

Common Quality Major Deficiencies in ANDAs

Generic Drugs Forum (GDF) 2025

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Everyone deserves confidence in their
next dose of medicine.

Pharmaceutical quality

assures the availability, safety, and efficacy of
every dose

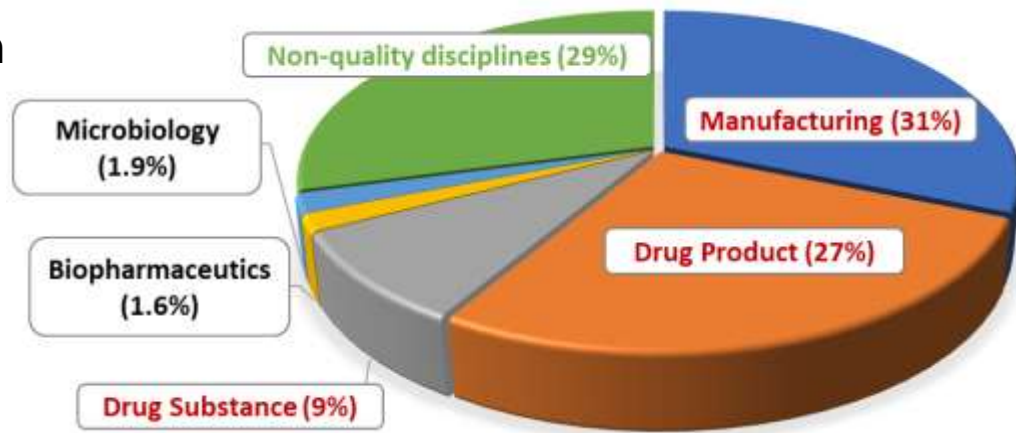
Learning Objectives

- Discuss quality major deficiencies issued in the first cycle major Complete Response Letters (CRLs) in Fiscal Year (FY) 2023.
- Provide recommendations to minimize quality major deficiencies and improve ANDA submission quality.

Overview



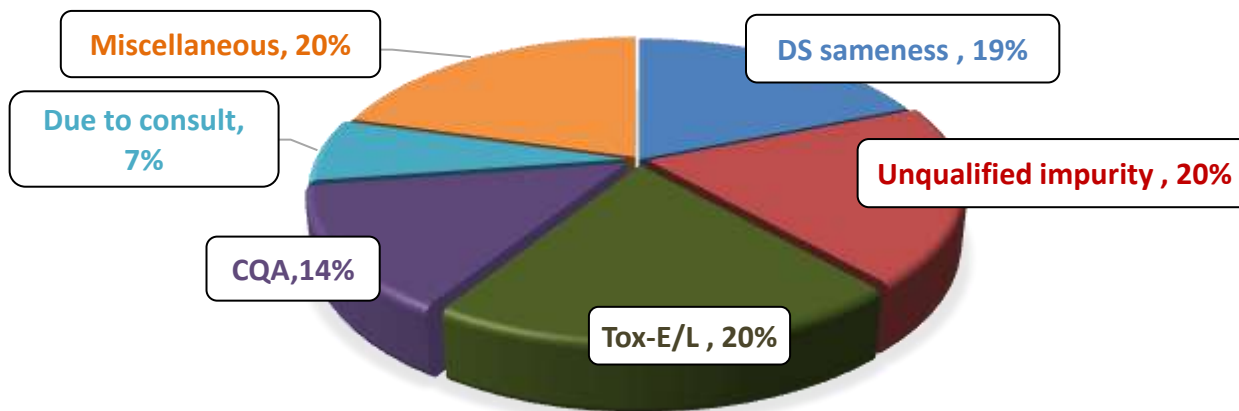
- 284 first cycle major CRLs issued in FY2023
- 429 major deficiencies identified
- Over 70% are quality related
- Top pharmaceutical quality disciplines with major deficiencies:
 - Manufacturing (~ 90% facility & ~ 5% process)
 - Drug Product (DP)
 - Drug Substance (DS)



Non-quality disciplines (29%)

