Post-approval changes in Complex Generics from Drug Product/CMC Perspectives

David Awotwe-Otoo, PhD.
Senior Pharmaceutical Quality Assessor (SPQA)
Office of Pharmaceutical Quality Assessment I/OPQ
CDER | US FDA

SBIA – Generic Drug Forum – April 11, 2024

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user

Drugs are no different

Pharmaceutical quality -
assuring **every** dose is safe and effective, free of contamination and defects

It is what gives patients confidence in their next dose of medicine

Complex Generic Drug Products

- Complex drug products are defined as product with:
  - **Complex active ingredient** (i.e., Peptides, naturally sourced ingredients, complex mixtures of APIs)
  - **Complex routes of delivery** (e.g., Locally acting drugs, complex ophthalmological products and otic dosage forms formulated as emulsions or gels)
  - **Complex formulation** (e.g., liposomes and colloids)
  - **Complex dosage forms** (e.g., MDIs, DPIs and TDS)
  - **Complex drug-device combination products** (e.g., pre-filled auto-injector products, DPIs, MDIs)

Post-Approval Changes (PAC) to Complex Generic Drugs

- **21 CFR 314.70** - requires FDA notification of changes made to each condition established in an approved application either via a supplement or the annual report.
  - **314.70(a)(1)(i):** ….the applicant **must notify FDA** about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to **describe the change fully**
    - ✓ *Submit a supplement for change, if required*
    - ✓ *Clearly list all proposed change(s) in the cover letter*
  - The holder of the application must **assess the effects of the change before distributing** a drug product made with a manufacturing change
    - ✓ *Provide supporting data for proposed change(s)*

Risk-based Reporting Categories

21 CFR 340.70(b)-(d): A supplement must be submitted based substantial, moderate or minimal **potential to have an adverse effect** on the identity, strength, quality, purity or potency of the drug product as they relate to the safety or effectiveness of the product

Major Changes

- PAS – Changes implemented after FDA approval

Moderate Changes

- CBE 30 – Implement change 30 days following supplement receipt by FDA
- CBE 0 – Implement change immediately after supplement receipt at FDA

Minor Changes

- Annual Report – Notification after implementation

Current Post-Approval Changes(PAC) Guidance

1995	SUPAC-IR
1997	SUPAC-IR & ANSWERS
1997	SUPAC-MR
1997	SUPAC-SS
1998	PAC-ATLS
2004	CHANGES TO APPROVED NDAS & ANDAS
2014	CMC POST-APPROVAL CHANGES DOCUMENTED IN ANNUAL REPORTS
2018	POST- APPROVAL CHANGES TO DRUG SUBSTANCES
2022	COMPARABILITY PROTOCOLS FOR POSTAPRROVAL CHANGES TO CMC INFORMATION IN NDA, ANDA OR BLA

Challenges with Post-Approval changes to Complex Generic Products

- As more complex generic drugs get approved by FDA, the need for transparency and clarity regarding the lifecycle management of these products become dire
- Intricacies associated with these complex generic drug products present significant challenges to their post-approval changes
  - Filing categories for certain proposed changes not clearly defined per current post-approval guidance documents
  - Overly conservative approaches to post-approval changes due to lack of applicable guidance document

Regulatory Barriers

Filing Categories

PAS?
CBE-30?
CBE-0?
AR?

Types of Changes

- Formulation Changes
- Batch Scale Up/Down
- Site Transfers
- Primary Packaging Component changes
- Device constituent part mold and/or sub-assembly facilities
- Excipient Source Changes

Data Requirements

- Number of batches?
- In vivo/In vitro BE Requirements?
- Use of in-vitro approaches, modelling and simulation for changes that may require in-vivo BE studies for complex dosage forms for major changes?
- Immunogenicity studies as function of impurity profile?
- Will full stability data be required for change(s) in MOC of parts in direct contact with DP?

