Keys to Success for Complex Generics

Robert Lionberger

Director

Office of Research and Standards

Office of Generic Drugs

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Complex Products in GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables, implantable drugs
- Complex drug-device combination products
  - Transdermals, metered dose inhalers (MDIs)
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

GDUFA: Generic Drug User Fee Amendment
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Pre-ANDA Communications with FDA

- General Guidances
  - Draft guidance for industry, Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (Jan 2017)
  - https://www.fda.gov/media/102349/download
- Product-Specific Guidances (PSGs)
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- Pre-ANDA meetings
  - Draft guidance for industry, Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (Oct 2017)
  - https://www.fda.gov/media/107626/download
  - MAPP: Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings
  - https://www.fda.gov/media/130874/download
- Controlled Correspondence
  - Draft guidance for industry, Controlled Correspondence Related to Generic Drug Development (Nov 2017)
  - https://www.fda.gov/media/109232/download

Pre-ANDA Meeting Growth

- FY2019: 113 pre-ANDA meeting requests
- FY2018: 83 pre-ANDA meeting requests
- FY2017: 27 pre-ANDA meeting requests

- FDA has exceeded all GDUFA II goals related to pre-ANDA meetings!
  - First year meetings tripled!
  - Second year 50% increase!
  - Thanks to the staff from OGD and OPQ who have successfully implemented this new program!

Keys to Success for Complex Generics

- Why is the RLD (Reference Listed Drug) complex?
- What is the scientific and regulatory landscape
  - Guidance and Citizen Petitions
- Pay attention to the science
- Use the pre-ANDA program
- Monitor changes to the RLD and the regulatory landscape during ANDA review

Two Examples

- Epinephrine Injection
  - ANDA 090589
    - Submitted on November 21, 2008
    - Approved on August 16, 2018
  - Pre-ANDA program did not exist
  - No Product-Specific Guidance prior to submission
  - No GDUFA goal dates until GDUFA II

- Fluticasone propionate; Salmeterol xinafoate (FP/SX) Inhalation Powder
  - ANDA 208891
    - Submitted on December 29, 2015
    - Approved on January 30, 2019
  - Pre-ANDA program being piloted
  - Product-Specific Guidance available prior to submission
  - GDUFA goal dates from submission

Today's focus on is what FDA has learned from reflecting on these two approvals

Auto-Injector Example

Why was Generic Product Development Complex?

- Overall risk profile of the product: High
  - Emergency, life-threatening, rare to sporadic use by a variety of users, including lay persons
- Differences in the approved products
  - RLD with yellow-capped carrier tube and no cap over needle end; Generic with no carrier tube and yellow cap over needle end
  - Different shape of blue safety release
  - RLD with oval shape; Generic with U-shaped body
  - RLD orange needle shield extends and locks after use; Generic orange needle shield locks but is not extended

Science and Regulatory Landscape

- In 2008, no publicly available information about the development of complex products with user interface differences
- Later
  - Citizen Petitions
  - General Guidance
  - Product-Specific Guidance

