U.S. FOOD & DRUG ADMINISTRATION

Analysis of ANDA Quality Related Major Deficiencies

2024 GRx+BioSims

ANDA Deficiency Trends:
Common Issues to Improve ANDA Submission Quality

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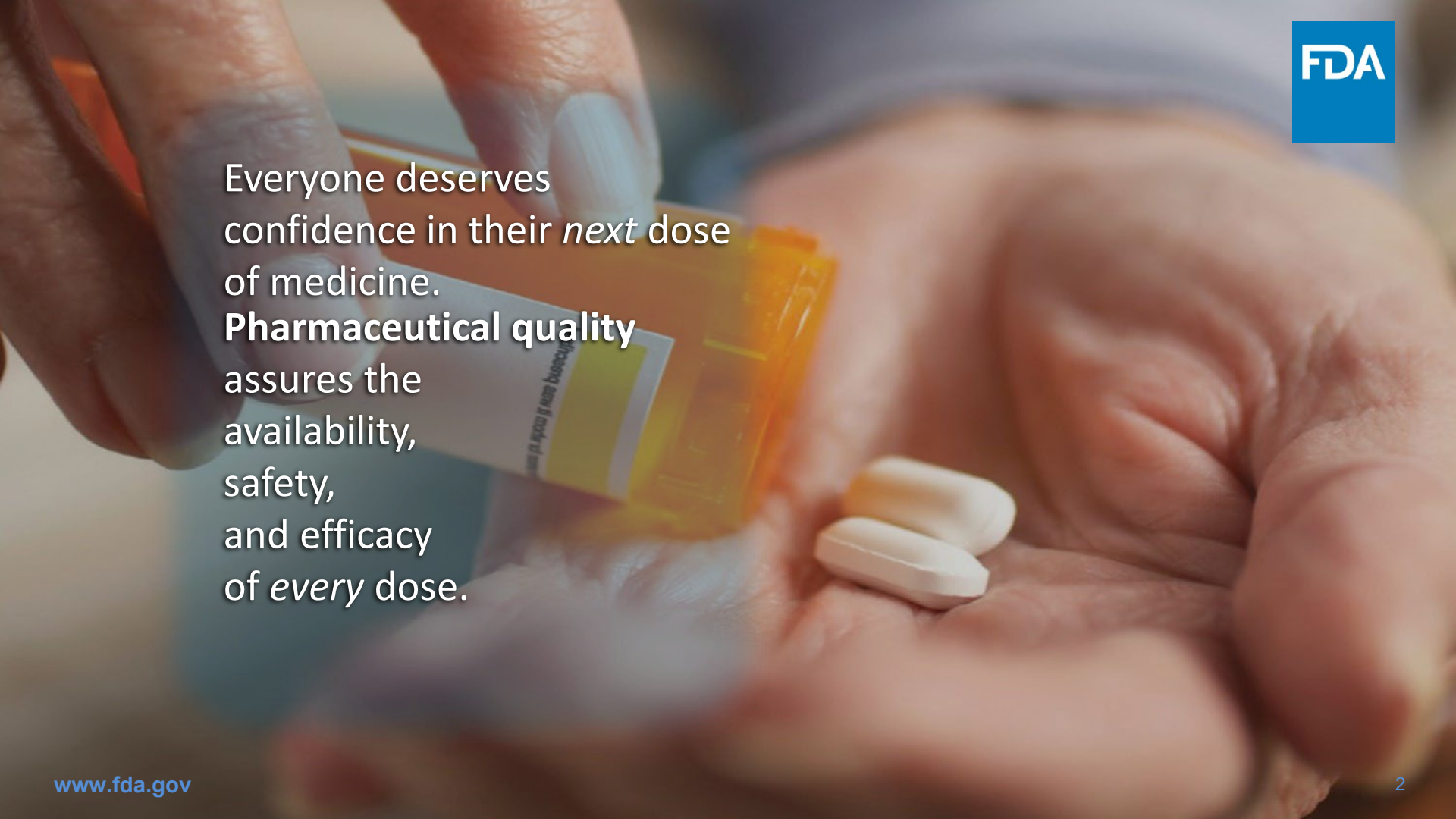
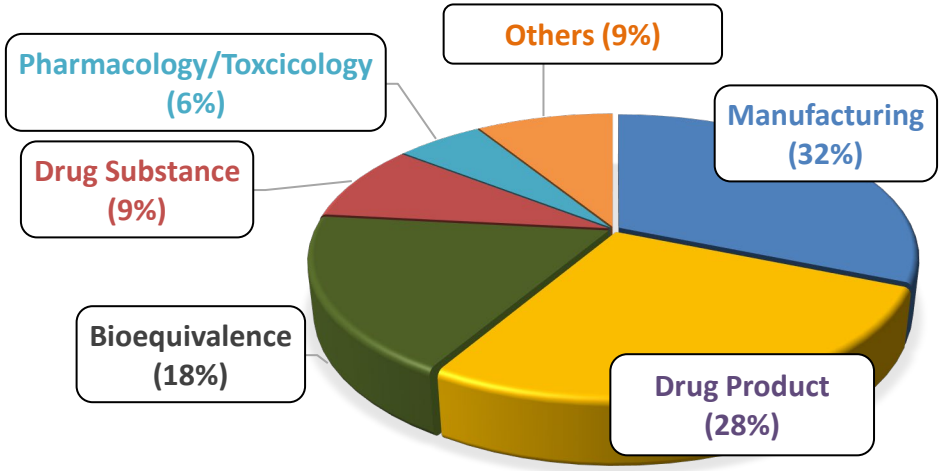

Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Outline

- Analysis of quality related major deficiencies issued in the first cycle major CRLs issued in Fiscal Year (FY) 2023
- Summery and recommendations

Overview

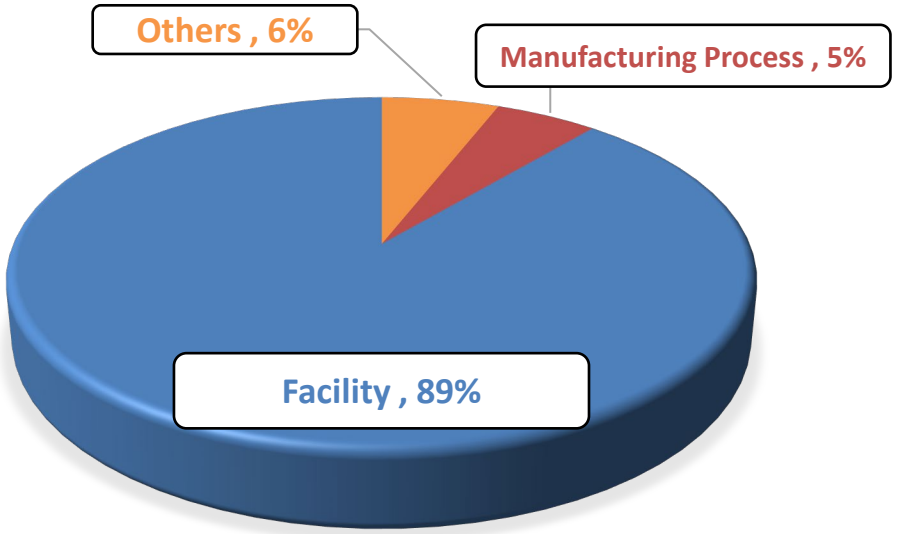
- 284 first cycle major CRLs issued in FY2023
- 429 major deficiencies identified
- Top pharmaceutical quality disciplines with major deficiencies:
  - Manufacturing (facility & process)
  - Drug Product (DP)
  - Drug Substance (DS)



Others (9%)
- Clinical comparative analysis: 3.1%
- Microbiology: 1.9%
- Biopharmaceutics: 1.6%
- Clinical: 0.9%
- Clinical/Pharmacology/Toxicology: 0.7%
- Risk Evaluation and Mitigation Strategy: 0.7%

