Comparability Protocols
Implementation and Case Studies

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Outline

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INTRODUCTION

- **Definition**: A Comparability Protocol (CP) is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC post-approval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product.
BACKGROUND

- Application holders must notify the FDA of a change to the conditions established in an approved application in accordance with 21CFR 314.70 and 601.12
- Change(s) are categorized into one of three reporting categories (PAS,CBE-0/30 or Annual report) corresponding to whether the change has major, moderate or minor potential for adverse effect on the critical quality attributes of the drug product
- Comparability protocols are an optional way to manage post-approval changes
INTENT OF A COMPARABILITY PROTOCOL

• A CP describes the specific tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the lack of adverse effect of one or more proposed CMC changes.

• The supplement containing the CP must be approved before distribution of a drug product produced with the change

• A CP, once approved, can be for a one-time change, or may be used repeatedly for a specified type of change over the life cycle of a product
• A CP can be useful in providing predictability for applicants who anticipate the need to implement future changes (i.e., raw material or packaging component) to an approved product

• A CP may allow for a reduced filing category depending upon the extent of knowledge regarding the product and process, risk associated with the changes and adequacy of control strategy

• May reference other FDA or ICH Guidance documents
BASIS FOR THE PROPOSED CHANGE(S) SUBMITTED IN THE CP

• Prior Knowledge
• Development of the drug substance and its manufacturing process
• Pharmaceutical Development (development of the product and its manufacturing process)
• Process validation activities and commercial scale production experience
• Quality risk management activities
CONTENT OF A COMPARABILITY PROTOCOL SUBMISSION

• Summary of the CP submission using tabular, narrative, or graphic representations, as appropriate
• Description and rationale for the proposed change(s)
• Supporting information and analysis (prior knowledge, risk assessment, development batches)
• Comparative assessment of quality attributes before and after the change(s) should be included as a component of the planned tests and studies.
• Characterization tests and studies which assess the effect of the proposed change(s) on product quality
• Validated Analytical procedures should be described in the CP or incorporated by reference to those previously submitted in the application
• Should indicate a proposed reporting category
CHANGES FOR WHICH A CP IS NOT APPROPRIATE

• In certain cases, the FDA review division may recommend submitting the change in a regular PAS rather than in a CP because the complexities associated with the change result in an unacceptably high risk to product quality for that specific product.

• (i.e., new drug substance supplier external to approved DMF, reduced final product testing, when a facility PAI is required, when data from safety and efficacy studies are needed to assess the effect of the change).
CONSIDERATIONS BEFORE IMPLEMENTATION

• Review approved CP risk assessment and compare with current knowledge to confirm that planned changes are still valid
• Update risk assessment; if found to be different, this may affect the risk level or reporting category that was initially proposed in the original CP
• May have to modify the CP, or reporting category or both
• Confirm adequacy of control strategy
FACILITY CONSIDERATIONS

• If any impacted facility is not capable of implementing the change in accordance with CGMP, the approved CP should not be implemented.

• Instead, the applicant should follow applicable regulations and guidance documents, not the approved CP, to determine the appropriate reporting category for the change.
REPORTING CHANGE(S) PER APPROVED COMPARABILITY PROTOCOL

• Report the changes under the approved reporting category established in the CP

• Provide the supporting data in accordance with provisions outlined in the CP; (i.e., batch records, COAs, stability data...., and any changes to the risk assessment or statement that the risk assessment has not changed)
CHANGE IN LEVEL OF RISK?

- Report unexpected results that may have affected the tests or studies (if any)
- A summary of deviations and investigations performed (if any)
- Evaluation of the impact of the change on product quality
- Conclusions reached after evaluation of studies conducted to support the change
AFTER IMPLEMENTATION

• Any new information regarding the change(s) (i.e., stability data) that is generated after implementation should also be included in the next annual report. After a CP is approved, annual reports for each affected application should provide updates on the status of changes covered by the CP.
History of ANDA CP review

• Limited experience with comparability protocols in ANDAs since issuance of initial 2003 draft guidance

• Consistent approach for CP review began after issuance of the April 2016 version of the guidance

• Survey results show:
  
  – 122 comparability protocols submitted in 46 ANDA(s)
  
  – 6 comparability protocols submitted in 6 PAS(s)

• Most these CPs are still under evaluation; a few approved (only PAS).

  – Following two slides provided by Geoffrey Wu, CDER, FDA ---2017 IFPAC Annual Meeting Presentation
Our Experience - ANDAs

Dosage Form Distribution

- IR Tablets/Capsules/ODT: 23, 52%
- ER/DR Tablets/Capsule: 6, 14%
- Injections (solutions/powder): 5, 11%
- Oral liquid: 3, 7%
- Inhalation: 2, 5%
- Sublingual Film: 2, 5%
- Transdermal: 1, 2%
- Ophthalmic: 1, 2%
- Vaginal Ring: 1, 2%

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Our Experience - ANDAs

Change Type Distribution

- Container/Closure System (CCS) 27, 22%
- CCS and Packaging site 17, 14%
- Drug Substance Source 19, 16%
- Manufacturing Site (drug product) 17, 14%
- Manufacturing Site (drug substance) 6, 5%
- Testing Facility 3, 2%
- In-Process Test Removal 2, 2%
- Manufacturing Process 11, 9%
- Components and Composition 20, 16%
Case Study #1

• **Filing:** CP submitted in PAS with a proposed reduction in filing category to CBE 30

• **Purpose:** Change in non-release controlling excipient (from bovine to vegetable-based source) for multiple applications within the same drug product family (i.e., steroidal manufactured by dry mixing process, non-steroidal manufactured by wet granulation process..)
• **Regulatory Classification**: Represents a change in the technical grade and/or specifications of a non-release controlling excipient SUPAC (IR); requires PAS
Supporting Documentation: Minimum submission requirements

