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REGULATORY SCIENCE CHALLENGES FOR COMPLEX GENERICS – INDUSTRY PERSPECTIVE

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EXPLORING THE FUTURE OF
GENERICS AND BIOSIMILARS

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Bridging Science and Regulation: Challenges and Lessons from Complex Generics Case Studies

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The views expressed in this presentation are my personal opinions and do not reflect the views or positions of Amneal Pharmaceuticals

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Case Study 1: Comprehensive Immunogenicity Risk Assessment for Peptide-Based Complex Products

Agency feedback sought on additional study requirements for new impurity in test product (not present in RLD) or known impurity ≥ 0.10% and RLD but less than 0.5%

Preliminary FDA response

Provide data to inform the immunogenicity risk assessment (establish that proposed drug product does not pose an increased risk of immunogenicity as compared to RLD)

1. Assessing ability of purified impurities to induce an adaptive immune response

2. Assessing the ability of minimally manipulated formulated drug product to induce an innate immune response

Revised FDA response

Provide **Immunogenicity risk assessment** that takes into consideration a complete characterization of your product, including product aggregates, leachables and other impurities.

Additional in-vitro/in-silico testing to support your immunogenicity assessment may be requested in situations where the comparative impurity or aggregation profile indicates the presence of a new impurity or aggregation state, or a markedly elevated level of an impurity or aggregation state

Next Steps

Navigating data requirements during mid-cycle review

- Additional investigation required on what constitutes as "markedly elevated levels" *for an impurity to warrant an immunogenicity risk assessment.*

- Clear understanding on orthogonal techniques *and final expectations on what constitutes a definitive approach for conclusive results.*

-- Collaborate to increase scientific understanding to use Immunogenicity risk assessment instead of adaptive/innate immunogenicity study

Case Study 2: A Comparative Analysis of FDA vs. EMA on Impurities and Immunogenicity

FDA guidance

- A **new peptide related impurity level higher than 0.5 percent** of the drug substance could raise concerns about the potential risk of immunogenicity.

- **Applicants should identify each peptide-related impurity that is 0.10 percent** of the drug substance or greater. Depending on the potential immunogenicity risk, applicants may be asked to also identify peptide-related impurities present below this threshold.

- Applicant should provide justification for why the presence of such impurity would not be expected to affect the safety of the proposed generic synthetic peptide… including with respect to the risk of immunogenicity related to peptide-related impurities

- Based on the information provided, **FDA may recommend that additional non-clinical immunogenicity evaluations** be completed for the proposed generic synthetic peptide.

EMA guidance

- **Immunogenicity of peptides is of lesser concern than that of proteins due to their size.**

- Changes or modifications (e.g. deamidations) of a small number of amino acids are not noticeably immunogenic.

- **If the total amount of peptide-related impurities does not exceed the respective amount of peptide-related impurities of the originator product, this is not considered as a concern even if a given peptide-related impurity is absent in the originator.**

- In case a novel type of impurity occurs, i.e. differing from the drug substance in a few amino acid modifications, this novel impurity should be reduced as far as possible since reliable prediction of immunogenicity is not feasible.

- According to the Ph. Eur. general monograph 'Substances for Pharmaceutical Use', **peptide-related impurities should be reported above 0.1%, identified above 0.5% and qualified above 1.0%.**

Opportunities

Regulatory standards are not fully harmonized with other international agencies, such as the EMA, creating challenges in the global development and approval of complex peptide products.

Harmonizing regulatory expectations could lead to more streamlined global approval process

Case Study 3: Ensuring Consistency in Finished Product Characterization Data Requirement

Scientific Challenges

Recommendations provided during review:

Studies be conducted on samples of at least three exhibit batches of proposed product tested on or near release and at the end of the proposed shelf life, and at least three batches of the RS/RLD of different ages prior to expiry (as available) – Studies should be conducted directly on the formulated drug product solution. Minimize and justify sample manipulation

Use multiple orthogonal validated methods

Addressing those Challenges

Characterizing development or feasibility batches at release and at the proposed shelf-life end, using the same process as exhibit batches (EBs), provides valuable insights into product attributes. Strategic planning of these tests allows data collection during the review, facilitating more efficient reviews and potentially enabling first-cycle approvals without waiting for end of shelf-life.

