From Bench to Approval: the Role of GDUFA Research in Promoting Complex Generics

Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop

Session 6: Implementing GDUFA Science in Product Development and ANDAs

Yan Wang, PhD

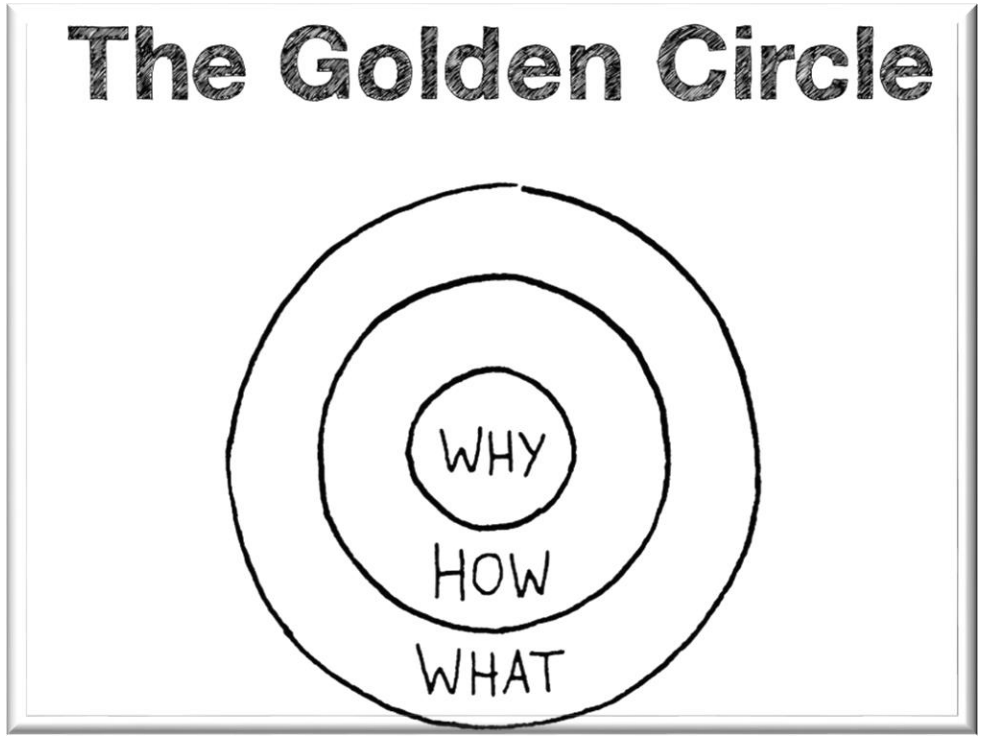
Lead Pharmacologist

Division of Therapeutic Performance, Office of Research and Standards

OGD | CDER | U.S. FDA

May 6, 2022

GDUFA Research: Why, How, and What?



WHY

➢What is the purpose of GDUFA research program?

✓The overall purpose is to promote generic development and facilitate the assessment of generic drugs.

HOW

➢How do we conduct research?

✓Conducting targeted research projects through Internal and external collaborations.

WHAT

➢What do we do with research outcomes?

✓Develop product specific guidances.

✓Facilitate generic development programs via addressing regulatory inquiries.

✓Support ANDA assessment and approval.

GDUFA Research for Supporting PSGs

When do we conduct research to support PSGs?

- Before/during development of new PSGs
  - Analysis of potential research gaps can help refine the types of studies FDA may recommend to support a BE approach.
- After posting of PSGs
  - Research gaps identified after a PSG can help support potential revisions to types of studies or methods that may be used for a particular bioequivalence (BE) approach for further improving the BE recommendation.
  - Research can facilitate the assessment of particular tools/methods that are used to conduct BE studies.

