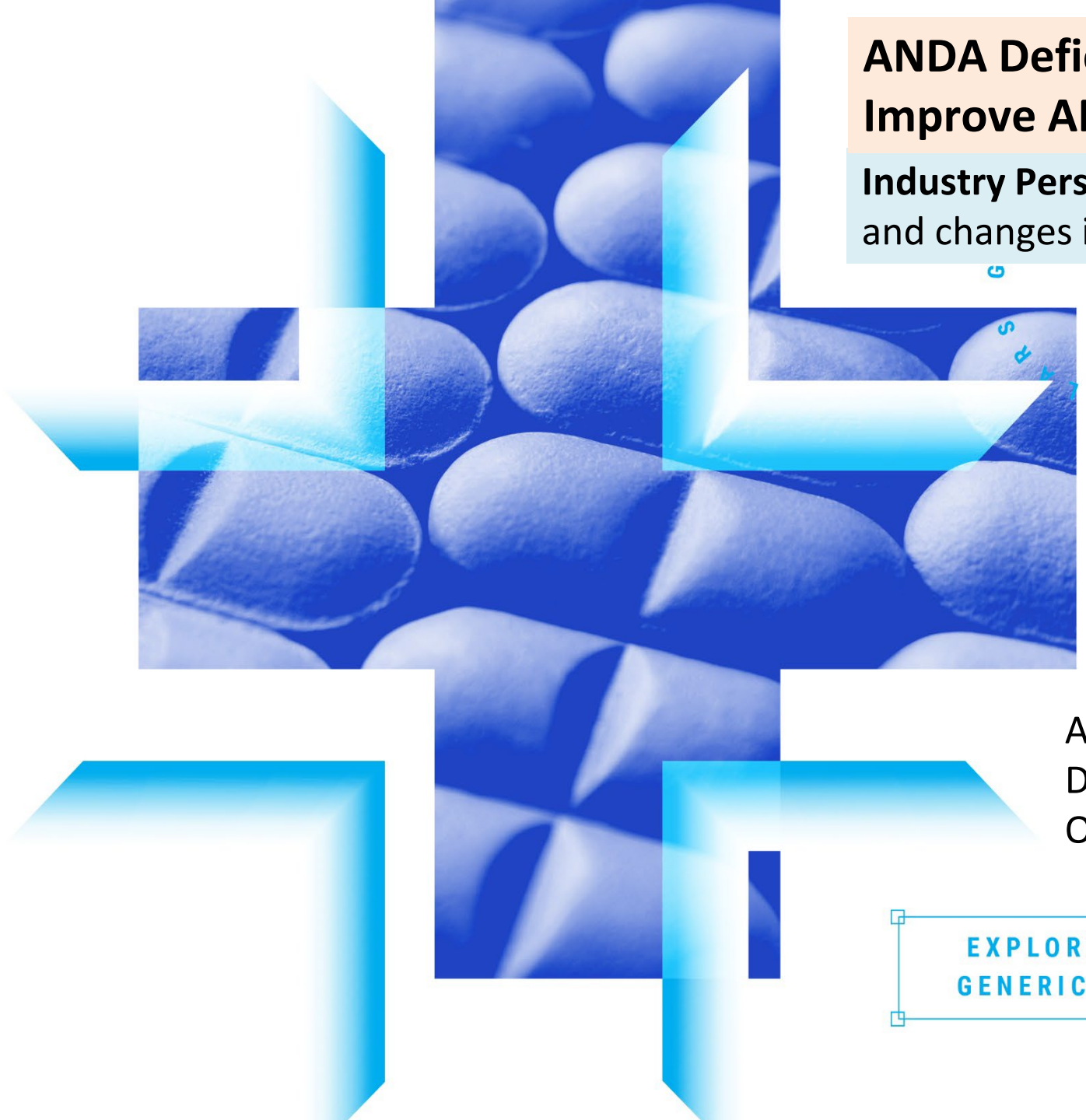

ANDA Deficiency Trends: Common Issues to Improve ANDA Submission Quality

Industry Perspective: Frequently received comments and changes in data requests and on review consistency

GRx+ Biosims™

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October 21, 2024

EXPLORING THE FUTURE OF GENERICS AND BIOSIMILARS

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Industry Perspective : Frequently received comments and changes in data requests and on review consistency.