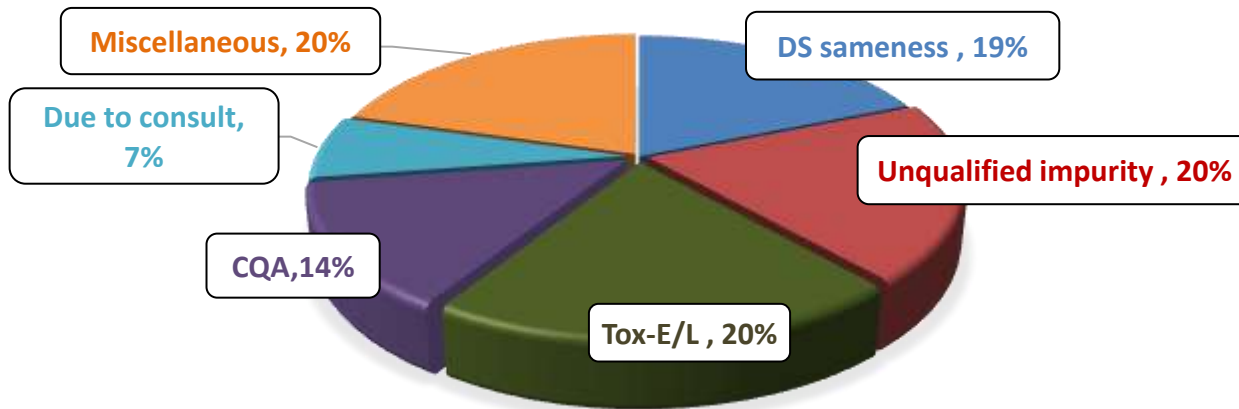
- Bioequivalence: 18%
- Pharmacology/Toxicology: 6%
- Others: 5%

Drug Product Related Major Deficiencies



- **Tox-E/L:** missing safety assessment of extractables/leachables (E/L) or inadequate assessment of E/L
- **Unqualified impurities:** missing toxicological studies to qualify unqualified impurities in drug product
- **DS sameness:** insufficient data to demonstrate drug substance (DS) sameness esp. for complex active ingredient
- **CQA:** critical quality attribute (CQA) not identified or controlled
- **Due to consult:** inadequacy(ies) identified through consult for safety assessment, device design, immunogenicity risk, etc.

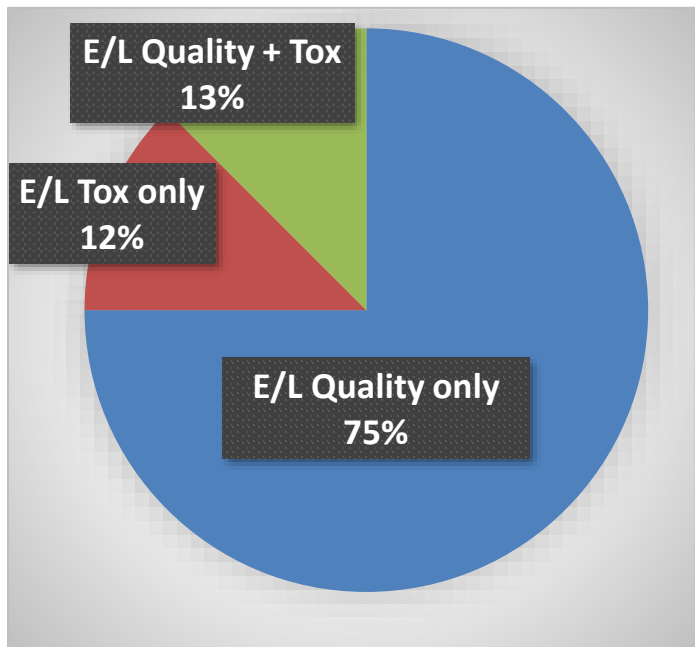
Drug Product Related Major Deficiencies



- **Miscellaneous** (each less than 5%): e.g.,
 - unacceptable analytical method for quality control
 - unacceptable packaging system to assure adequate product performance due to inadequate dosing accuracy or potential safety risk
 - insufficient long-term stability data to establish expiration dating when accelerated and intermediate stability data are both failed
 - unacceptable drug substance source
 - unacceptable physical properties for drug product
 - Insufficient data to support drug/device compatibility for the proposed product