ICH Guidelines to Post-Approval Changes

- ✓ Provide opportunity for science- and risk-based approaches to drug product development and regulatory decisions
- ✓ Provide valuable information in assessment of CMC changes across product lifecycle

Q8(R2) *Early stage of product lifecycle*

Q9

Q10

Q11 *Focus: Early stage of product lifecycle*

Q12

Q14

Focus: Commercial phase of product lifecycle

- ✓ Complement and add flexibility to regulatory approaches to post-approval CMC changes described in Q8 & Q10
- ✓ Provides a harmonized framework to facilitate management of post-approval CMC changes more predictably
- ✓ Defines categorization of post-approval changes to CMC, Established Conditions (EC), Post-Approval Change Management Protocols (PACMP) and Product Lifecycle Management (PLCM) concepts

ICH Q12 – Established Conditions (EC)

- Elements of the control strategy in an application (i.e., product and process parameters, facility and equipment operating conditions, in-process controls, finished product specifications and associated methods and frequency of monitoring and control) that are necessary to assure process performance and product quality.
  - If any EC is changed, it requires a (post approval) regulatory submission
  - Supportive information does not require regulatory submission, if changed
- The extent (number and how narrowly defined) of ECs varies based on
  - Product and process understanding
  - Characterization
  - Firm's development approach
  - Potential risk to product quality
- Product and process understanding can come from development studies, platform knowledge and/or commercial experience

Established Conditions (Cont'd)

- After identifying ECs;
  - Applicant may follow existing regulations and guidance (e.g,. CANA guidance) reporting category to make post-approval changes or
  - Propose alternate reporting category (e.g., CBE 30 instead of a PAS) with justification
- Reporting category is dependent of potential risk to quality
  - Risk assessment should follow approaches described in ICH Q9
  - Consider overall control strategy and possible concurrent changes
- Increases transparency between Industry and regulatory authorities
  - **Industry** – Better design of products with fewer problems in manufacturing since decisions are made based on process understanding and risk mitigation
  - **Agency** – Improve quality of information in required regulatory submissions as well as quality of review

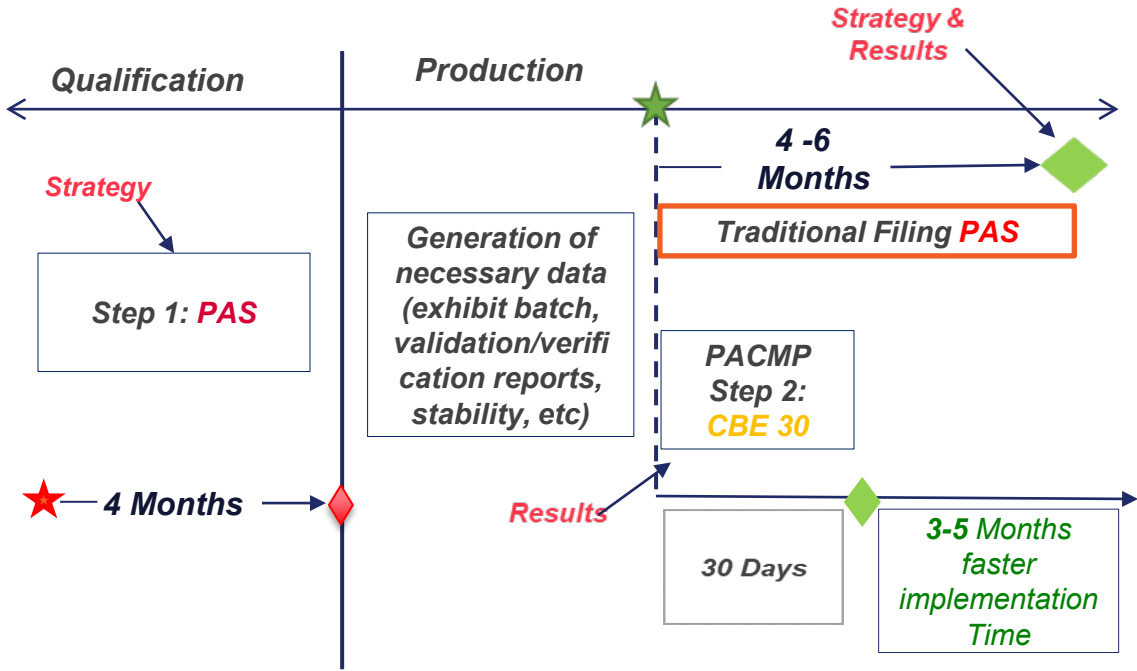
Post-Approval Change Management Protocol (PACMP)

- Provides predictability and transparency regarding the information required to support a CMC change and the submission required for the change
  - Referred to as **Comparability Protocol** in the US
- May be submitted with original application or as a stand-alone submission (PAS)
- Can be submitted to address one or more changes for a single product or may address one or more changes to be applied to multiple products