An Example: GDUFA Research for Supporting PSGs

Contains Nonbinding Recommendations

Draft Guidance on Levonorgestrel

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Levonorgestrel

Dosage Form; Route: Intrauterine Device; intrauterine

Strength: 52 mg

Recommended Studies: Two studies: in vitro and in vivo/ex vivo

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

- Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD).
- Equivalent physicochemical and mechanical characteristics including 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) Degree of crosslinking of poly(dimethylsiloxane) elastomer (PDMS) used in the drug reservoir and the drug rate controlling membrane; 3) Mechanical properties of the drug reservoir and the drug rate controlling membrane; 4) Appearance, memory, mechanical properties of the T-body; and 5) Breaking force of the removal thread comparable to the Reference Standard (RS).
- Same dimensions with respect to each component as the RS.

A. Comparative in vitro drug release

Acceptable comparative in vitro drug release of levonorgestrel 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.

B. In vivo/ex vivo clinical study

Type of study: In vivo/ex vivo study of residual levonorgestrel and serum levonorgestrel
Design: One year, single-dose, randomized, parallel in vivo study
Strength: 52 mg
Subjects: Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive. The enrolled population should include a sufficient number of nulliparous women.
Prerequisite: Twelve months of in vitro levonorgestrel drug release data demonstrating comparable release profiles for the test product and the RS product should be available prior to placing the test product in study subject.

Analytes to measure:

1. Residual amount of Levonorgestrel (following test product implantation and removal of test product at months 3, 6, and 12)
2. Levonorgestrel in serum at months 1, 3, 6, and 12 (collect serum sample prior to LNG-IUS removal for subjects scheduled for removal on the same day)

Bioequivalence based on (90% CI of T/R ratio of residual amount of levonorgestrel should be within 95.00%-105.26%)**:** Residual amount of Levonorgestrel at month 12

Additional comments: The following elements should be incorporated into BE study designs:

1. **Inclusion criteria**:
   - Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive methods and are willing to use an intrauterine contraceptive to prevent pregnancy for 3 – 12 months. (Women are eligible if they have a prior bilateral tubal ligation).
   - Investigator finds that patient has suitable general and uterine conditions for inserting the levonorgestrel intrauterine system.
   - Has regular menstrual cycles (21 - 35 day cycles) without hormonal contraceptive use
   - If subjects at increased risk for infectious endocarditis (prosthetic heart valves, rheumatic heart disease, previous endocarditis) are not excluded from the study population, the protocol should state, *prophylactic antibiotics should be considered prior to insertion and removal of intrauterine contraception in high risk patients.*
2. **Exclusion criteria:**
   - Women with a prior transcervical tubal sterilization procedure (e.g., Essure)
   - Postmenopausal woman
   - Known or suspected pregnancy
   - Lactating
   - Use of another hormonal contraceptive within 30 days of levonorgestrel intrauterine system placement for the study
   - Vaginal delivery, cesarean delivery, or abortion within six weeks prior to levonorgestrel intrauterine system insertion (uterus should be fully involuted before a postpartum insertion).
   - History of ectopic pregnancy
   - Women with a uterine cavity that measures less than 6 cm or greater than 10 cm
   - Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity
   - Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy
   - Postpartum endometritis or infected abortion in the past 3 months
   - Known or suspected uterine or cervical neoplasia
   - Known or suspected breast cancer or other progestin-sensitive cancer, now or in the

➢ Levonorgestrel intrauterine system

A novel in vitro/ex vivo combination approach was developed based on the understanding on formulation design and drug release mechanisms.

The research gaps identified:

➢ Prior to PSG posting:

New statistical acceptance criteria for the in vivo/ex vivo study.

A modeling approach was used.

➢ Post PSG posting:

Assessment on qualitative (Q1) sameness of silicone elastomers.

