Generic Drug User Fee Amendments (GDUFA) research and the product-specific guidance (PSG) program for complex products: Challenges and notable advances

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AAM GRx + Biosims 2023 WorkShop
October 3, 2023

Disclaimer

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Overview

- Product-specific guidances (PSGs) for complex products
  - Overview of the PSG program and aims
  - New commitments under GDUFA III: PSG goal dates and forecast list
- Examples of challenges and notable advances in the bioequivalence recommendations for complex products
  - Oligonucleotide and peptide drug products
  - In vitro BE approaches for injectable drug substance and nasal suspension products
  - Orally inhaled drug products; alternative approaches to comparative clinical endpoint bioequivalence studies

GDUFA Research and PSGs

- PSGs outline FDA's current thinking on the studies and information that are recommended to demonstrate a proposed generic drug product is therapeutically equivalent to a specific Reference Listed Drug (RLD).
- A PSG may include more than one option to demonstrate BE. In these instances, an applicant can consider which option, or alternative to those recommendations, may be appropriate for their development program.
- GDUFA III commitment includes goal dates for posting of PSGs for NDAs approved after Oct 1, 2022, that are complex products; 50% within 2 years of NDA approval and 75% within 3 years.
- GDUFA III commitment also includes posting a public PSG forecast list of upcoming new and revised PSGs.

PSG Public Forecast List

- *Upcoming Product-Specific Guidances for Generic Drug Product Development* is a public facing web page that lists all new and revised PSGs, for both complex and non-complex generic drug products, that FDA's plans on issuing in the next 12 months
- The PSG forecast list is updated on a quarterly basis
- For revised PSGs, the planned revision categories briefly describe the nature of the anticipated revisions.
  - **Critical revision:** PSG revision includes additional bioequivalence (BE) study(ies) or evidence recommended that is necessary to establish BE
  - **Major (in vivo or in vitro) revision:** PSG revision includes additional BE study(ies) or evidence recommended that is necessary to establish BE
  - **Minor revision:** Any revision to a PSG that is not considered critical or major, including but not limited to when a PSG is to be revised to add an in vivo or in vitro BE option, to clarify recommended study design, to certain study(ies), to provide alternative (less burdensome) approaches
  - **Editorial revision:** PSG revision includes non-substantive changes

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

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Introduction

Content current as of: 05/22/2023

Planned New PSGs for Complex and Non-Complex Generic Drug Products Updated August 21, 2023

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Product Complexity	Planned Publication
Adagrasib	Oral	Tablet	216340	Non-Complex	02/2024
Air Polymer-Type A	Intrauterine	Foam	212279	Complex	08/2024
Amikacin Sulfate	Inhalation	Suspension, Liposomal	207356	Complex	05/2024
Amoxicillin; Clarithromycin; Vonoprazan Fumarate	Oral	Capsule, Tablet, Tablet	215152	Non-Complex	11/2023
Amoxicillin; Vonoprazan Fumarate	Oral	Capsule, Tablet	215153	Non-Complex	11/2023
Aprepitant	Intravenous	Emulsion	216457	Complex	02/2024
Aripiprazole	Oral	Tablet	207202	Complex	Within the next 12 months
Atorvastatin Calcium	Oral	Suspension	213260	Non-Complex	05/2024
Azacitidine	Oral	Tablet	214120	Non-Complex	11/2023
Baclofen	Oral	Granules	215422	Non-Complex	02/2024
Bexagliflozin	Oral	Tablet	214373	Non-Complex	05/2024

Planned Revised PSGs for Complex and Non-Complex Generic Drug Products Updated August 21, 2023

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application	Planned Revision Category with Description	Product Complexity	Planned Publication
Acetaminophen; Butalbital	Oral	Capsule	088831	Minor Revision: Remove recommendation on a strength due to safety concerns	Non-Complex	02/2024
Aclidinium Bromide	Inhalation	Powder, Metered	202450	Editorial Revision: Update the language Minor Revision: Clarify in vivo and in vitro study designs; Add recommendations for device comparisons	Complex	05/2024
Aclidinium Bromide; Formoterol Fumarate	Inhalation	Powder, Metered	210595	Editorial Revision: Update the language Minor Revision: Clarify in vivo and in vitro study designs; Revise recommendations for device comparisons	Complex	05/2024

Oligonucleotide and Peptide Drug Products

Approved Synthetic Oligonucleotide Drugs

There are 13 approved synthetic oligonucleotide drug products. Most are anti-sense oligos (ASO) that have non-natural, chemically modified, backbones and bases:

- e.g., phosphorothioate, morpholino ring, methylated ribose

Proprietary name	Active ingredient	Category	Oligo Length
VITRAVENE	Fomivirsen sodium	Phosphorothioate ASO	21
MACUGEN	Pegaptanib sodium	Phosphate oligonucleotide aptamer	28
KYNAMRO	Mipomersen sodium	Phosphorothioate ASO	20
EXONDYS 51	Eteplirsen	Phosphorodiamidate morpholino ASO	30
SPINRAZA	Nusinersen sodium	Phosphorothioate ASO	18
ONPATTRO	Patisiran sodium	Double-stranded siRNA	19+2 (antisense)
TEGSEDI	Inotersen sodium	Phosphorothioate ASO	20
GIVLAARI	Givosiran sodium	Double-stranded siRNA	21+2 (antisense)
VYONDYS 53	Golodirsen	Phosphorodiamidate morpholino ASO	25
VILTEPSO	Viltolarsen	Phosphorodiamidate morpholino ASO	21
OXLUMO	Lumasiran	Double-stranded siRNA	21+2 (antisense)
AMONDYS 45	Casimersen	Phosphorodiamidate morpholino ASO	22
LEQVIO	Inclisiran	Double-stranded siRNA	21+2 (antisense)