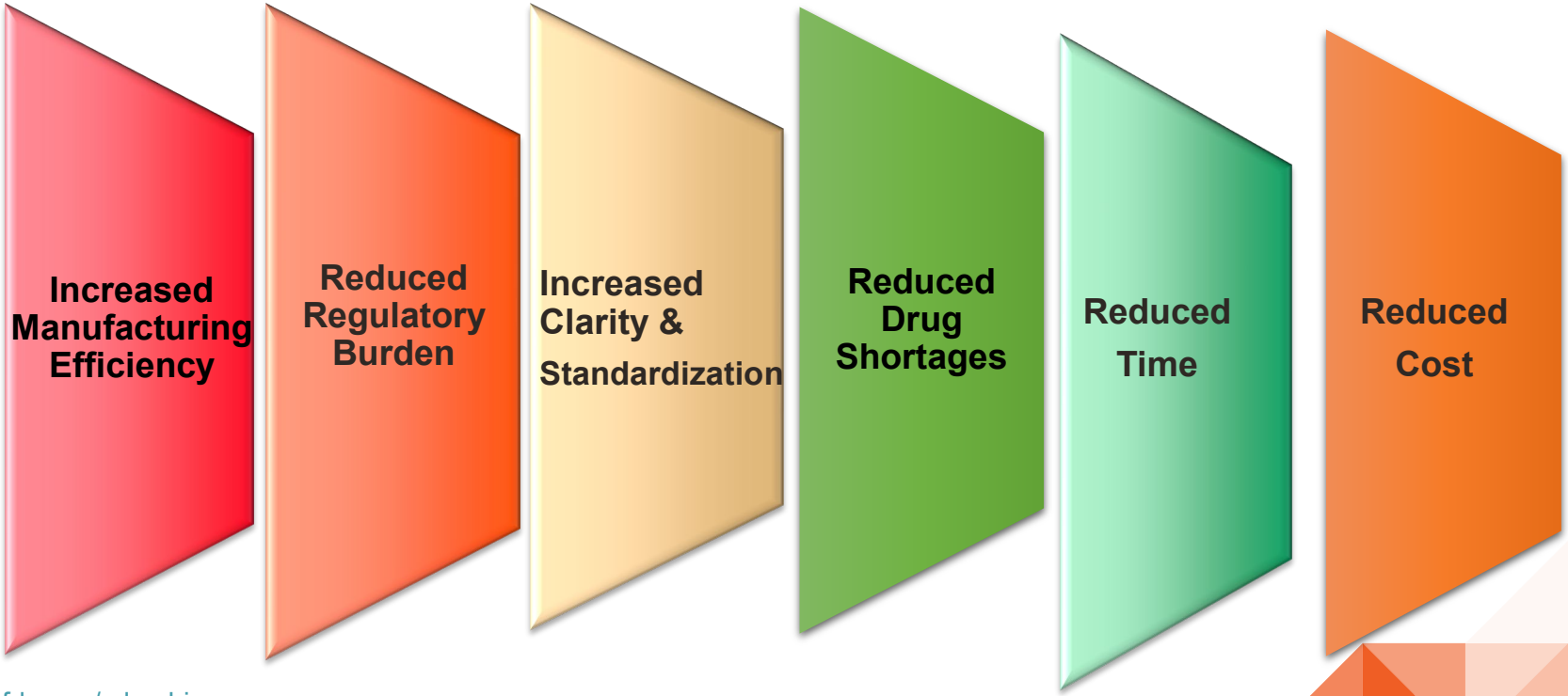
A CMC change that would require supportive efficacy, safety (clinical or non-clinical) or human PK/P data **IS NOT** suitable for inclusion in a PACMP

ICH Q12 - Post-Approval Change Management Protocol (PACMP)

- Submission of a written protocol
- Protocol reviewed and approved by FDA in advance of execution
- Tests and studies carried out as outlined in protocol
  - If results/data generated meet acceptance criteria and conditions in protocol are met, applicant submits information to FDA according to category in approved protocol
  - If acceptance criteria and/or other conditions stated in the protocol are not met, the change cannot be implemented using this approach