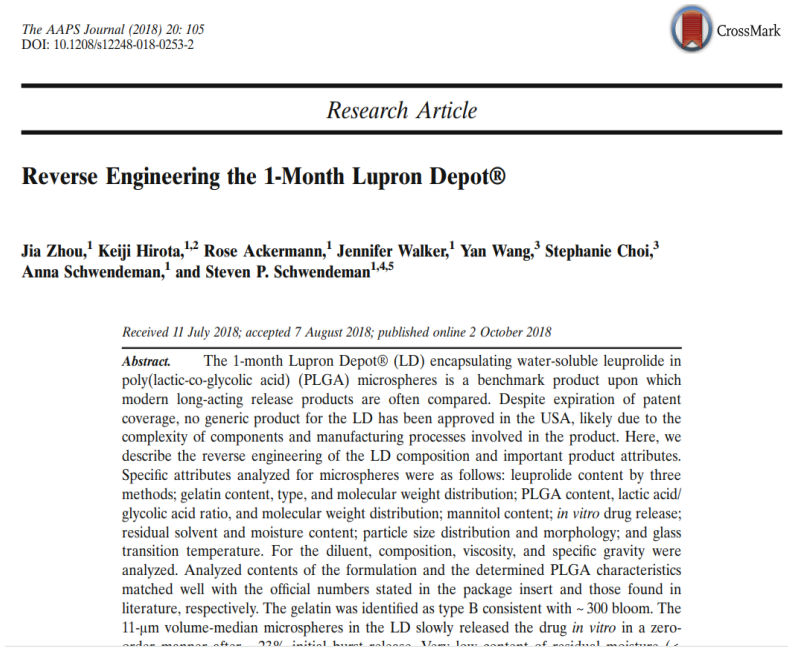
The possibility of using an accelerated in vitro drug release testing (IVRT) to replace the need for multiple-year real time IVRT.

GDUFA Research for Supporting Generic Drug Development

How does research support generic drug development?

- GDUFA research publications are a valuable resource that generic industry can utilize to support their generic drug development program.
- Improved understanding of complex drug products enables FDA to provide more effective feedback to generic applicants via regulatory inquires (i.e., controlled correspondence, pre-ANDA meetings).

Examples of Publications Containing Readily Adaptable Methods



The AAPS Journal (2018) 20: 105
DOI: 10.1208/s12248-018-0253-2

CrossMark

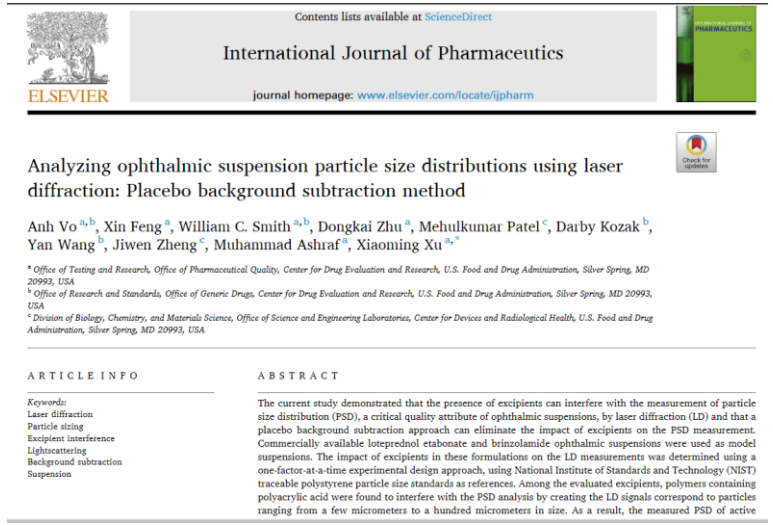
Research Article

Reverse Engineering the 1-Month Lupron Depot®

Jia Zhou,[1] Keiji Hirota,[1,2] Rose Ackermann,[1] Jennifer Walker,[1] Yan Wang,[3] Stephanie Choi,[3] Anna Schwendeman,[1] and Steven P. Schwendeman[1,4,5]