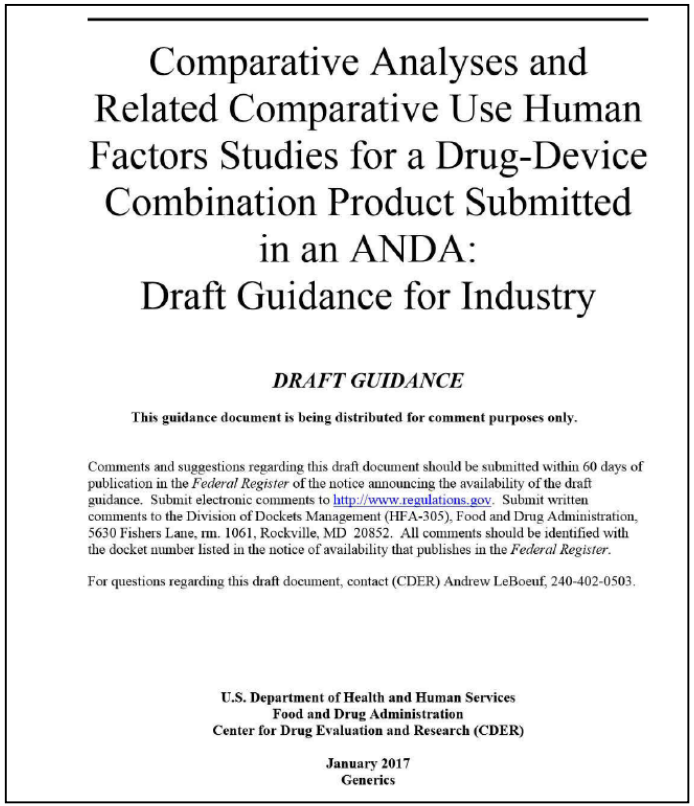
Citizen Petitions

- FDA Response to King Pharmaceuticals (Jul. 29, 2009) (Docket No. FDA-2007-P-0128/Docket No. FDA-2009-P-0040)
  - Auto-injectors/Imitrex (Sumatriptan succinate)
- FDA Response to Dey Pharma L.P. (May 27, 2010) (Docket No. FDA-2009-P-0578)
  - EpiPen/Emergency-use auto-injectors
- Key point of these petitions responses is that they indicate that some externally visible design differences between the generic and brand combination products may be acceptable

Guidance for Drug-Device Products User Interface

- Use the controlled correspondence process for early feedback on patient use issues

- Use the pre-ANDA meeting process if comparative use human factors studies may be part of your submission



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

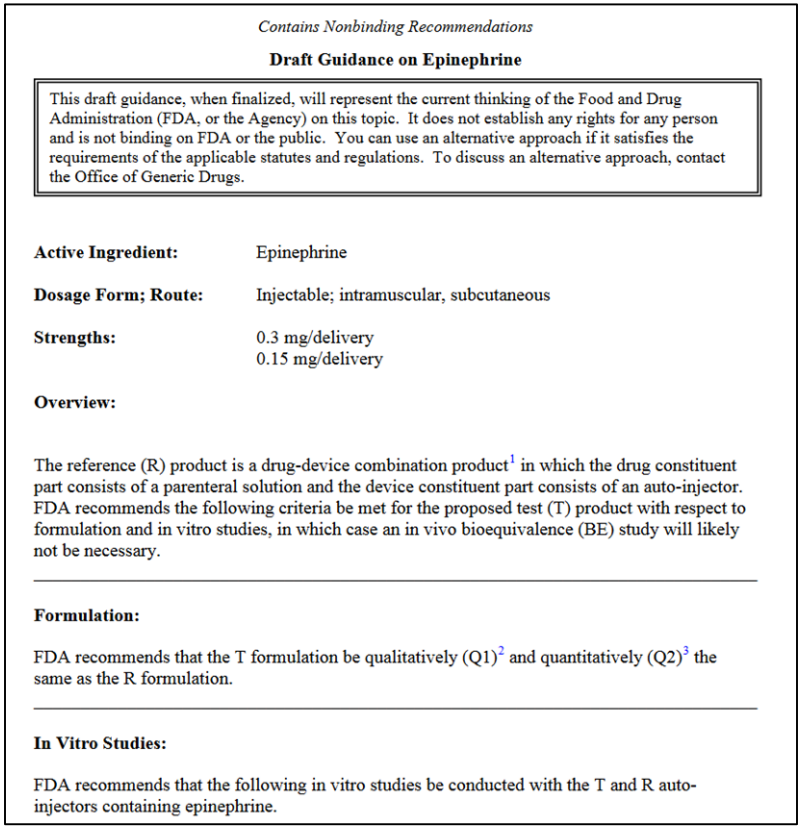
Draft PSG for Epinephrine Autoinjector (AI)

Posted December 2016

In Vitro Studies for BE:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle Integrity Post-Injection

Device Considerations



Contains Nonbinding Recommendations

Draft Guidance on Epinephrine

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: Epinephrine

Dosage Form; Route: Injectable; intramuscular, subcutaneous

Strengths: 0.3 mg/delivery
0.15 mg/delivery

Overview:

The reference (R) product is a drug-device combination product[1] in which the drug constituent part consists of a parenteral solution and the device constituent part consists of an auto-injector. FDA recommends the following criteria be met for the proposed test (T) product with respect to formulation and in vitro studies, in which case an in vivo bioequivalence (BE) study will likely not be necessary.

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the R formulation.

In Vitro Studies:

FDA recommends that the following in vitro studies be conducted with the T and R auto-injectors containing epinephrine.

Changes during ANDA review

- The device submitted in the original ANDA is not the approved device
  - Design iteration occurred in the ANDA review process
- No mechanism to discuss comparative use human factors studies with FDA prior to conducting them
- The RLD labeling and instructions for use (including injection time) changed multiple times during ANDA review

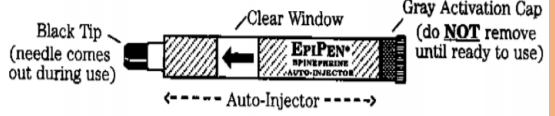
RLD and its Changes

NDA-019430/S012 (2001)	NDA-019430/S053 (2012)	NDA-019430/S061 (2016)

DIRECTIONS FOR USE

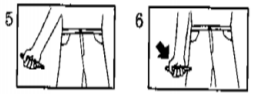
--Follow these directions *only* when ready to use.
--Never put thumb, fingers, or hand over black tip.
--Do NOT remove gray activation cap until ready to use.

1) Familiarize yourself with the unit.



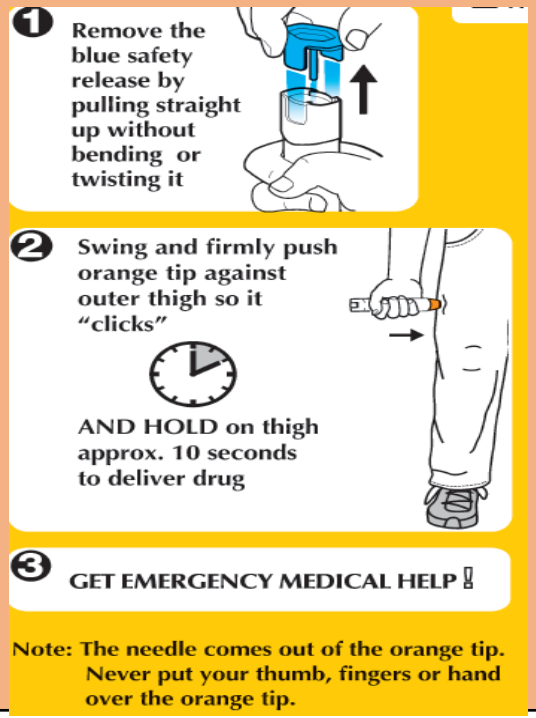
2) Grasp unit, with the black tip pointing downward.
3) Form a fist around the auto-injector (black tip down).
4) With your other hand, pull off the gray activation cap.

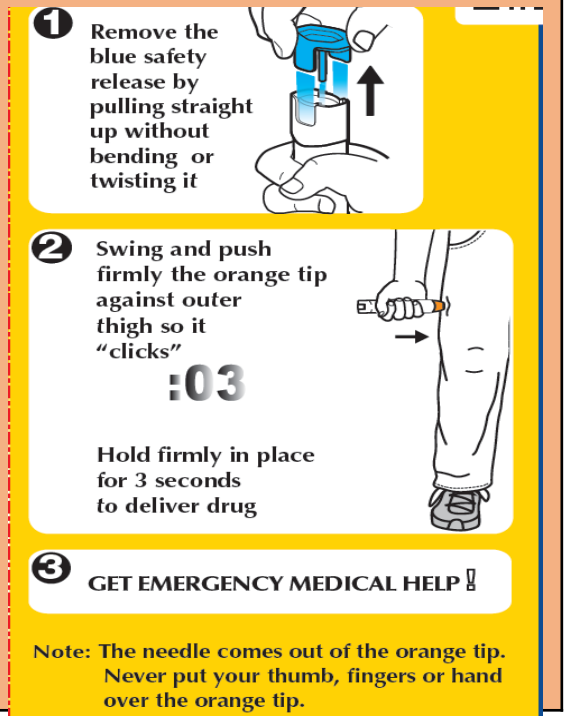
5) Hold black tip near outer thigh.
6) Swing and **jab firmly** into outer thigh so that auto-injector is perpendicular (at a 90° angle) to the thigh.



7) Hold **firmly in thigh** for several seconds.

IMMEDIATE
-- Go imme
nearest h
room.





Regulatory Landscape Changes

- Since 2008, FDA's thinking on combination products in ANDAs has evolved
  - Device cGMPs, device robustness
- See October 2018 DIA-FDA Complex Generic Drug-Device Combination Products workshop

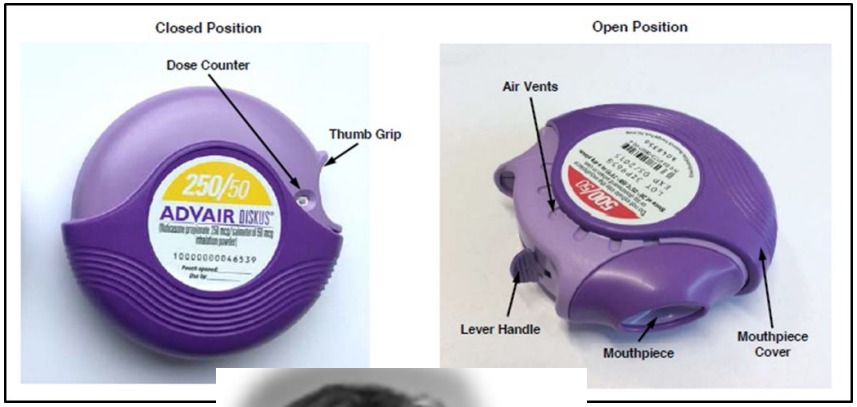
What FDA Learned

- Make guidance available before development whenever possible
- Iterative communication before ANDA submission
  - Standard Controlled Correspondence is a 60 day cycle
- Meet with FDA before conducting comparative use human factors studies for ANDAs
- How to communicate better about the changing regulatory landscape for combination products

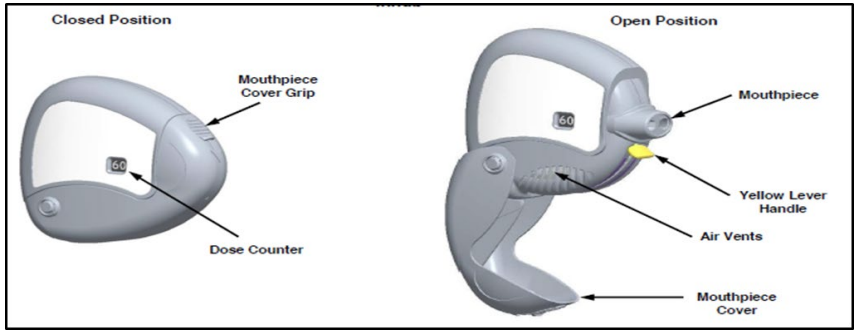
Inhalation Example

Why was Generic Product Development Complex?

RLD



ANDA



Why was Generic Product Development Complex?

- When the “site of drug action” is systemic we use pharmacokinetic studies to establish bioequivalence (BE)
- When drugs are delivered directly to the site of action we need to develop new methods
  - Comparative clinical endpoint BE studies
  - Characterization-based approaches (Q3)
  - Weight of evidence
    - Combined in vitro and in vivo performance measures

Tools for Generic Inhalation Products

- Almost no generic competition in the Orally Inhaled and Nasal Drug Product (OINDP) space
- Poster child for “complex generics”
  - In GDUFA II negotiations
  - In the FDA Commissioner’s Drug Competition Action Plan (DCAP)
- OGD has built new tools
  - Scientific Tools (Research Results)
  - Regulatory Tools (Guidance, pre-ANDA meetings)

Draft PSG for FP/SX Dry Powder Inhaler

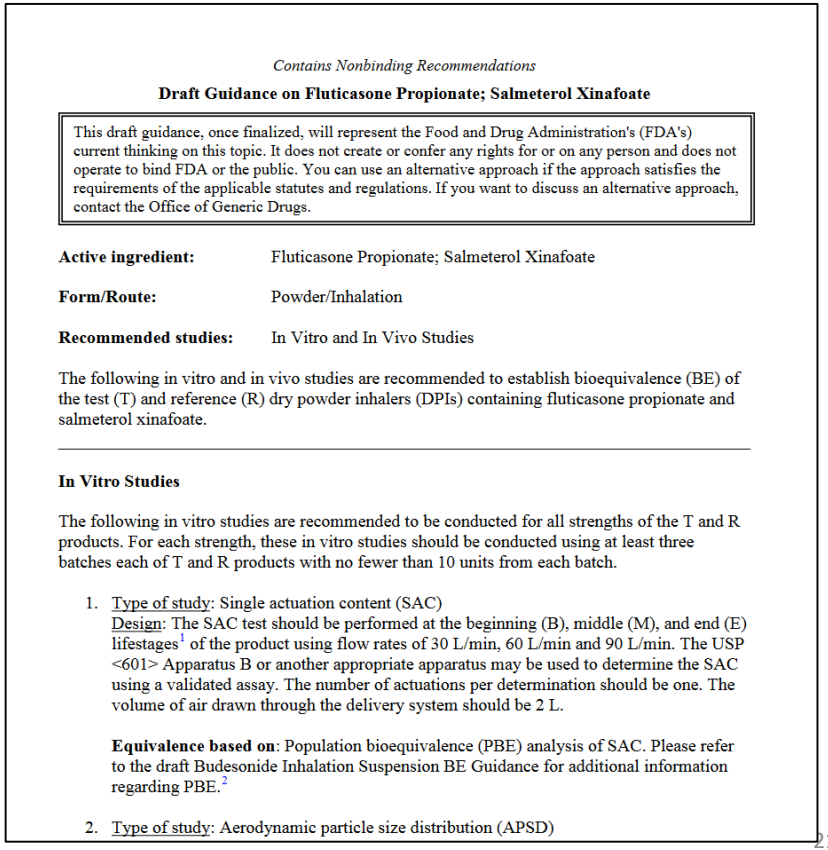
Posted September 2013

Studies for BE:

- In vitro BE
- PK BE
- Clinical endpoint BE

Device Considerations

First generic Dry Powder Inhaler was approved in January 2019



Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

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Active ingredient: Fluticasone Propionate; Salmeterol Xinafoate

Form/Route: Powder/Inhalation

Recommended studies: In Vitro and In Vivo Studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing fluticasone propionate and salmeterol xinafoate.

In Vitro Studies

The following in vitro studies are recommended to be conducted for all strengths of the T and R products. For each strength, these in vitro studies should be conducted using at least three batches each of T and R products with no fewer than 10 units from each batch.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[1] of the product using flow rates of 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one. The volume of air drawn through the delivery system should be 2 L.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE.[2]

2. Type of study: Aerodynamic particle size distribution (APSD)

FP: Fluticasone Propionate
SX: Salmeterol Xinafoate

GDUFA Regulatory Science Initiatives for OINDPs

- Identification of formulation and device variables which are important for successful development of generic OINDPs

- Development of clinically relevant in vitro and in silico tools and methodologies for prediction of in vivo regional drug deposition and dissolution from OINDPs, and to assess their applicability in generic OINDPs development programs

- Identification, validation and standardization of novel techniques that may have the potential to reduce the burden of current BE requirements for generic OINDPs.

Research Origins

- Early work: Robert Price and Jag Shur
  - Particle characteristics are critical
- Build out tools that would measure this impact
  - CFD (for lungs and for device)
  - Dissolution
  - Realistic mouth-throat models
- Explore use of systemic PK for BE
  - Conduct in vivo PK study of different formulations
  - Build PBPK models of the lung to aid deconvolution

CFD: Computational fluid dynamics
PBPK: Physiologically-based Pharmacokinetic

Research Overview

- For a deep dive
  - New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products
    - January 9, 2018 (8:30 a.m. – 4:30 p.m.), FDA White Oak Campus
    - https://www.fda.gov/Drugs/NewsEvents/ucm576064.htm
    - Recording is available

What FDA Learned

- Guidance availability and pre-ANDA meetings can lead to less time in review
- Regulatory science is the foundation for complex product development and review
  - Communicate scientific advances internally to review staff
- Focus research and pre-ANDA meetings on new BE approaches for inhalation products
- Optimize the meeting interactions and provide stable consistent regulatory advice

How to use the Pre-ANDA Process Effectively

- Order of interactions with FDA
  - Industry should pay careful attention to the research results that have been published as they provided significant insight into key product characteristics needed to ensure equivalence
  - Prototype generic device first
    - Identify any user interface issues
  - In vitro characterization of RLD batches and potential ANDA products

How to use the Pre-ANDA Process Effectively

- Order of interactions with FDA
  - PK study
    - Batch to batch variability?
  - Design comparative clinical endpoint BE study or discuss alternative approach
    - Product Development Meeting for alternative approach
    - Controlled Correspondence for protocol questions if there is a PSG
    - Product Development Meeting if there is no PSG

How to Use the Pre-ANDA Process Effectively

- FDA's current experience is that inhalation ANDAs have a large number of first cycle deficiencies
  - Read our general guidance on inhalation products
  - Read our Product-Specific Guidance on inhalation products
  - Use controlled correspondence to ask specific questions about general or product-specific guidance
  - Use Product Development Meeting if you propose something different than in the PSG
  - Use Pre-submission meeting to make the review more efficient

Pre-ANDA Continuity

- Meetings provide FDA the opportunity to see the landscape of incoming complex generic ANDAs
  - Ability to communicate internally and think on complex challenges prior to ANDA submission
- For pre-submission meetings, FDA will identify representatives of the ANDA review team to participate in the meeting
  - FDA will communicate the results of the product development meeting or other pre-ANDA interactions to the review team
- Meetings are automatically pulled into the ANDA program once the ANDA is submitted using the pre-assigned ANDA number associated with the meeting request
  - Using the pre-assigned ANDA number for controlled correspondence will also aid this linkage

Keys to Success for Complex Generics

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