Advantages

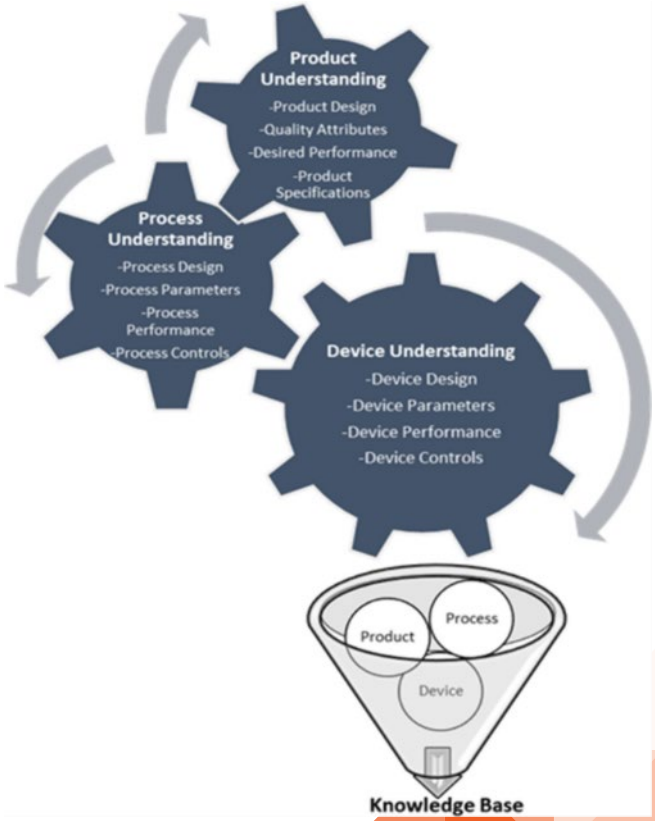

Increased Manufacturing Efficiency
Reduced Regulatory Burden
Increased Clarity & Standardization
Reduced Drug Shortages
Reduced Time
Reduced Cost

Post-Approval Changes to Drug-Device Combination (DDC) Products

- Lack of specific/outdated guidance for DDCs present regulatory challenges to post-approval changes
- **2004** - Changes to an Approved NDA or ANDA Guidance – Only 2 examples for "Device" – Both PAS
  - **Manufacturing Site Move (IV.B.3)** – "A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient …. Examples of these types of drug products include … transdermal systems, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps."
  - **Container Closure Change (IX.B.3)** – "A change in the primary packaging components for any drug product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler.)"
- **2015** - Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products (CDER/CBER)

Post-Approval Changes to Drug-Device Combination (DDC) Products – MDI and DPI

- DDC products are subject to cGMP requirements of 21 CFR part 4 for drugs and devices
- Design controls apply to combination products to ensure there are no negative interactions between constituent parts, resulting in a product that is **safe and effective and performs** as expected
- Post-approval changes therefore require a thorough understanding of product, device and process
- Split Review of DDCs between CDRH and CDER/CBER



Correlation between DPI/MDI components' attributes and DP CQAs

DS CQAs

Assay, PSD, Particle surface properties (static charge), morphic form (e.g., amorphous, crystalline, hydrate), morphology (e.g., shape, crystal habit, texture, surface area), residual solvent content, impurities

DP CQAs

Assay, DDU, ASPD, Leacheables, net content, device characteristics such as component dimensions, specific resistance to air flow