Received 11 July 2018; accepted 7 August 2018; published online 2 October 2018

Abstract. The 1-month Lupron Depot® (LD) encapsulating water-soluble leuprolide in poly(lactic-co-glycolic acid) (PLGA) microspheres is a benchmark product upon which modern long-acting release products are often compared. Despite expiration of patent coverage, no generic product for the LD has been approved in the USA, likely due to the complexity of components and manufacturing processes involved in the product. Here, we describe the reverse engineering of the LD composition and important product attributes. Specific attributes analyzed for microspheres were as follows: leuprolide content by three methods; gelatin content, type, and molecular weight distribution; PLGA content, lactic acid/glycolic acid ratio, and molecular weight distribution; mannitol content; *in vitro* drug release; residual solvent and moisture content; particle size distribution and morphology; and glass transition temperature. For the diluent, composition, viscosity, and specific gravity were analyzed. Analyzed contents of the formulation and the determined PLGA characteristics matched well with the official numbers stated in the package insert and those found in literature, respectively. The gelatin was identified as type B consistent with ~ 300 bloom. The 11-μm volume-median microspheres in the LD slowly released the drug *in vitro* in a zero-



Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Analyzing ophthalmic suspension particle size distributions using laser diffraction: Placebo background subtraction method

Anh Vo [a,b], Xin Feng [a], William C. Smith [a,b], Dongkai Zhu [a], Mehulkumar Patel [c], Darby Kozak [b], Yan Wang [b], Jiwen Zheng [c], Muhammad Ashraf [a], Xiaoming Xu [a,*]

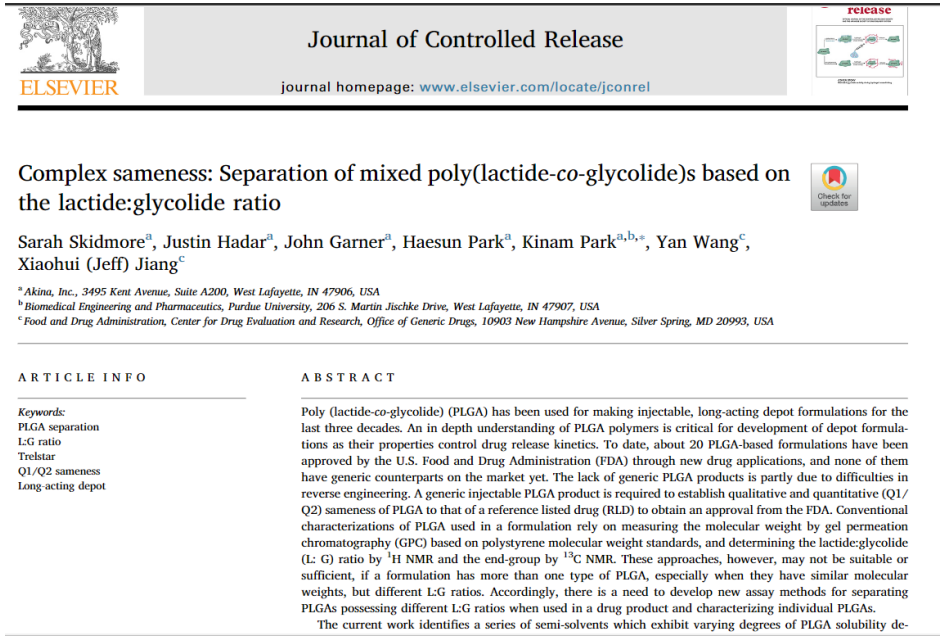
[a] Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
[b] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
[c] Division of Biology, Chemistry, and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

ARTICLE INFO

Keywords:
Laser diffraction
Particle sizing
Excipient interference
Lightscattering
Background subtraction
Suspension

ABSTRACT

The current study demonstrated that the presence of excipients can interfere with the measurement of particle size distribution (PSD), a critical quality attribute of ophthalmic suspensions, by laser diffraction (LD) and that a placebo background subtraction approach can eliminate the impact of excipients on the PSD measurement. Commercially available loteprednol etabonate and brinzolamide ophthalmic suspensions were used as model suspensions. The impact of excipients in these formulations on the LD measurements was determined using a one-factor-at-a-time experimental design approach, using National Institute of Standards and Technology (NIST) traceable polystyrene particle size standards as references. Among the evaluated excipients, polymers containing polyacrylic acid were found to interfere with the PSD analysis by creating the LD signals correspond to particles ranging from a few micrometers to a hundred micrometers in size. As a result, the measured PSD of active



Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Complex sameness: Separation of mixed poly(lactide-*co*-glycolide)s based on the lactide:glycolide ratio

Sarah Skidmore[a], Justin Hadar[a], John Garner[a], Haesun Park[a], Kinam Park[a,b,*], Yan Wang[c], Xiaohui (Jeff) Jiang[c]

[a] Akina, Inc., 3495 Kent Avenue, Suite A200, West Lafayette, IN 47906, USA
[b] Biomedical Engineering and Pharmaceutics, Purdue University, 206 S. Martin Jischke Drive, West Lafayette, IN 47907, USA
[c] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

ARTICLE INFO

Keywords:
PLGA separation
L:G ratio
Trelstar
Q1/Q2 sameness
Long-acting depot

ABSTRACT

Poly (lactide-*co*-glycolide) (PLGA) has been used for making injectable, long-acting depot formulations for the last three decades. An in depth understanding of PLGA polymers is critical for development of depot formulations as their properties control drug release kinetics. To date, about 20 PLGA-based formulations have been approved by the U.S. Food and Drug Administration (FDA) through new drug applications, and none of them have generic counterparts on the market yet. The lack of generic PLGA products is partly due to difficulties in reverse engineering. A generic injectable PLGA product is required to establish qualitative and quantitative (Q1/Q2) sameness of PLGA to that of a reference listed drug (RLD) to obtain an approval from the FDA. Conventional characterizations of PLGA used in a formulation rely on measuring the molecular weight by gel permeation chromatography (GPC) based on polystyrene molecular weight standards, and determining the lactide:glycolide (L: G) ratio by ^{1}H NMR and the end-group by ^{13}C NMR. These approaches, however, may not be suitable or sufficient, if a formulation has more than one type of PLGA, especially when they have similar molecular weights, but different L:G ratios. Accordingly, there is a need to develop new assay methods for separating PLGAs possessing different L:G ratios when used in a drug product and characterizing individual PLGAs.

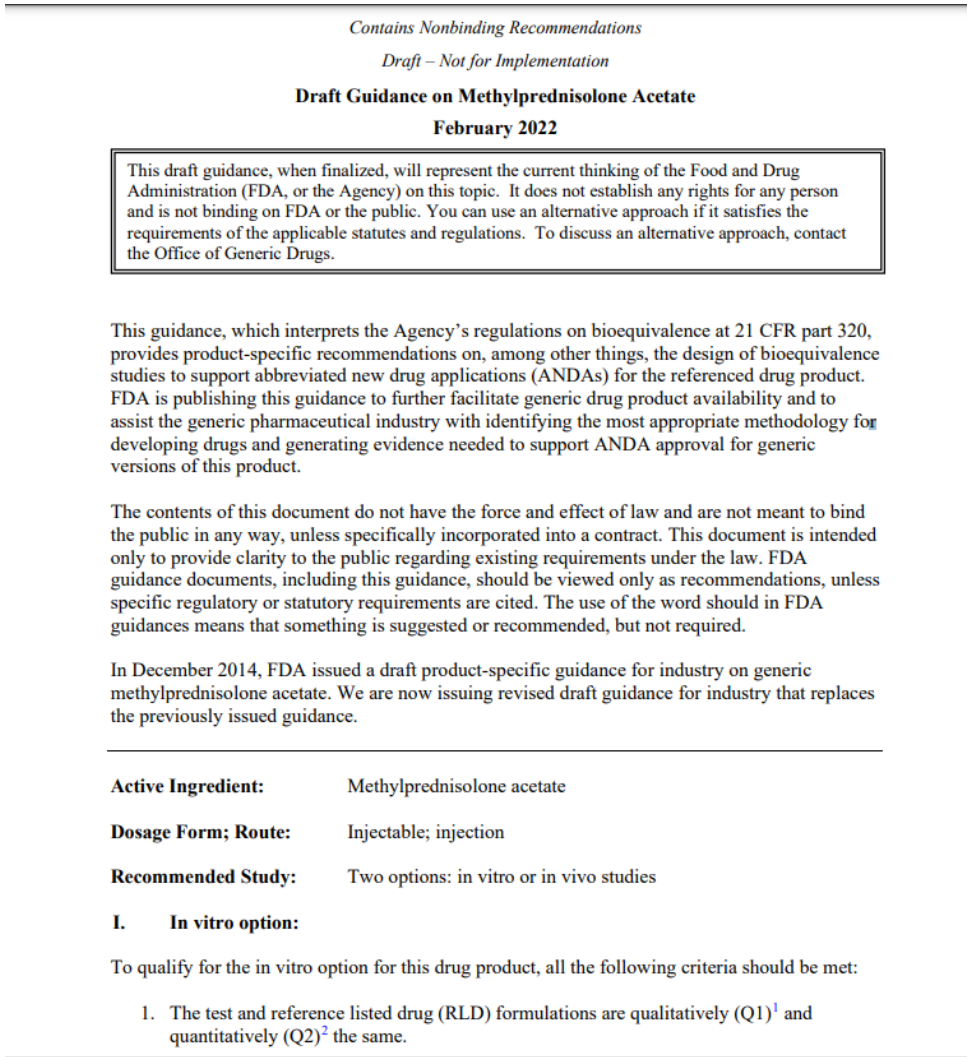
The current work identifies a series of semi-solvents which exhibit varying degrees of PLGA solubility de-