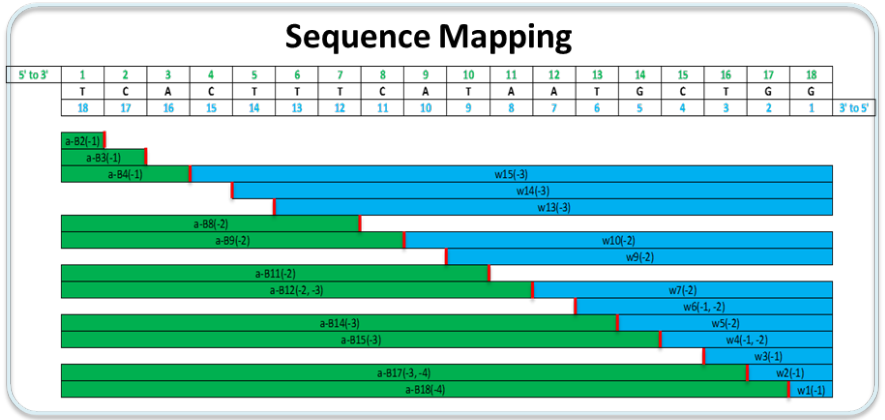
Oligonucleotide Regulatory Challenges

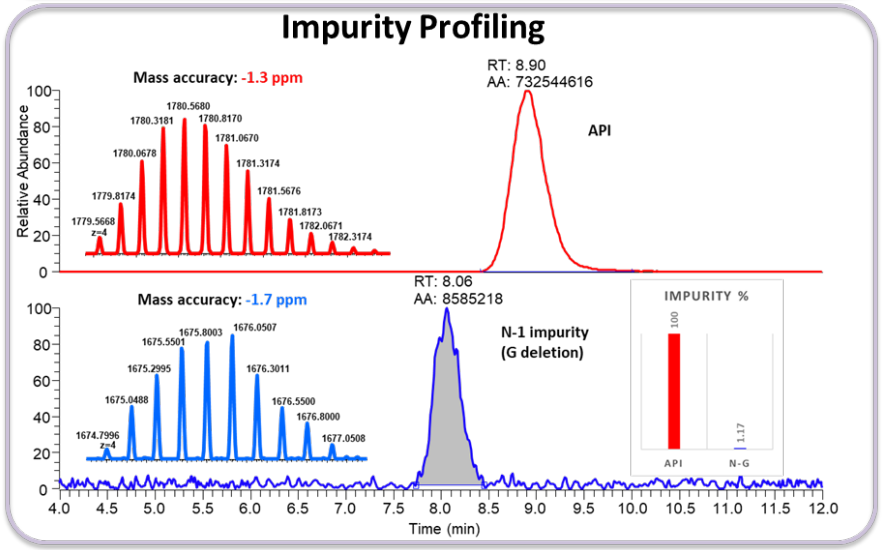
- Currently no ICH[1] to address quality expectations such as impurity reporting, identification and qualification thresholds, but PSGs have been posted for these products
  - Impurity characterization
  - Reaction conditions (e.g., activator used) affects phosphorothioate stereochemistry, which also affects the pharmacologic properties[2]
    - Large number of potential diastereomers = $2^{(\text{number of phosphorothioate bonds})}$
  - Most impurities exist as mixtures of closely related molecules that can coelute with the active ingredient
    - Lack of analytical methods to adequately resolve impurities
  - Immunogenicity risk assessment
    - Local inflammation and/or thrombocytopenia and potential immunomodulatory effects

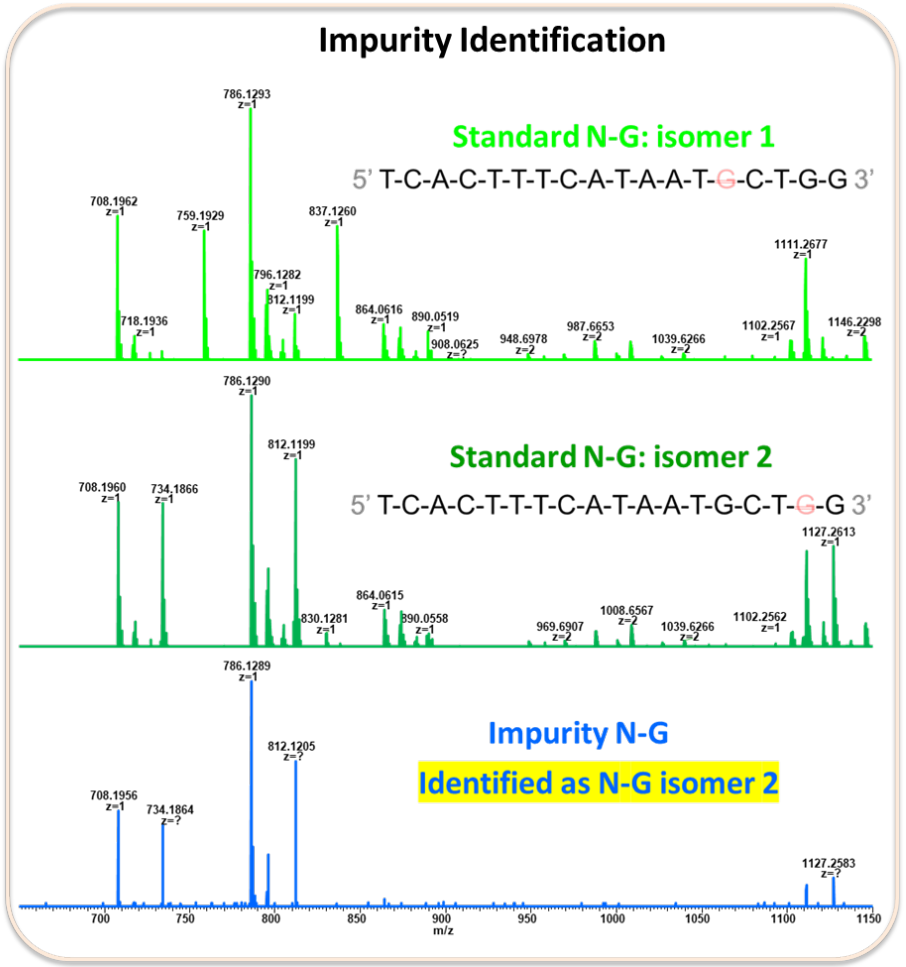
1. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
2. Iwamoto N, et al Nat Biotechnol. 2017, 35(9), 845-851