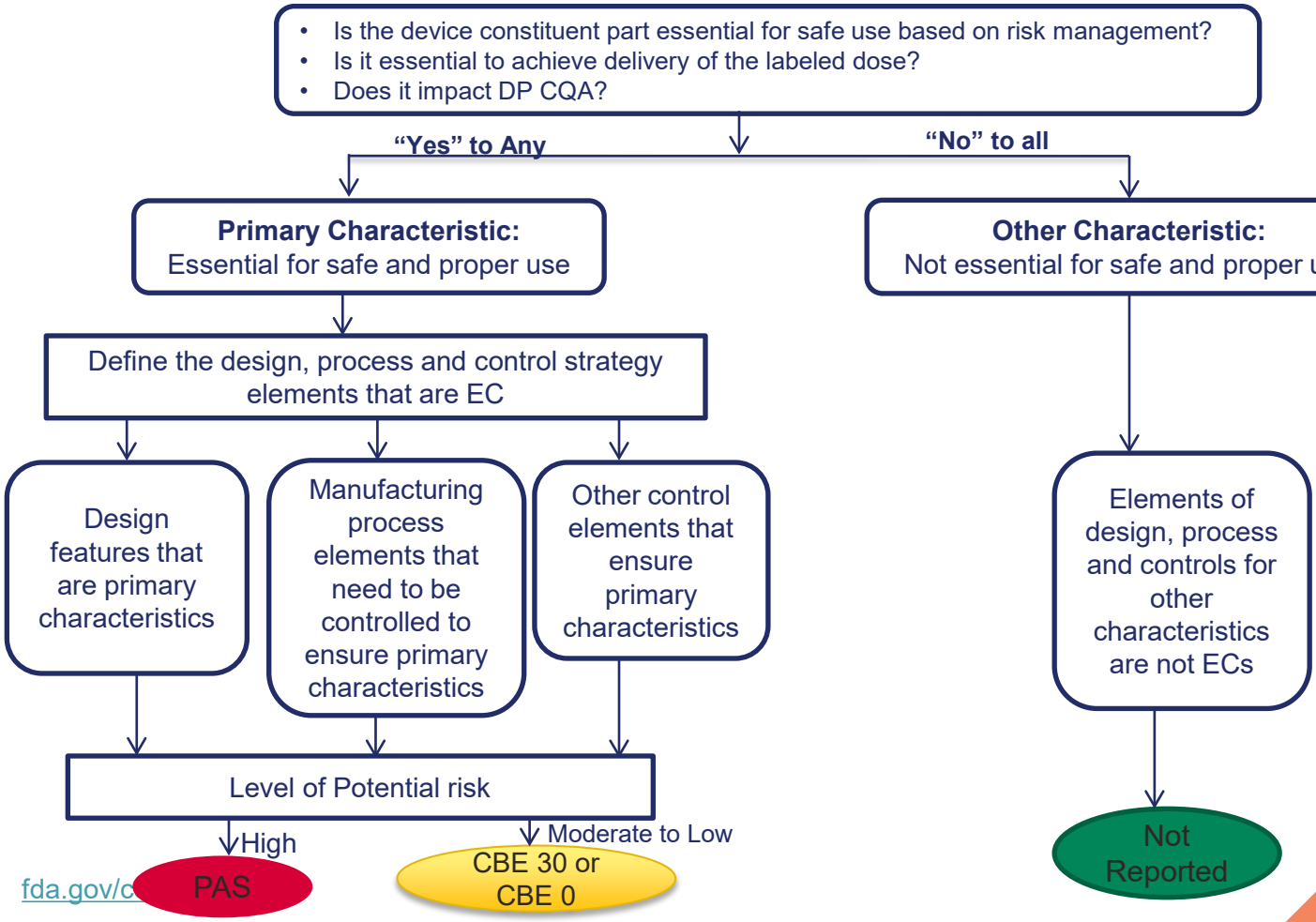
Excipient CQAs

Assay, PSD, Particle morphology (e.g., shape, crystal habit, texture, surface area, rugosity), flow properties, amorphous content, impurity profile, etc.

Device/CCS CQAs

Device components
Materials used
Geometry and dimensions
Secondary Packaging

Identifying EC and Reporting Categories for Device Constituent Parts



Challenge Question

An Applicant submits a **CBE 30** to propose the extension of micronization pressure process parameter range during micronization of the drug substance used in the manufacture of a Dry Powder Inahalation (DPI) drug product. Applicant cites section VII.C.1.b of the PAC Guidance to support proposed change. Should this supplement be:

A. Granted CBE 30?

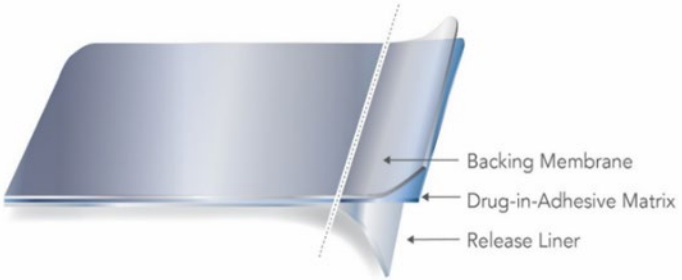
B. CBE 30 be elevated to PAS per section VII.B.1 of the PAC Guidance?

Reason: Proposed revision to the drug substance micronization process parameters **may** affect the particle size distribution for the drug product, which is critical to the drug product delivery

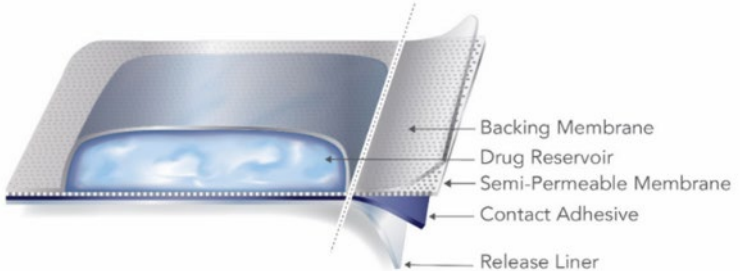
Post-approval changes in Transdermal Delivery Systems

- Changes in the formulation component and/or semipermeable films or laminates could have significant effect on drug release and/or product adhesion/wear characteristics

Matrix Type Transdermal or Topical Delivery System



Reservoir Type Transdermal or Topical Delivery System



Type of change	Criticality of proposed change	
	CBE 30	PAS
Component/Composition		• New Backing Film; reformulated backing film • New Release liner • Internal Release controlling membrane component change • New Adhesive/adhesive component change • New API • New Strength
Manufacturing/Testing Site changes	• Alternate site for approved adhesive • Addition of contract testing site	New/alternate DP manufacturing site

Type of change	Criticality of proposed change	
	CBE 30	PAS
Process Changes	• Process Yield change • Adhesive mixing procedure change • Scale up >10X • Change in order of addition	• Major DS process change (e.g., change in ROS)
Specification Changes	• DP analytical method revisions	• Relaxation of DP/DS impurity levels • In vitro test specification changes e.g., changes in release liner peel or Shear specifications) • In vitro drug release specifications/method changes
Container Closure System		New Primary CCS (pouch or tray)
Miscellaneous	Shelf-life extension	Reduced or bracketing stability testing

Challenge Question

An Applicant submits a CBE 30 to propose an increase in batch size (<10X), changes to components of the adhesive and source of foil within the pouch material. The data submitted to support the proposed changes indicate that the changes do not adversely affect product quality. Should the supplement be:

A. Downgraded to a CBE 0 based on the data?

B. Granted CBE 30 as submitted?

C. Elevated to PAS due to the potential high-risk change to the adhesive component

Reason: Any proposed change to the adhesive/adhesive component represents a change in the component of the formulation and has a substantial potential to have an adverse effect on product quality. The adhesive of a TDS is critical to the safety, efficacy and quality of the drug product since it is in intimate contact with the drug and/or other excipients that may alter either the adhesive properties and/or influence the release of the drug.

Generic Synthetic Peptide Drug Products

- FDA defines Peptides as any alpha amino acid polymer composed of 40 or fewer amino acids
- In May 2021, FDA released the guidance for submission of **ANDAs for certain highly purified synthetic Peptide Drug Products that refer to RLDs of rDNA origin**
  - Based on current state of technology for peptide synthesis and characterization, applicants can submit ANDA application under section 505(j) of the FD&C Act, for synthetic peptide drug products that reference previously approved peptide drug products of rDNA origin
  - Generic synthetic peptide drug product must demonstrate “sameness” as the RLD of rDNA origin
  - Generic synthetic peptide API must be characterized to show that peptide-related impurities present are same or lower than those found in RLD
  - Any new specified peptide-related impurity that may be present must not be more than 0.5% and appropriate justification provided on why/how its presence would not be expected to affect the safety and effectiveness of the generic product compared to the RLD

Post-Approval changes in Generic Synthetic Peptide Drug Products

- In the absence of a specific post-approval changes guidance for generic synthetic peptide drug products, post-approval changes decisions have been based on a combination of risk assessment and knowledge gained from the original submission
- Especially for a change in the approved drug substance or drug substance manufacturing process in an approved ANDA:
  - Applicant must demonstrate that the new peptide drug substance is thoroughly characterized to show that all peptide-related impurities are the same or lower than the approved drug substance
  - Characterize any new specified peptide-related impurity and justify why the presence of such new impurity would not be expected to affect the safety and effectiveness of the drug product compared with the approved product

Post-Approval changes in Generic Peptide Drug Products

- Characterization of generic synthetic drug substance should provide adequate information on
  - Primary sequence and physicochemical properties
  - Secondary structure
  - Oligomer/aggregation studies
  - Biological activities

Some common post-approval changes in generic synthetic peptide drugs

PAS

- Addition of alternate DS supplier
- Change in the DP manufacturing process
- Addition of alternate sterile manufacturing area
- Change in prefilled syringe supplier
- Relaxation of DS/DP impurity specification limits

CBE 30

- Use of additional autoclave/new lyophilizer with same design and operating principle
- Change in batch size and process parameters
- Addition of alternate analytical testing site for DS/DP
- Revision to analytical controls of excipients

Conclusion

- Improve the quality of submission by using science-based and risk-based approach to assess the impact of proposed change(s) on product quality
- Demonstrate good product and process understanding in your supplement
  - Adopt modern quality techniques with focus on sound science for assessing and mitigating risks of poor product and process quality(e.g., QbD, CQA, CPP, CMA and Control strategy)

Thank You!

"Mr. Colton, do we stand behind our products?"