- To develop analytical methods for facilitating reverse engineering of complex products.
- To help better understand qualitative sameness of complex excipients.

- To develop new analytical methods to enable generic development of poly (lactide-co-glycolide) (PLGA) polymers-based products when a mixture of PLGAs is used in the formulation.

- The properties of complex products are often interrelated, and not straight forward to measure or compare.
- To develop new methods serving as a potential starting point to resolve the technical difficulty during development.

Examples of Efficient Communications via Regulatory Inquires



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Methylprednisolone Acetate

February 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

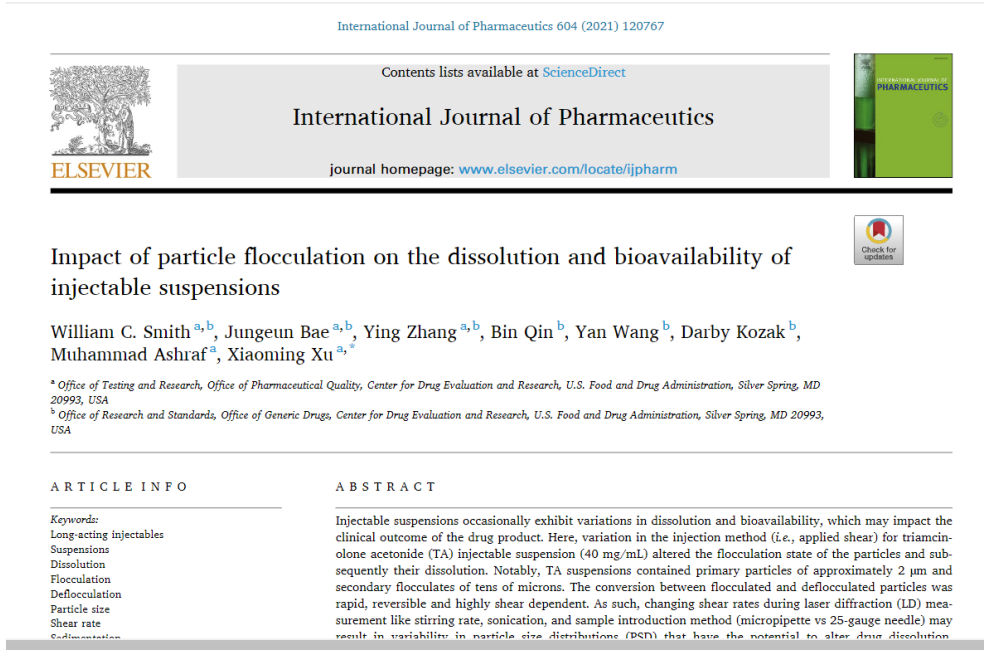
In December 2014, FDA issued a draft product-specific guidance for industry on generic methylprednisolone acetate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Methylprednisolone acetate
Dosage Form; Route:	Injectable; injection
Recommended Study:	Two options: in vitro or in vivo studies

I. In vitro option:

To qualify for the in vitro option for this drug product, all the following criteria should be met:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same.



