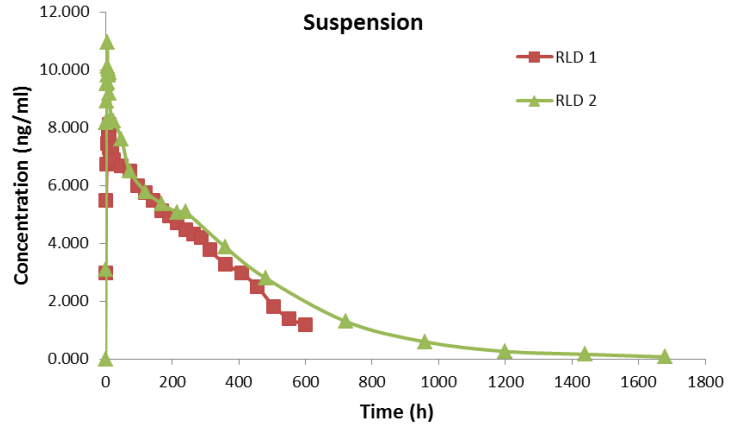


Same product & same strength





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

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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**.

Source: http://medicalfuturist.com/top-10-trends-shaping-future-pharma/

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.


QUESTIONS?
COMMENTS?
CONCERNS?