Major Deficiencies:

- Facilities
  PAI - cGMP
- Extractable & Leachable
- Impurities
- Data to support shelf-life

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Major Deficiencies: Facilities inspection

Facilities inspection

PAI/ cGMP

- Finished product / Drug substance / Intermediate/ Testing facilities
- Clinical /Bio-Analytical facilities

Impact on Review and Approval Timeline

1. **Data requirement for additional facility qualification while withdrawing the original facility from ANDA:** How much information required? e.g., one batch vs. three batches, stability data, various one-time studies for characterization, in-use, admixture, and BE studies.
2. **GDUFA III, Major to minor policy:** It is helpful as the review time is reduced to 5 months for standard product and 4 months for priority review.

Major Deficiencies: Extractables and Leachables

Deficiencies:	1. Requiring Pharmacology / Toxicology Assessment
	2. Requiring new method and method validation for new leachable.

Impact on Review and Approval Timeline

1. Number of drug product batches for the leachable testing
2. Leachable testing requirement and acceptable AET levels for device component that comes in contact with the drug product /patient **only** during administration.
3. Method validation for extractable and leachable studies
4. Extent of Data for identification of leachables to be included in the submission.

Major Deficiencies: Impurities

Deficiencies:	
	1. Impurities requiring Pharmacology/ toxicology assessment
	2. Pending technical consult
	3. New method and validation for new impurities

Impact on Review and Approval Timeline

1. Deficiencies are occasionally based on impurities listed in academic research papers. It is nearly impossible to form these impurities in API or drug product.
2. Method validation is challenging since procurement of these impurities or synthesis of these impurities are difficult since most of the times, the impurities themselves are unstable.
3. Applicant proposes wider impurity limit based on Pharm/Tox. However, the applicant is asked to tighten the limit based on trend and RLD data.

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Major Deficiencies: Data to support shelf -life

Data to support shelf- life

- Actual long-term stability data is required to establish shelf-life ("significant change' in accelerated and intermediate stability data)
- Drug product stability studies at the end of shelf -life, namely, admixture, In use studies, drug substance and drug product sameness, immunogenicity

Impact on Review and Approval Timeline

1. ANDA approval time is limited by 24-month shelf-life long-term stability data.
2. More than 24 months for approval impacts on receiving exclusivity for first to file (30 months), CGT exclusivity, and product availability for limited generic.

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2nd/3rd Review cycle

Newer Deficiencies are received in 2nd /3rd review cycle

- Newer deficiencies are received in 2nd and 3rd review cycles
- Deficiencies were received in the DRL and responded to in an amendment. No further questions were received on the same deficiency during the 2nd review cycle. However, a follow-up deficiency on the same DRL deficiency were received as an information request after an amendment to 2nd CRL or in the subsequent CRLs.

BE summary tables Invitro studies

Missing BE summary tables Vs studies listed in Product specific guidance

- Missing BE summary tables (namely - topical, DPI)
- New invitro studies are getting added in the PSG. Hence, it would be helpful if Agency can update the summary tables to include the expectation for the new invitro studies. This will help the Industry to submit the required information in the original ANDA.

Reason for repeat deficiency

Repeat Deficiency on earlier received deficiency

- Sometimes, we receive repeat deficiency (in the subsequent CRL/DRL of same ANDA) for which we have provided the justification earlier. However, we do not see a detailed rationale of why the earlier justification was not acceptable. A reasoning of why the earlier justification was not acceptable would immensely help the Applicant to better respond the repeat deficiency.

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Sterile Products

Container closure integrity testing (CCIT) in release and stability

- CCIT been requested in addition to the Sterility testing in certain products at release and stability. (FDA guidance on *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products)*

Tightening of Limits

Set the limits tighter than USP monograph

- In certain cases, Agency requests to tighten the limit (than USP monograph) based on trend/RLD data.
- Compliance to American Chemical Society (ACS) monograph over and above USP monograph for inorganic compound.

Thank you