International Journal of Pharmaceutics 604 (2021) 120767

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Impact of particle flocculation on the dissolution and bioavailability of injectable suspensions

William C. Smith [a,b], Jungeun Bae [a,b], Ying Zhang [a,b], Bin Qin [b], Yan Wang [b], Darby Kozak [b], Muhammad Ashraf [a], Xiaoming Xu [a,*]

[a] Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

[b] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

ARTICLE INFO

Keywords:
Long-acting injectables
Suspensions
Dissolution
Flocculation
Deflocculation
Particle size
Shear rate

ABSTRACT

Injectable suspensions occasionally exhibit variations in dissolution and bioavailability, which may impact the clinical outcome of the drug product. Here, variation in the injection method (i.e., applied shear) for triamcinolone acetonide (TA) injectable suspension (40 mg/mL) altered the flocculation state of the particles and subsequently their dissolution. Notably, TA suspensions contained primary particles of approximately 2 μm and secondary flocculates of tens of microns. The conversion between flocculated and deflocculated particles was rapid, reversible and highly shear dependent. As such, changing shear rates during laser diffraction (LD) measurement like stirring rate, sonication, and sample introduction method (micropipette vs 25-gauge needle) may

- Proposals to develop alternative in vitro only approach for establishing BE of generic methylprednisolone acetate were received in pre-ANDA meeting requests.

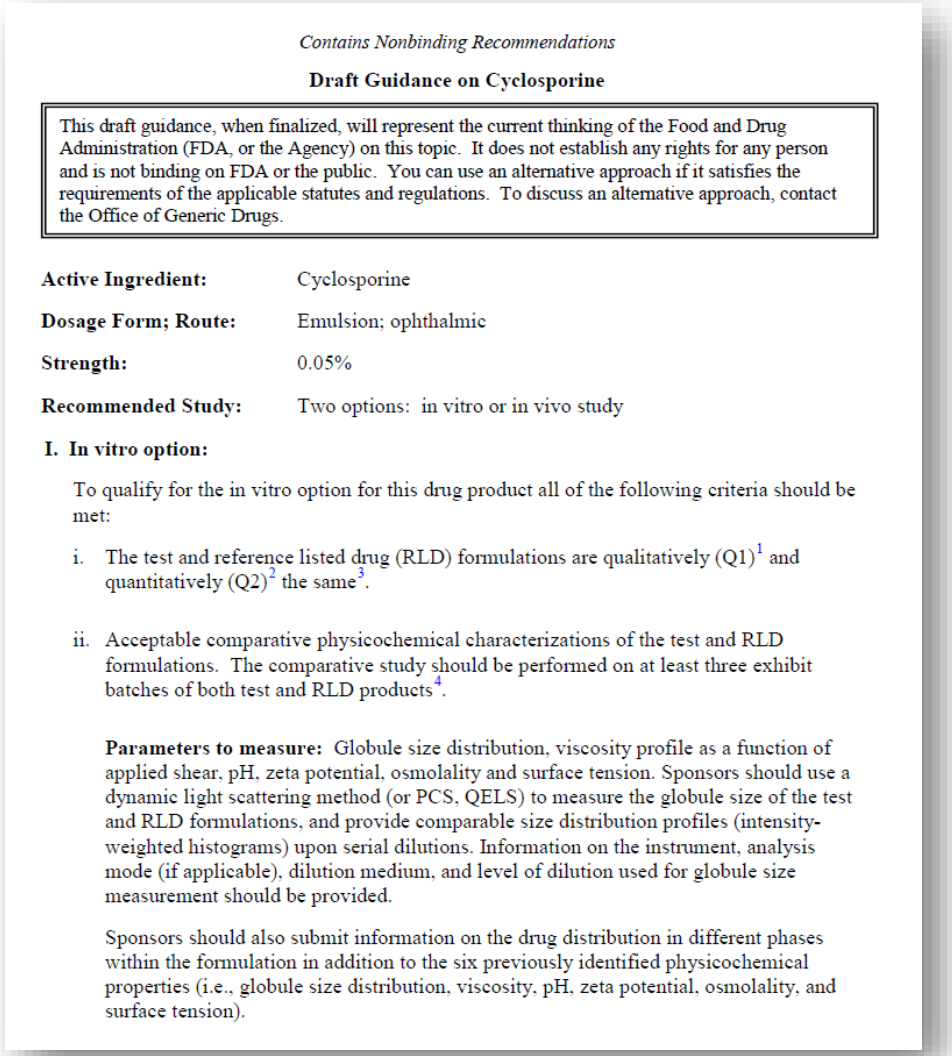
- Based on the improved understanding obtained through internal/external research projects on injectable suspensions with particle size in micro range, we were able to agree with the proposed alternative in vitro BE approach and updated the PSG to ensure timely communications.