Opportunities to Enhance Collaboration

- ✓ Identify tools to further develop end of shelf-life data for FP characterization, leachable studies, in-use and Immunogenicity studies during the first cycle review period
- ✓ Clarity on expected characterization techniques and study recommendations (through guidance or educational avenues) to allow applicants to submit a complete and acceptable study report

Case Study 4: Addressing Uncertainty in Critical Excipient Characterization – Focus on Polymers

Scientific Challenges

Greater understanding required on characterization of critical excipients (e.g. PLGA polymers).

Additional attributes may be identified and recommended for characterization upon review

Addressing those Challenges

Additional/new development activities during review cycle considerably increases the response times and impacts the approval timelines.

Opportunities to Enhance Collaboration

- Agency's guidance on suitable characterization techniques and study recommendations for critical excipients will be extremely helpful.
- Guidance on polymer sameness is needed for complex, rate-controlling polymers, such as PLGA.
- FDA guidance is available for **liposomes**; a similar document is needed for **microsphere**-based drug products

Case Study 5: Defining Tight Acceptance Criteria for Variable Release Formulations – Leveraging IVIVC and PBPK Models

Scientific Challenges

Stringent Acceptance Criteria: Tight limits for variable release formulations.

IVIVC models, PBPK models, etc., are positioned as the sole pathways for justification.

Impact Assessment

Limited Acceptance of IVIVC: Agency has historically not favored IVIVC models for setting broader acceptance criteria

Using IVIVC models becomes a challenge for Q1Q2 formulations

Opportunities to enhance Collaboration

Standardized recommendations on acceptable IVIVC (in vitro-in vivo correlation) models will be helpful

A guidance document or workshop on employing IVIVC models for variable release formulations would be beneficial.

Regulatory Challenges and Opportunities to Enhance Collaboration between FDA and Industry

- **Delayed Goal Dates for Complex Generics**: Missed target dates for complex generics due to involvement from multiple review divisions (e.g., CDRH, Toxicology, Facility Inspections).
- **Clear Benefits from Communication between Industry and Agency**: PDEV meetings have been extremely useful and productive. Detailed feedback on any deficiencies can help companies better understand regulatory requirements and adjust their development strategies accordingly.
- **Streamlining Bioequivalence Requirements**: Potential to adopt risk-based approaches to simplify bioequivalence studies for complex products, accepting innovative study designs (e.g., adaptive designs) that allow interim modifications, potentially reducing study time and review delays.
- **Increased Support for Regulatory Science Research and Collaboration from the Industry**: More funding and support for regulatory science research is essential to develop new evaluation methods for complex generics
- **Need for Specific Guidance on Complex Generics**: Since the introduction of complex generics, more detailed and product-specific FDA guidance is necessary, including insights on post-approval changes.
- **Harmonizing Global Regulatory Standards**: Align regulatory standards with international bodies to foster a more efficient global market for complex generics.
- **Need to establish post-approval commitment policies to support the enhancements**

Through collaborative efforts, we may be able to jointly:

1. Solve the ***complex challenges*** intrinsic to generic and biosimilar drug product development through ***innovation*** rather than a “one-size-fits-all” methodology

2. Establish a ***streamlined approach*** to bring ***safe, effective, affordable*** generic and biosimilar products to the patients that need them

Acknowledgments

Dr Srinivas Kone (Chief Scientific Officer, Generics)

Dr Pavan Kumar Gangavarapu (VP, Global Regulatory Affairs)

Maryll Toufanian (SVP, Regulatory Strategy and Government Affairs)

Kiran Kolhe (VP, Regulatory Affairs)

Rakhi Jajoo (Deputy General Manager, Scientific Regulatory Excellence)

Praveen Jain (Senior General Manager, Regulatory Affairs)