DP Major Deficiencies

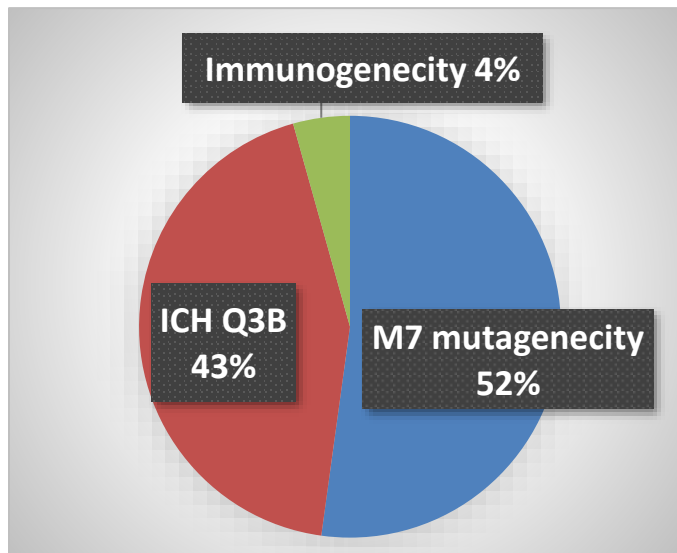
– Extractables/Leachables



- **E/L Quality only:** inadequate assessment of E/L (e.g., inadequate E/L method validation, incomplete E/L assessment, etc.) that is insufficient to facilitate a safety consult to Pharmacology/Toxicology
- **E/L Tox only:** lack of safety/toxicological evaluation data to qualify the identified leachables
- **E/L Quality + Tox:** inadequate assessment of E/L, such that safety/toxicological evaluation is indicated

DP Major Deficiencies

– Unqualified Impurities



- **M7 mutagenicity** –missing (Q)SAR data to assess potential mutagenetic risk of a degradation product
- **ICH Q3B** –missing safety data to qualify proposed acceptance criteria above the ICH Q3B qualification threshold for a degradation product without mutagenetic risk
- **Immunogenicity** –missing data to assess immunogenicity risk of peptide related impurity

DP Major Deficiencies

– DS Sameness

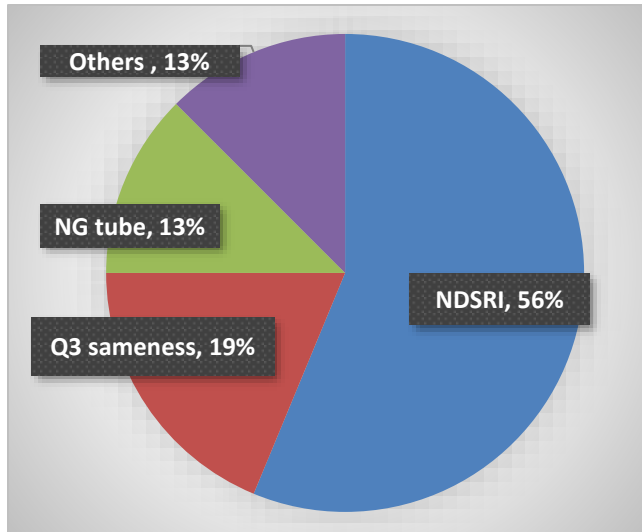
DS Sameness: Insufficient data to demonstrate drug substance (DS) sameness

- All related applications are peptide-containing drug products
- All without sufficient comparative data of secondary structure and aggregation profile of the proposed generic and the RLD to demonstrate DS sameness

In addition to DS sameness issue, all related applications do not contain sufficient comparative data of peptide related impurity profile between the proposed generic and the RLD, either for purpose of assessing potential immunogenicity risk or establishing quality control strategy.