GDUFA Research for Supporting ANDA Assessment and Approval

How does research support ANDA assessment and approval?

- Developing appropriate acceptance criteria for determining qualitative (Q1) sameness of complex polymeric excipients in parenteral, ophthalmic, and otic products.
- Providing technical support during ANDA assessment to obtain approval.

An Example: GDUFA Research for Supporting ANDA Approval



Contains Nonbinding Recommendations

Draft Guidance on Cyclosporine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Cyclosporine

Dosage Form; Route: Emulsion; ophthalmic

Strength: 0.05%

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3].

ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The comparative study should be performed on at least three exhibit batches of both test and RLD products[4].

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided.

Sponsors should also submit information on the drug distribution in different phases within the formulation in addition to the six previously identified physicochemical properties (i.e., globule size distribution, viscosity, pH, zeta potential, osmolality, and surface tension).

Research was conducted to investigate:

- Impact of process parameters on critical quality attributes:
  - Z. Rahman et al. Mol. Pharmaceutics. 2014, 11, 3. DOI: 10.1021/mp400484g
- Globule size distribution:
  - H. Qu, et al. *Int J Pharm*, 2018, 538, p.215-222. DOI: 10.1016/j.ijpharm.2018.01.012
  - P. Petrochenko, et al. *Int J Pharm*, 2019, 550, p229-239. DOI: 10.1016/j.ijpharm.2018.08.030
  - M. Hu et al. *AAPS J*. 2018, 20(3):62. DOI: 10.1208/s12248-018-0212-y
- Rheology:
  - P. Petrochenko, et al. *Int J Pharm*, 2019, 550, p229-239. DOI: 10.1016/j.ijpharm.2018.08.030
- Drug distribution:
  - Y. Dong et al. *J Pharm Sci* (2019) 108, 2002-2011, DOI: 10.1016/j.xphs.2019.01.003
  - Y. Dong et al. *J Control Release* (2019), 313, 96-105, DOI: 10.1016/j.jconrel.2019.09.010
  - Y. Dong et al. *J Control Release* (2020), 327, 360-370, DOI: 10.1016/j.jconrel.2020.08.020
- In vitro drug release:
  - Robert Bellantone, et al. *Int J Pharm,* 2022, 121521. DOI: 10.1016/j.ijpharm.2022.121521
  - Robert Bellantone, et al. *Int J Pharm,* 2022, 121521. DOI: 10.1016/j.ijpharm.2022.121521

Summary

- The GDUFA research program supports projects that improve the understanding of complex products/issues which promotes generic drug development and approval.
- The early identification of specific scientific and regulatory knowledge gaps is critical for generating targeted research outcomes.
  - Proactively understand the reference product to determine any under investigated areas that could be critical for generic development and approval.
  - Cumulate feedback on practical challenges faced by generic applicants during development via regulatory inquiries.
- New methods developed through GDUFA research can serve as a starting point to facilitate generic development.

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION