Drug shortages have unfortunately become a routine occurrence as evidenced by the FDA's recent public updates and reports presented to the U.S. Congress. An innovator's top priority is ensuring drug availability to the patient. Application of ICH Q12 and the FDA's Comparability Guidance (2016) have never been more important. Rondaxe Pharma's Senior Advisor, Donald N. Klein, Ph.D., presented the following poster at the AAPS Conference (August 10 – 12, 2020). During the presentation and discussion with Dr. Klein, applicable solutions were evaluated.

In his last 12 years (2005 – 2017) at the FDA, Dr. Klein resolved many drug shortages as a member of a CDER reviewing team. Even though Dr. Klein has retired from the FDA, he is currently mentoring Ms. Angela Ha who is a University of Washington Biomedical Regulatory Affairs (BRAMS) graduate student. Specifically, Ms. Ha's required Practicum will focus on drug shortages and the current regulatory environment. At the conclusion of Ms. Ha's evaluation of the publicly available FDA drug shortage documents, Dr. Klein has arranged for her to discuss (November, 2020) her Practicum with Ms. Valerie Jensen, CDER Drug Shortage Associate Director. Rondaxe Pharma and Dr. Klein appreciate the CDER Associate Director's willingness to educate the next generation of regulatory experts such that drug shortages will soon be a history lesson.

Ensure your Drug is Always Available: Comparability Protocol or PACMP

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PURPOSE

The pharmaceutical industry must routinely be evaluating and updating their approved applications (ANDA, NDA, PMA, BLA, NADA, and ANDA) for needed comparability protocols (CP) or post-approval change management protocols (PACMP) to ensure the drug or the combination product is always available. The COVID-19 pandemic has accentuated the reason for industry to have the ability to efficiently implement a new regulatory starting material supplier, a new API supplier, and a primary packaging component. The respective applications must be prepared to ensure either the drug or the combination product is always available.

CRITICAL RESOURCES

- **ICH Q12** Pharmaceutical Product Lifecycle Management (2019)
  - **PACMP:** Enables planning and implementation of future changes to established conditions in an efficient and predictable manner
- **Comparability Protocols** (2016), CDER/CBER
  - **CP:** Comprehensive, prospectively written plan for assessing the effect of a proposed CMC post-approval change(s) on the identity, strength, quality, purity, and potency
- **ANDA Submissions PAS under GDUFA** (2017), CDER/CBER
- **MAPP 5015.6 Rev 1** Review of Grouped Product Quality Supplements (2016), CDER
- **SOPP 8422** Processing of Trans-BLA Submissions (2011), CBER
- **CDRH** has approved comparability protocols by applying the CDER/CBER guidances and by discussions with the applicant
- **# 156 Comparability Protocols** (2016), CVM

CP or PACMP SCENARIOS

Adding a Regulatory Starting Material (RSM) Supplier

- **NDA:** Analgesic drug; Extended release via osmotic pump capsule
- **CP or PACMP submitted as a Prior Approval supplement**
  - Comparison of the manufacturing process of the RSMs
  - Comparison of the RSM's acceptance specifications
    - The RSM's acceptance specifications should be similar
    - Purge experiments (ICH Q11) as previously done in the application
  - Manufacture 2 drug substance batches with the new RSM; compare the release data
  - 6 months of LT stability data of the 2 drug substance batches via the new RSM
  - Commitment to manufacture 1 drug product batch and generate stability data (LT)

❖ ***New Supplier of RSM may be implemented by a CBE-30***

Adding a New Primary Elastomeric Closure and Vial

- **ANDA (6), BLA (3), and NDA (5):** Small volume parenterals
- **CP or PACMP submitted as a Prior Approval supplement**
  - Detailed component comparison of the current (Type III DMF) to the proposed primary packaging system (Type III DMF)
  - Extractable and leachable comparison: Current *vs* proposed primary components
  - 2 drug product batches manufactured; and Release data compared
  - 6 M stability data (upright and inverted; LT and ACC); and supportive stability data (upright and inverted; LT and ACC)
  - Grouped supplement with the NDA as the Lead supplement presenting the comparability protocol or the PACMP

❖ ***New packaging system is available by a CBE-30***

- ***NDAs (1 - 4 yrs)***
- ***BLAs (1 – 4 yrs)***
- ***ANDAs (1 – 5 yrs)***

CP or PACMP SCENARIOS

Adding a Drug Product Site with modern Manufacturing and Packaging Equipment

- **NDA:** Oncolytic drug; Small volume parenteral
- **CP or PACMP submitted as a Prior Approval supplement**
  - Applicant discusses the proposed site with the review team (CDER (CMC and Micro) and ORA)
  - Comprehensive comparison of the current to the proposed manufacturing process and packaging process
  - Comprehensive comparison of the respective process by manufacturing 3 batches
  - Current and new batch Release data compared (3 batches)
  - 6 M stability (inverted and upright; LT and ACC) data and supportive data (LT and ACC; inverted and upright)
  - 3 validation runs at the proposed site

❖ ***New drug product site may be implemented by a CBE-30***

CONCLUSION

Ensure either the drug or the combination product is always available by using either a comparability protocol (CP) or a post-approval change management protocol (PACMP).

ACKNOWLEDGEMENT

Rondaxe Pharma, Inc.