DP Major Deficiencies

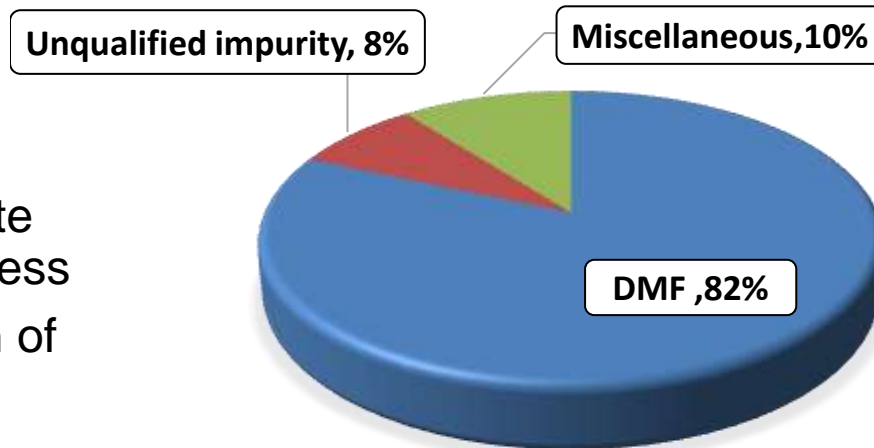
– Critical Quality Attributes



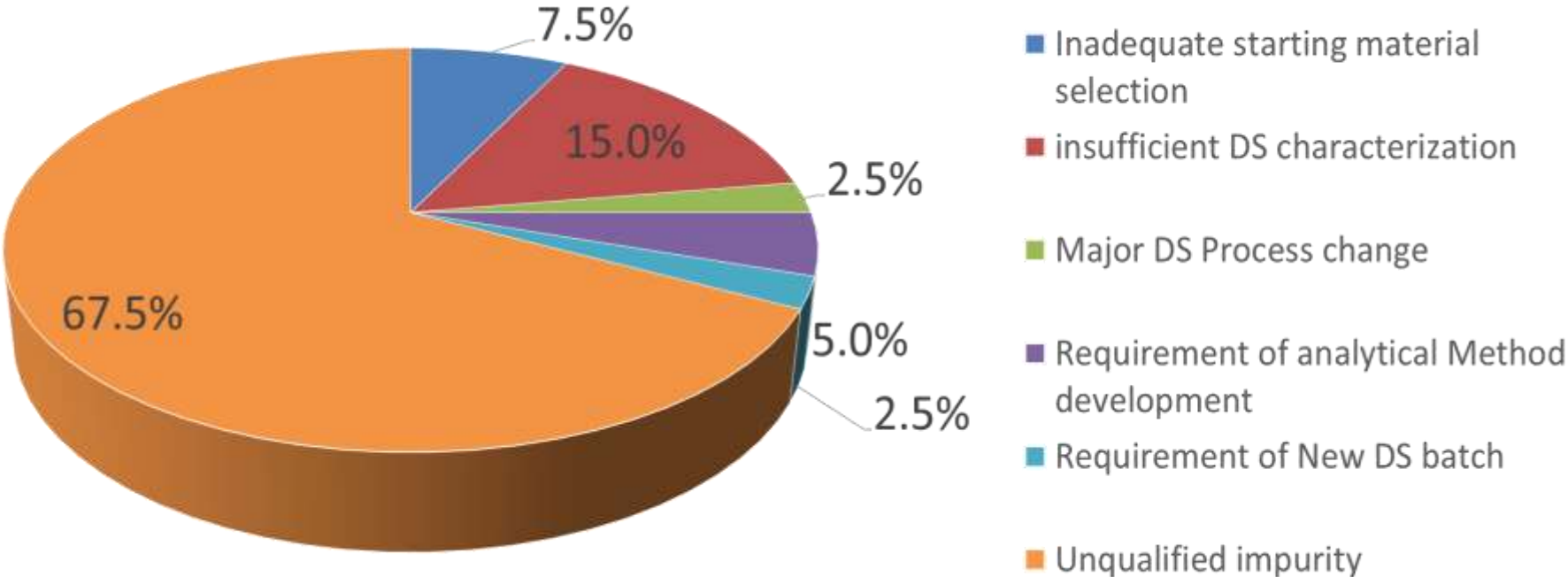
- **NDSRI** – missing or insufficient data to confirm presence of a nitrosamine drug substance related impurity (NDSRI) or other nitrosamine impurity(ies) in drug products known of high risk.
- **Q3 sameness** – missing or insufficient data to demonstrate physicochemical properties sameness for a complex formulation (containing nanomaterials) to the RLD formulation
- **NG tube** – inadequate nasogastric (NG) tube administration studies following labeling instructions
- **Others** – major deficiency associated with dissolution specification or need to develop method for controlling an elemental impurity

Drug Substance Related Major Deficiencies

- **DMF:** major deficiency identified in the referenced DMF for drug substance
- **Unqualified impurity:** missing toxicological studies to qualify an unqualified impurity in drug substance
- **Miscellaneous:**
 - Inadequate analytical method
 - Insufficient physical or chemical characterization data to demonstrate structure or drug substance sameness
 - Inadequate selection or justification of starting materials
 - Due to consult finding (mostly for safety assessment)



Analysis of DMFs w/ Major Deficiencies



Challenge Question #1

Which of the following areas are commonly found with major deficiencies by drug product assessment discipline for ANDAs?

- A. Qualification of impurity
- B. Evaluation of leachables
- C. Selection of starting materials
- D. All of above

Challenge Question #2

The most common drug substance related major deficiency is attributed to unqualified impurity(ies) present in drug substance.

- A. True
- B. False

Takeaways

- Manufacturing (largely facility related) (31%), drug product (27%) and drug substance (9%) are the top Quality disciplines identifying major deficiencies in the first assessment cycle
- FDA and GDUFA III initiatives have enhanced communication with applicants to minimize common deficiencies
 - PSGs, controls, development meetings, DRLs, IRs, and post CR meetings, workshops and webinars
- Key Recommendations to minimize quality major deficiencies
 - *Ensure Facility quality*
 - *Provide adequate quality data to demonstrate DS sameness for complex DS-containing DP and support proposed control strategy for CQAs including impurities and leachables*
 - *Strengthen communications between the ANDA applicants and DMF holders*

Acknowledgement

- SMEs from OPMA, OPQA I, II, and III

Pharmaceutical Quality Resources



Questions: CDER-OPQ-Inquiries@fda.hhs.gov