• Acceptance tests and specifications for animal based excipient versus vegetable based
• Executed Batch Record for the batch made with vegetable sourced material, in-process and final product data
• Process Validation Batch for the drug product made with vegetable sourced material
• Comparative data review to products manufactured with animal sourced excipient (all in-process and final product release testing data; long term stability in annual report
• Available CRT stability data and comparative stability data to product made with animal sourced excipient.
ASSESSMENT

• The proposed tests, specifications, methods and submission data requirements will adequately assess the impact of the proposed change to the drug product quality. Furthermore, the firm provided validation data for a small scale batch of a representative drug product (within the same product family) as justification for a downgrading of the submission reporting category: CP acceptable.
Case Study #2

- **Filing:** CP filed in pre-market application; proposed future reporting category; PAS

- **Purpose:** Provides for a post approval change in excipient grade of a release controlling excipient.

- **Regulatory:** Represents a change in the technical grade and/or specifications of a release controlling excipient SUPAC (MR) and requires PAS
Supporting Documentation: Minimum submission requirements

- Acceptance tests and specifications for new proposed excipient
- Executed Batch Records for the 3 batches along with in-process and final product test results.
- Three months accelerated stability data; 3 batches LT stability
- Multipoint dissolution profile using application test conditions for the changed drug product and the bio batch or marketed batch (unchanged drug product).
- A single-dose bioequivalence study. The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation.
ASSESSMENT

Proposed reduction in reporting category is not a requirement. There is significant risk associated with the change. What are the benefits? All required supporting documentation is established and agreed upon in advance of filing and implementation. This will expedite the review and processing of the post approval filing because of the mutually agreed upon criteria for approvability and increases chance of first cycle approval of the PAS. CP approved.
Case Study #3

• **Filing:** CP filed in pre-market application. Reporting category: Reduction from PAS to CBE- 30

• **Purpose:** Different packaging configuration for injectable product vial (flint tubing versus flint molded glass) with change in stopper (RTU vs. RTS stopper)

• **Regulatory:** Considered major change per ANDA Post Approval Changes Guidance
Supporting Documentation: Minimum submission requirements

• Executed batch record for DP including packaging records
• Container /closure acceptance tests and specifications including, summary of components, technical drawings, COAs and DMF LOAs
• In-process and final product test results
• 3 month accelerated stability data for executed batch
• Delamination study for proposed glass container
• Container closure integrity testing results
• Stopper sterilization validation results
Assessment

• The protocol adequately identifies the tests that need to be conducted and the acceptable limits that need to be achieved in order to support the identity, strength, quality, purity, and potency of the drug product. The protocol provides a description of the proposed changes, all tests that will be performed along with acceptance criteria that need to be met in order to demonstrate that the proposed changes in glass and stopper components will not adversely affect the final drug product. **APPROVED**
Case Study #4

• **Filing:** CP submitted in premarket ANDA proposing reduced reporting category of CBE 30.

• **Purpose:** For future alternate suppliers of the drug substance (DS)

• **Regulatory:** Considered major change

• **Supporting Documentation:** Proposed manufacturer, DS acceptance criteria and test data, additional physicochemical characterization of the DS. Drug product batch data analysis and stability testing plan.
ASSESSMENT

• It is inappropriate to use a comparability protocol for CMC changes that are likely to result in an unacceptably high or uncertain risk to product quality per 2016 CP Guidance.

• In the majority of cases, there will be additional differences (e.g., route of synthesis, process, solvents, and equipment). Without extensive knowledge and DMF access of both sources (i.e., old and new), an applicant cannot adequately describe the differences between the sources. **Recommend filing as traditional PAS per ANDA Changes Guidance.**
Case Study #5

- **Filing:** CP filed in pre-market application. Reporting category: Reduction from CBE-30 to annual report
- **Purpose:** The sponsor proposed a repetitive use of a CP to provide for the addition of alternate testing facilities to perform drug substance testing and excipient testing.
- **Regulatory:** Can be submitted as CBE-30 according to Guidance for Industry Changes to an Approved NDA or ANDA (April 2004)
Supporting Documentation Filed by Sponsor

- Actual change(s) implemented
- Method verification/transfer report(s), and
- Testing results for at least one batch of the drug substance and/or drug product.
- Any other data generated from implementing the site change
- Data evaluation to qualify the new testing site
- Satisfactory cGMP inspectional history.
Assessment

- Generally a one level downgrade is appropriate when a CP is considered, therefore, submitting in annual report is not acceptable. The firm was requested to reevaluate the risk and propose more a more restrictive reporting category. Protocol inadequate.
Case Study #6

• **Filing**: CP filed in pre-market application. Reporting category: The firm states that they “would file an appropriate supplement” if a change were to be made. No filing category specified.

• **Purpose**: CP for alternate suppliers of packaging configuration components (injectable product)
Supporting Documentation:

• Overall general description of the container closure system
• Commitment to submit an appropriate supplement for the component changes
• A generalized list of qualification tests to be performed
• DMF LOAs for the components
• Commitment to place product manufactured with the new component(s) in the long term stability program
Assessment

• A commitment to file an appropriate supplement is not sufficient. The comparability protocol should provide detailed description about the proposed change(s), analytical procedures, acceptance criteria, related commitments, etc. along with a reduced reporting category if appropriate. There is no risk assessment and the document lacks sufficient detail needed to evaluate the equivalence if a change were made. **Protocol Inadequate.**
THANK YOU!
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