Manufacturing Major Deficiencies

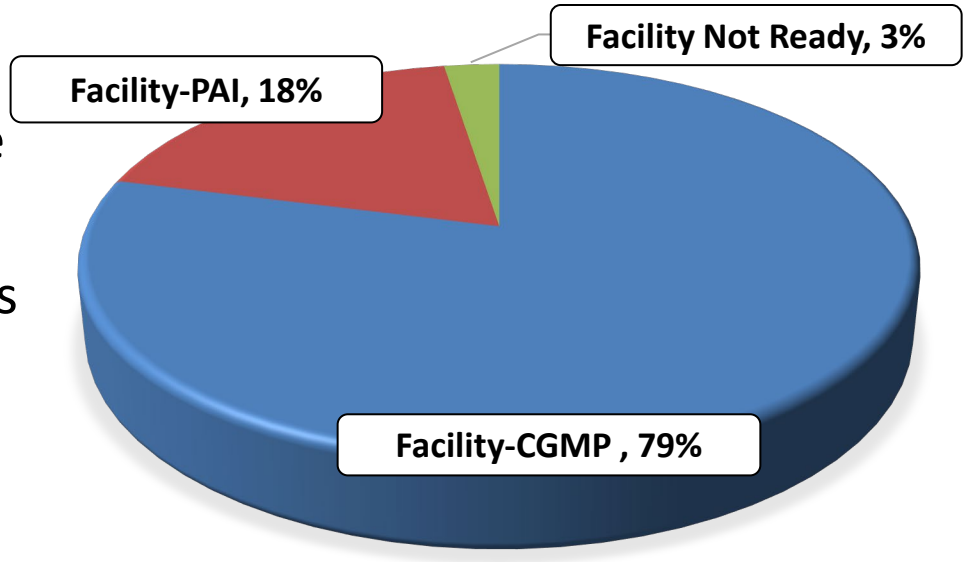
- **Facility related**
- **Manufacturing Process related**
- **Others***
  - Inspection on hold due to COVID travel restriction
  - Requiring CDRH consult for facility in next cycle
  - Need new batches to support other discipline review



*Not directly due to identified process/facility quality major deficiencies, and therefore excluded from the theme analyses for facility and process related major deficiencies.

Manufacturing Major Deficiencies – Facility Related

- **Facility-CGMP:** One or more facilities were withheld at the time of action due to surveillance inspectional deficiencies.
- **Facility-PAI:** One or more facilities were withheld at the time of action due to pre-approval inspectional (PAI) deficiencies.
- **Facility not ready (for inspection)**

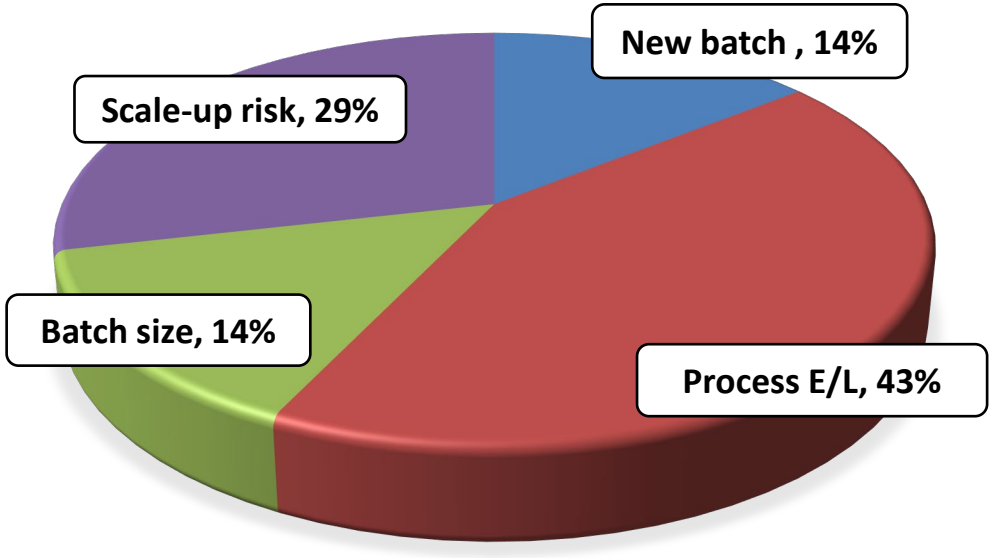


Outstanding Observation Categories from Form 483 Issued in PAIs

1	**Quality Assurance**
2	**Raw Material Testing**
3	**Post-Production: Shipping, Retain Samples, and Stability of the Drug Product**
4	**Laboratory**
5	**Causes of Microbiological Contamination**
6	**Facilities and Equipment**
7	**Production Procedures and Development**
8	**Data Integrity (Electronic or Paper Records)**

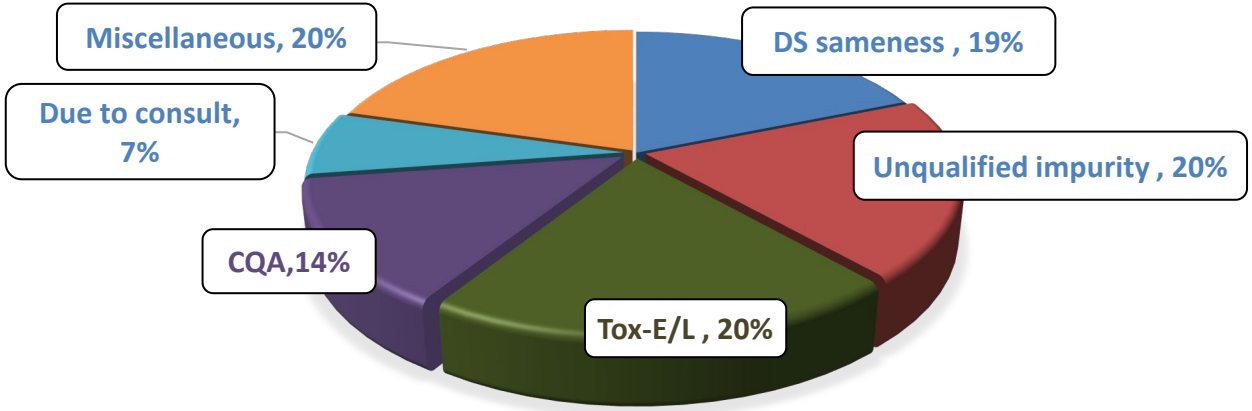
Manufacturing Major Deficiencies – Process Related

- **Process E/L :** need safety assessment for leachables from production equipment
- **Scale-up risk :** need new exhibit batches to support scale up*
- **Batch size:** exhibit batch size is inadequate
- **New batch:** need new exhibit batches due to formulation change



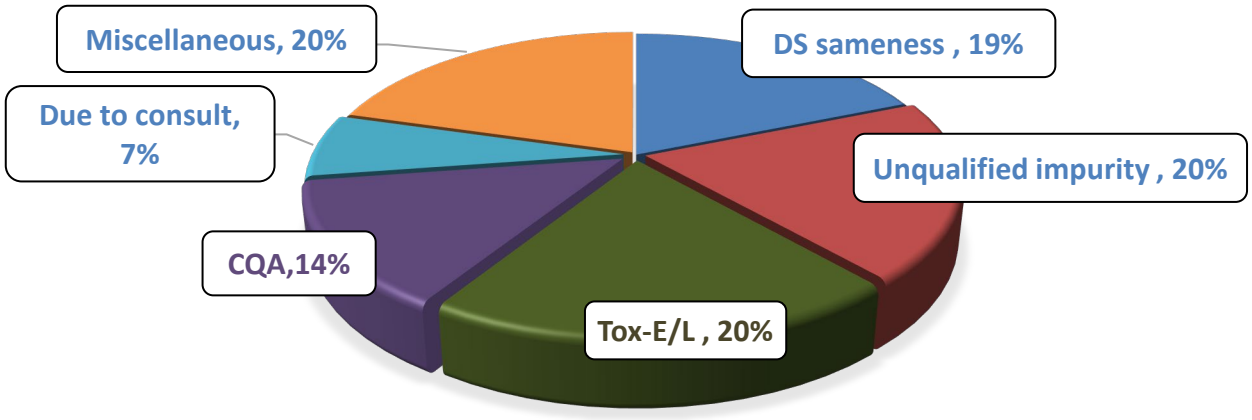
*For certain complex products, FDA recommends that one or more exhibit batch(es) should be manufactured at commercial batch size to mitigate the scale-up risk. Refer to the relevant quality guidance and/or product specific guidance for details.

Drug Product Related Major Deficiencies



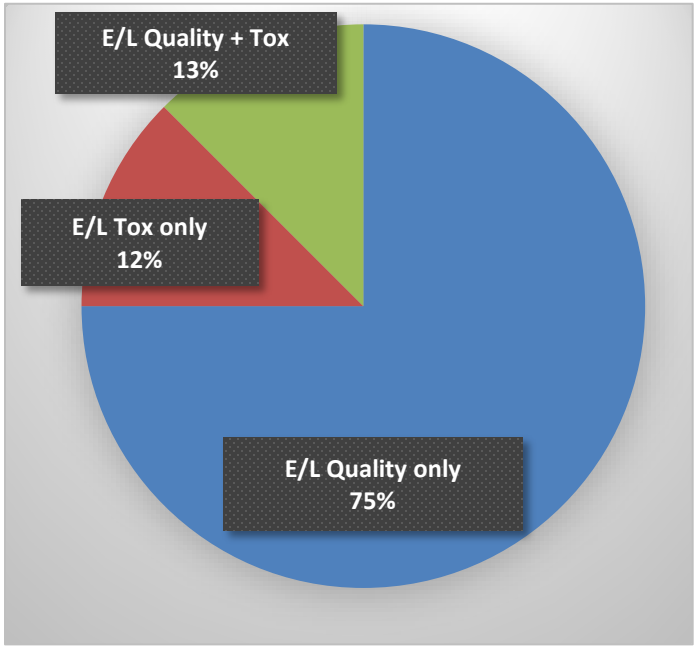
- **Tox-E/L**: need safety assessment of extractables/leachables (E/L) or inadequate assessment of E/L
- **Unqualified impurities**: need toxicological studies to qualify unqualified impurities in drug product
- **DS sameness**: insufficient data to demonstrate drug substance sameness esp. for complex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

Drug Product Related Major Deficiencies



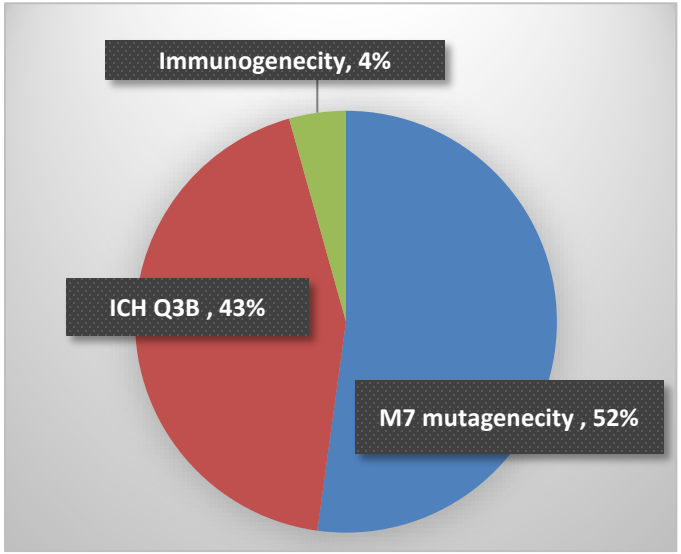
- **Miscellaneous** (each less than 5%): e.g.,
  - need new analytical method for quality control
  - need new packaging system to assure adequate product performance due to inadequate dosing accuracy or potential safety risk
  - need full term long-term stability data due to failure in accelerated and intermediate stability studies
  - need new drug substance source
  - unacceptable physical properties for drug product
  - Insufficient data to support drug/device compatibility and sustainability 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 do not warrant readiness of issuing a safety consult from DP 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 and need safety/toxicological evaluation

DP Major Deficiencies – Unqualified Impurities



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

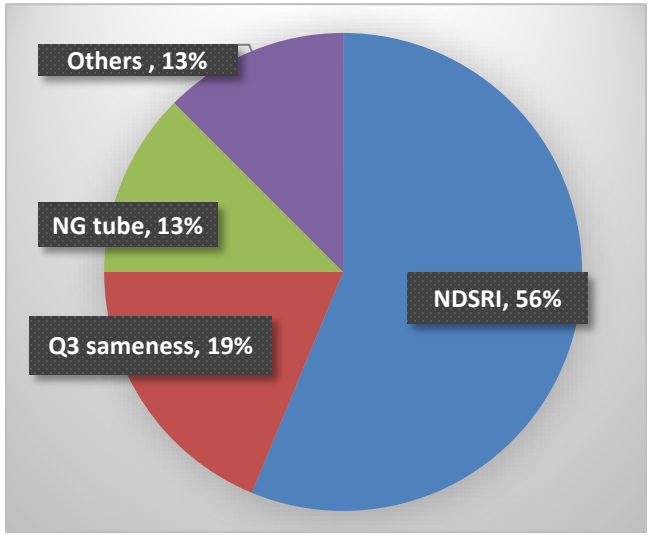
DP Major Deficiencies – DS Sameness

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

- All related applications are peptide-contained 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.

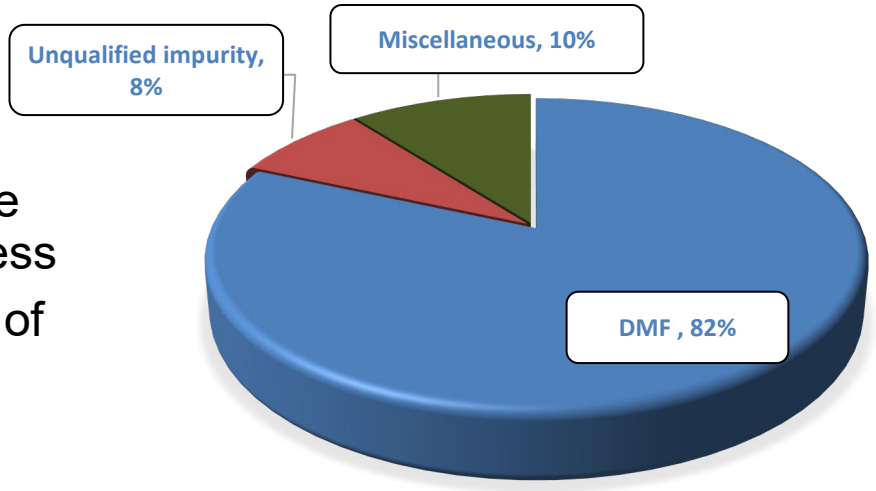
DP Major Deficiencies – Critical Quality Attributes



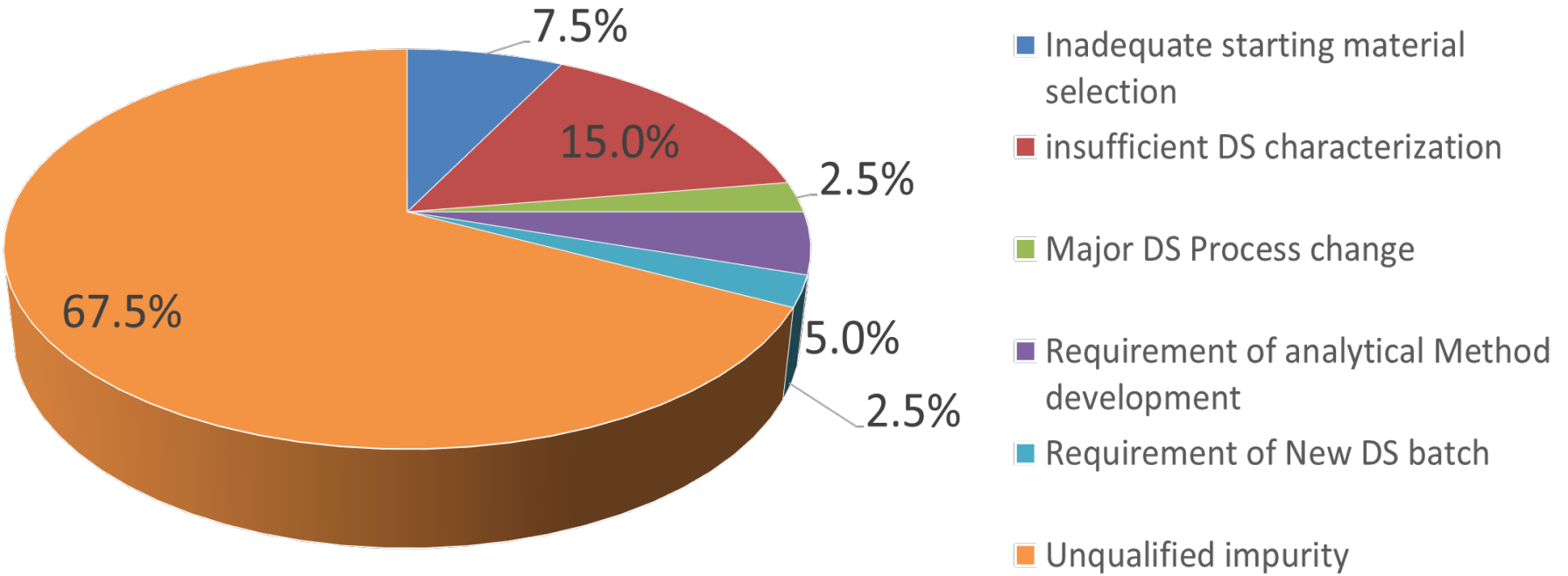
- **NDSRI –** need data to confirm presence of a nitrosamine drug substance related impurity (NDSRI) or other nitrosamine impurity(ies) in drug products known of high risk.
- **Q3 sameness –** need data to demonstrate physicochemical properties sameness for a complex formulation (containing nanomaterials) to the RLD formulation
- **NG tube –** need 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**: need toxicological studies to qualify an unqualified impurity in drug substance
- **Miscellaneous**:
  - Need new 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



Summary and Recommendations

- Manufacturing (largely facility related) (32%), drug product (28%) 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
  - *Ensuring Facility CGMP compliance*
  - *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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