Developing Analytical Methods to Characterize Chemical Structural Profile

GDUFA research has been developing and testing analytical methods and measurement procedures[1] that are capable of resolving highly similar oligonucleotide chemical structures.







1. Abdullah, A. M., et al. Journal of Mass Spectrometry 57.4 (2022): e4819.

Peptide Drug Products: Immunogenicity Risk Assessment

- The studies recommended in a PSG depends on the immunogenicity risk of the peptide product

	API sameness	Impurity profile	Adaptive Immune	Innate Immune	HOS and Oligomer (Aggregates)	Biologic activities
Octreotide Injectable	X				X	
Bremelanotide injection	X				X	
Vasopressin injection	X	X			X	
Secretin injection	X	X			X	X
Dasiglucagon injection	X	X		X	X	X
Semaglutide injection	X	X	X	X	X	X

- Not recommending a study in a PSG does not mean it will not be requested during review process.

Vasopressin PSG

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Vasopressin

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.

Active Ingredient:	Vasopressin
Dosage Form; Route:	Solution; intravenous
Strength:	20 units/mL (20 units/mL), 20 units/100 mL (0.2 units/mL), 40 units/100 mL (0.4 units/mL), 60 units/100 mL, (0.6 units/mL), and 200 units/10 mL (20 units/mL)
Recommended Study:	Request for waiver of in vivo bioequivalence study requirements

Waiver:

In vivo bioequivalence (BE) study may be waived on the basis that BE is self-evident (21 CFR 320.22(b)), for a generic vasopressin injection solution product that is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD). An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[3]

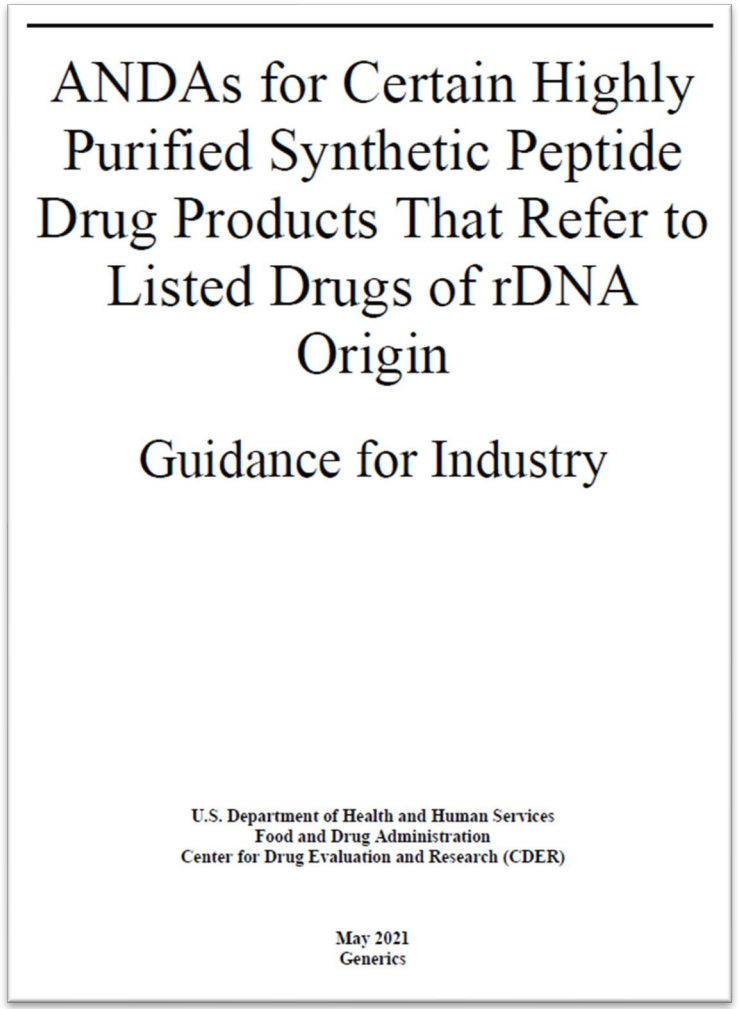
In addition to ensuring active pharmaceutical ingredient API sameness (i.e., same primary sequence), the following comparative analyses of the proposed generic vasopressin and the RLD product should be provided on at least three batches each of the proposed generic and the RLD aged under various conditions.[4]

1. API related impurity profile comparison: new impurities found in the proposed generic product but not in the RLD and impurities found at a significantly higher level in the proposed generic product than in the RLD, should be identified[5]
2. Comparative comparison of aggregation profile and any secondary structure

- Q1/Q2
- API sameness
- Peptide related impurity profile comparison*
- Comparative aggregation profile

*Immunogenicity assessment may be requested in situations where the comparative impurity or aggregation profile indicates the presence of an unusual new impurity or aggregation state, or a markedly elevated level of an impurity or aggregation state in the proposed generic product relative to the RLD.

Semaglutide Injection PSG

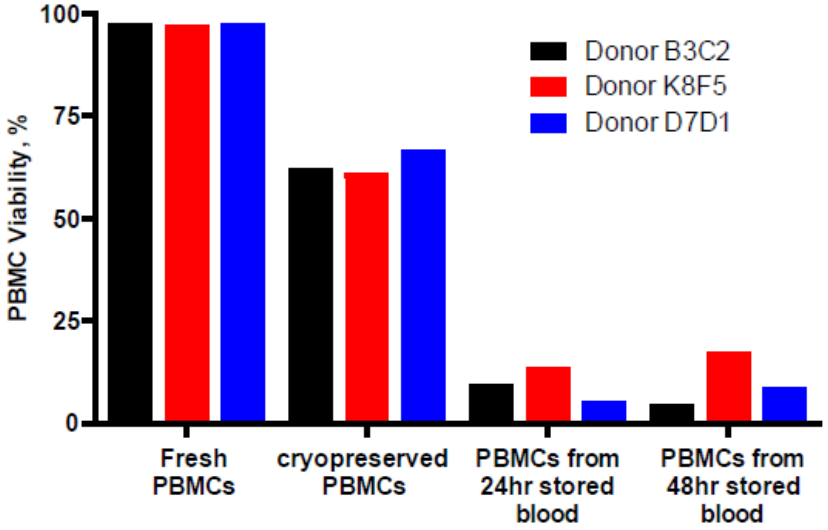


- PSG for semaglutide injection refers to the *Synthetic Peptide Guidance*
- Although specific to the five peptide products listed in the guidance, the scientific principles and elements of the guidance may be applied to other follow-on higher risk peptide products, such as semaglutide
- This guidance provides recommendations on addressing the potential immunogenicity risk for peptide-related impurities
  - Comparative impurity profile
  - Adaptive immune response (MHC binding)
  - Innate immunogenicity of the product

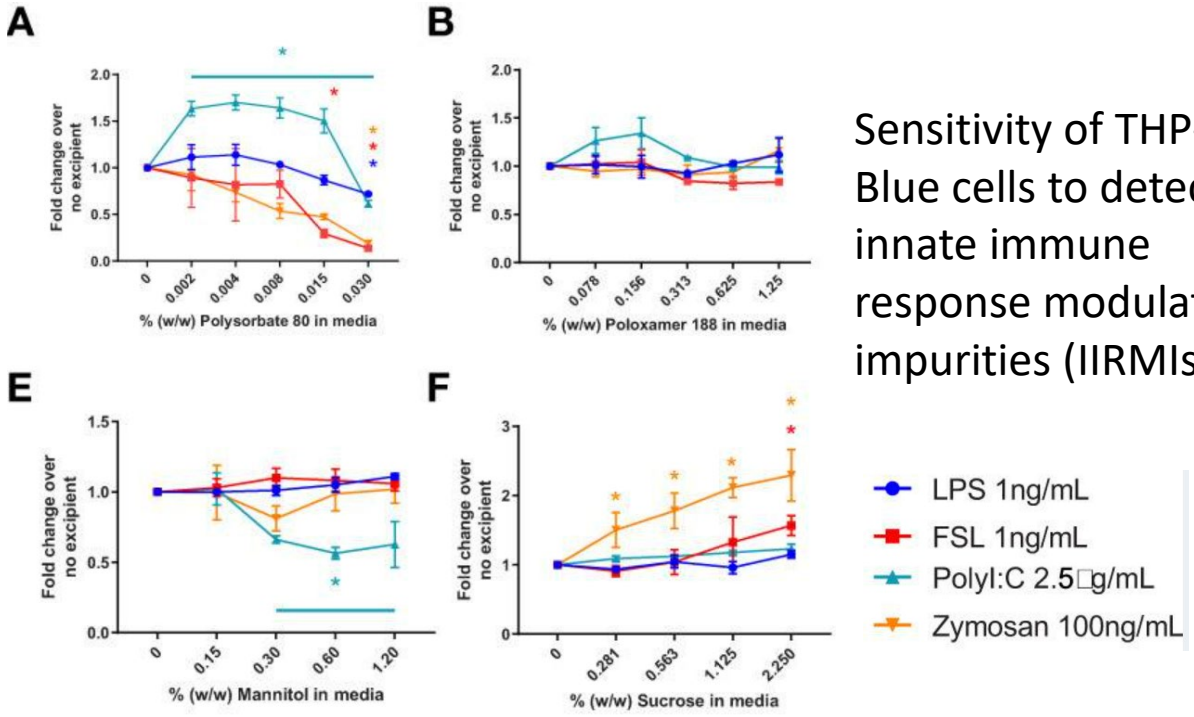
In Vitro Immunogenicity Assay Development

- In vitro immunogenicity assay development, validation, and appropriate study design and controls can present challenges.
- GDUFA research has examined impact of cell handling and formulation excipients on assay response.

Peripheral blood mononuclear cell (PBMC) viability with handling/storage



Holley, C. K., et al 2021 Molecules, 26 (24), p 7461.



Sensitivity of THP-1-Blue cells to detect innate immune response modulating impurities (IIRMIs)

Thacker et al., Frontiers in Immunology 13 (2022): 970499.

In vitro BE approaches for injectable drug substance and nasal suspension products

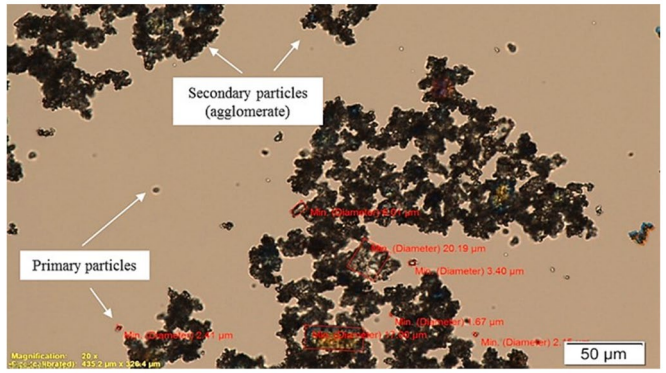
In Vitro BE Approaches for Injectable Drug Substance Suspensions

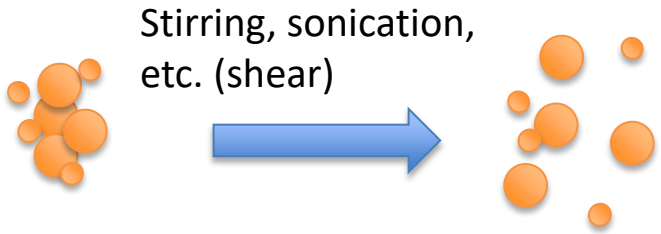
- BE studies with pharmacokinetic (PK) endpoints have been commonly recommended by FDA in PSGs for systemically acting injectable suspensions, but where research supports it, FDA has recommended in vitro BE studies for some injectable drug substance suspensions.
- Characteristics of these products are:
  - Drug substance particles are the only insoluble component in the formulation (or reconstituted formulation)
  - There are no insoluble excipients in the solution phase
  - Drug release does not rely on release controlling excipients (e.g., poly(lactic-co-glycolic acid) copolymer)
  - Dissolution rate is generally determined by particle size and solubility of the drug substance

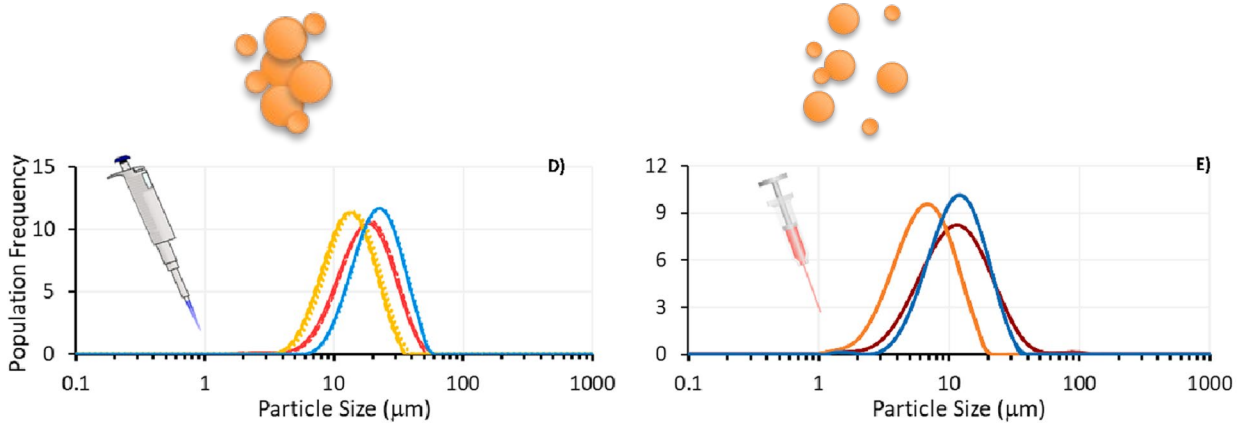
$$\frac{dC}{dT} = \frac{D \cdot A}{h \cdot V}(C_s - C_i)$$

In Vitro BE Challenges and GDUFA Research: Impact of Particle Flocculation

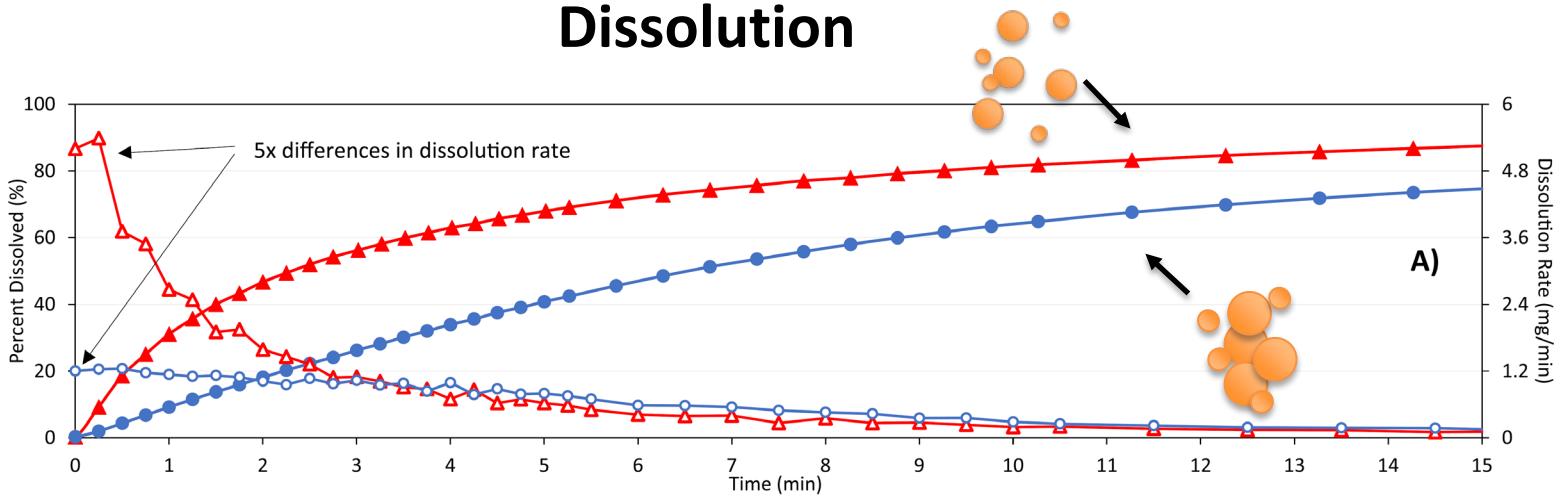
Triamcinolone acetonide injectable suspension







Dissolution

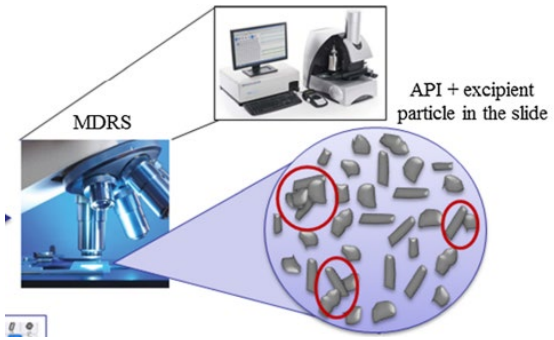


Smith, W.C., et al. International Journal of Pharmaceutics 604 (2021): 120767.

PSGs for Complex Nasal Spray Suspensions

GDUFA-funded research[1-3] supported the recent revision of nine PSGs on locally acting nasal spray suspension products to include an in vitro option to demonstrate bioequivalence (BE)

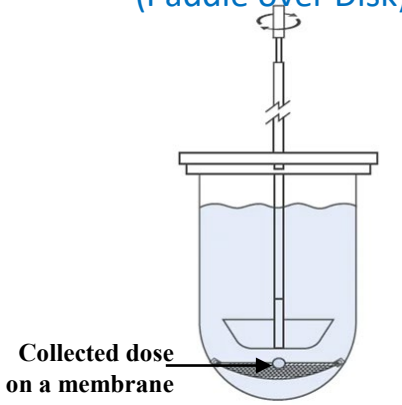
- Morphologically-directed Raman spectroscopy (MDRS) is capable of characterizing drug-specific particle size distribution (PSD) of nasal suspensions
- Dissolution studies using various systems (USP Apparatus 2, USP Apparatus 5, Transwell®) are sensitive in detecting differences in drug PSD
- Pharmacokinetic (PK) studies were sensitive in detecting differences in drug PSD



Available at FDA's PSG webpage:

Azelastine Hydrochloride; Fluticasone Propionate Nasal Spray, Metered (May 2023)
Fluticasone Furoate Nasal Spray, Metered (May 2023)
Fluticasone Propionate Nasal Spray, Metered (NDA 020121, May 2023)
Mometasone Furoate Nasal Spray, Metered (NDA 020762, May 2023)
Beclomethasone Dipropionate Monohydrate Nasal Spray, Metered (Aug 2023)
Budesonide Nasal Spray, Metered (Aug 2023)
Ciclesonide Nasal Spray, Metered (Aug 2023)
Mometasone Furoate; Olopatadine Hydrochloride Nasal Spray, Metered (Aug 2023)
Triamcinolone Acetonide Nasal Spray, Metered (Aug 2023)

USP <724> Apparatus 5
(Paddle over Disk)

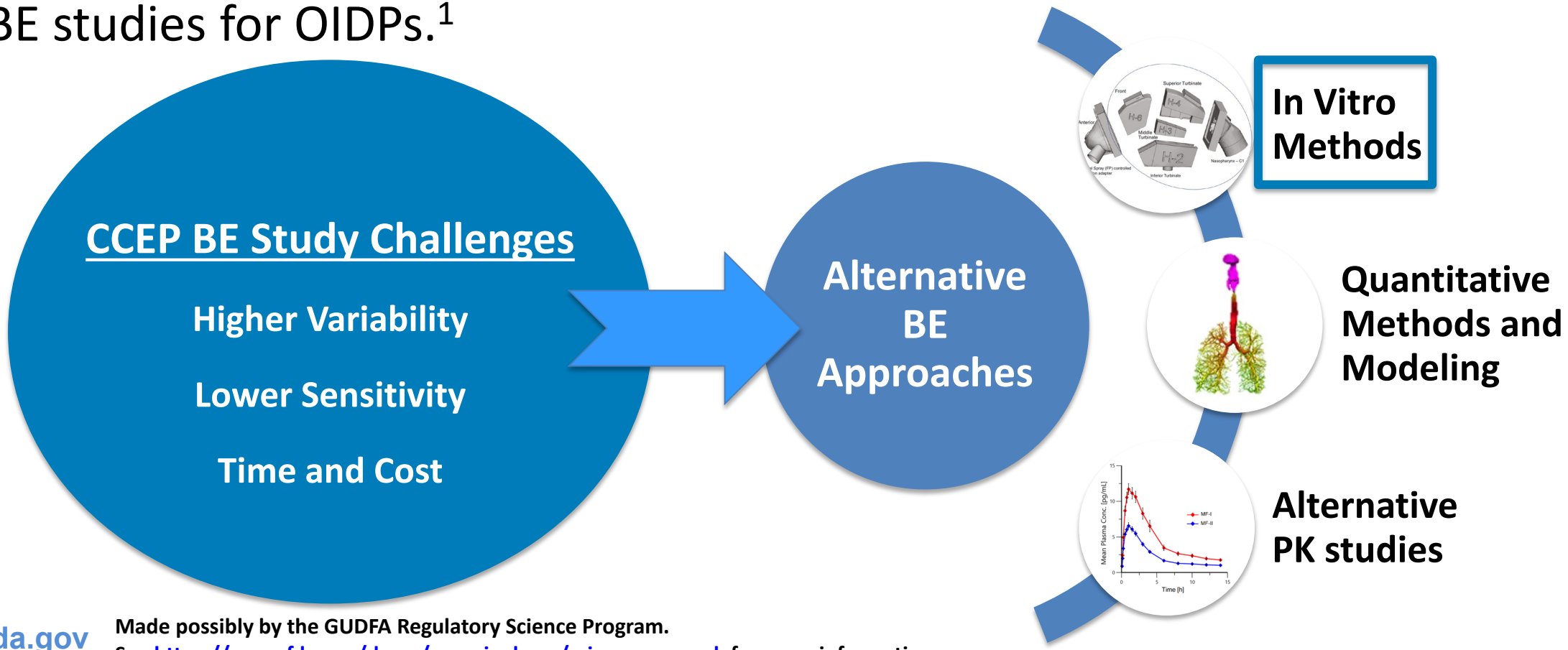


1. Thomas BJ, et al. *J Pharm Sci* 2021,110(7):2778-2788. 2. Farias G, Shur J, et al. *AAPS J* 2021, 23(4):73. 3. Hochhaus G, et al. *Respiratory Drug Delivery 2022*. Volume 1, 2022:47-54.

Orally inhaled drug products; alternative approaches to comparative clinical endpoint bioequivalence studies

Orally Inhaled Drug Products (OIDPs)

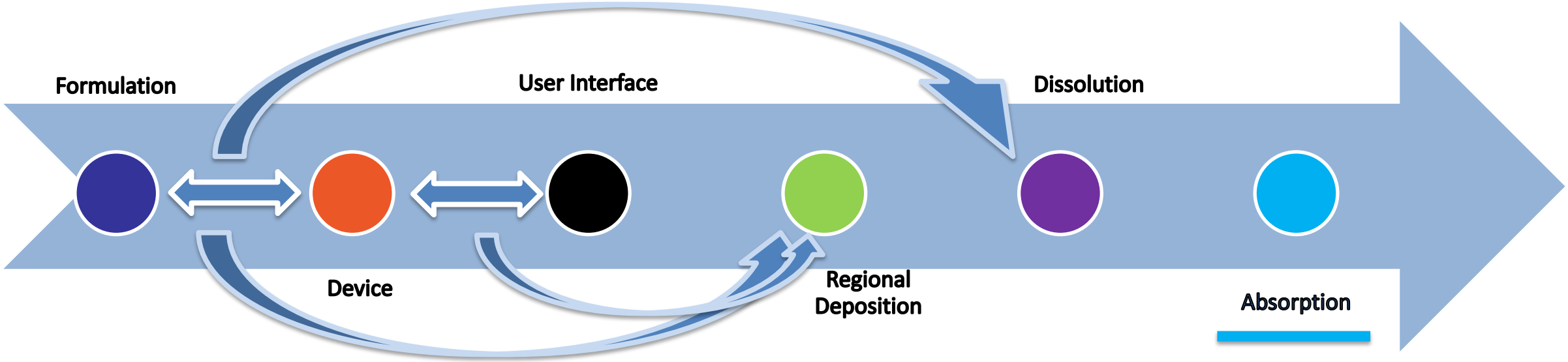
- Implement ***in vitro methods*** together with PK and certain other methods (e.g., in silico) as alternatives to the use of comparative clinical endpoint BE studies for OIDPs.[1]



Made possibly by the GUDFA Regulatory Science Program.
See https://www.fda.gov/drugs/generic-drugs/science-research for more information.

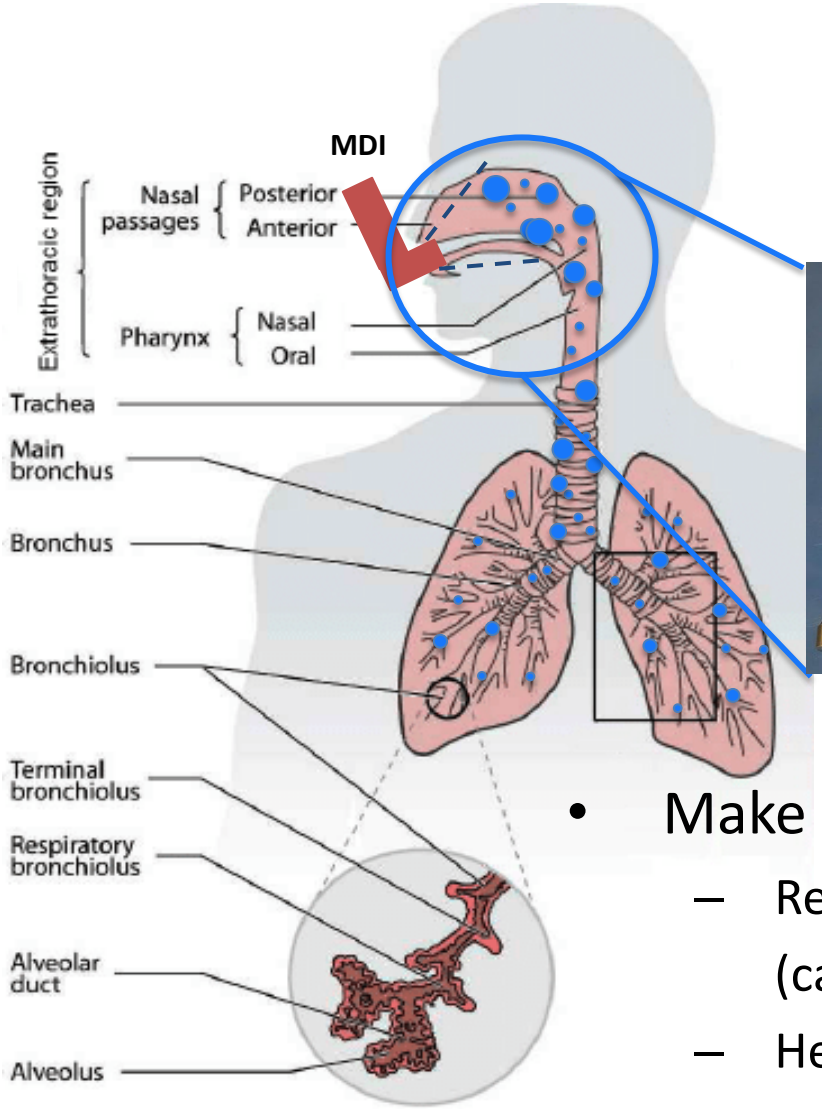
OIDPs: Challenges for Establishing BE

- Developing generics for **locally acting OIDPs** is challenging because of the ***multiple factors that can influence drug delivery to the site of action***

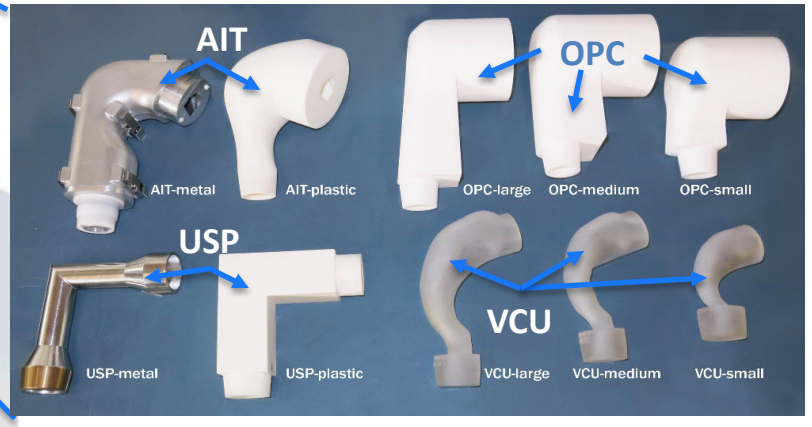


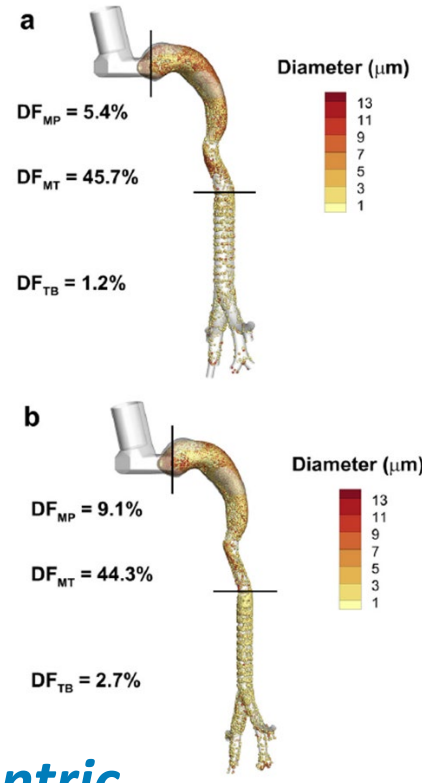
In Vitro Product Performance + Patient Factors

GDUFA Research: Modeling Regional Deposition



Mouth-Throat Models





CFD Models

Predicted deposition fractions in mouthpiece, mouth-throat, and tracheobronchial regions for a) healthy, and b) asthmatic lungs with MDI delivery[1]

- Make in vitro testing more ***patient-centric.***
  - Reflect more closely regional deposition seen in ***patients*** (capture variability seen in the clinical setting).
  - Help establish ***in vitro-in vivo correlations (IVIVCs).***

USP: United States Pharmacopeia induction port;
AIT: Alberta Idealized Throat;
OPC: Oropharyngeal Consortium;
VCU: Virginia Commonwealth University

1. Walenga RL, Longest PW.. Journal of Pharmaceutical Sciences. 2016;105(1):147-59.

Summary

- PSGs provide FDA's current thinking on the type of studies and information to support the development and approval of safe, effective, and high-quality generic drug products.
  - PSGs for complex product NDAs approved in GDUFA III have goal dates and FDA now posts a PSG forecast list on a quarterly basis that includes all new and revised PSG that FDA anticipates posting within the following 12-months
- Oligonucleotide drug products are a newer class of drug substance that present new analytical and immunogenicity assay challenges
- New in vitro based BE approaches for complex injectable and nasal suspensions offer generic applicants' additional options but may present additional need for analytical development and testing to support the method is fit-for-purpose
- Improved anatomical and in silico local lung deposition modeling of OIDPs offers alternatives to CCEP BE studies but selection and justification of models can present challenges.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