U.S. FOOD & DRUG ADMINISTRATION

Process deficiencies for ANDA's – a dive into trends

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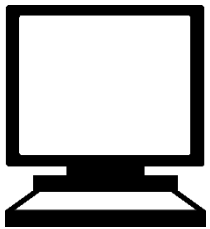
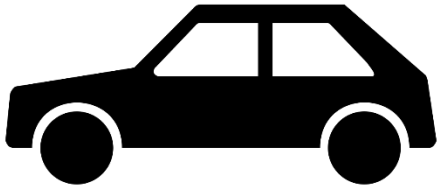
Indian Pharmaceutical Alliance

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.





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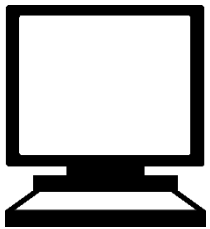
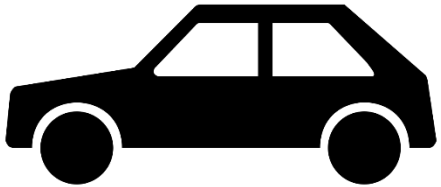



Drugs are no different.


Patients expect safe and effective medicine with every dose they take.


Pharmaceutical quality is
consistently meeting standards that ensure every dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Disclaimer

This presentation reflects the views of the speaker and should not be construed to represent FDA's views or policies.

Outline

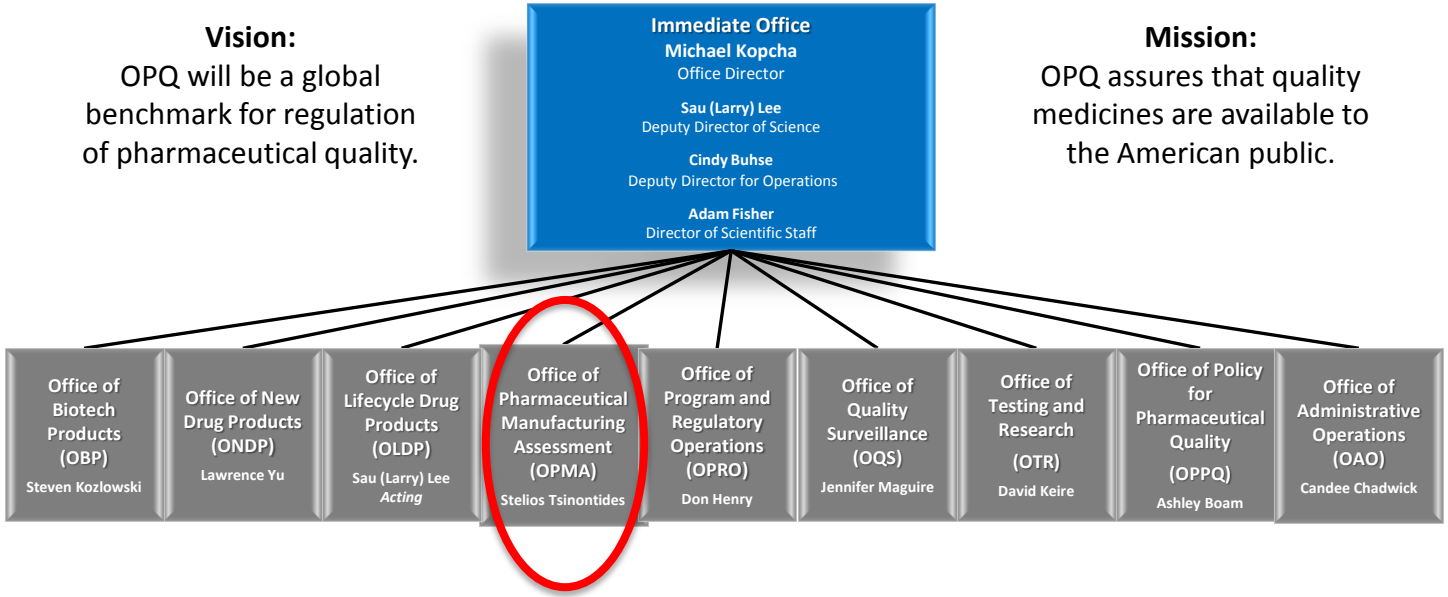
- ❑ OPMA Overview
- ❑ ANDA Deficiency Trends
- ❑ Points to consider

OPMA Overview

Office of Pharmaceutical Quality (OPQ)

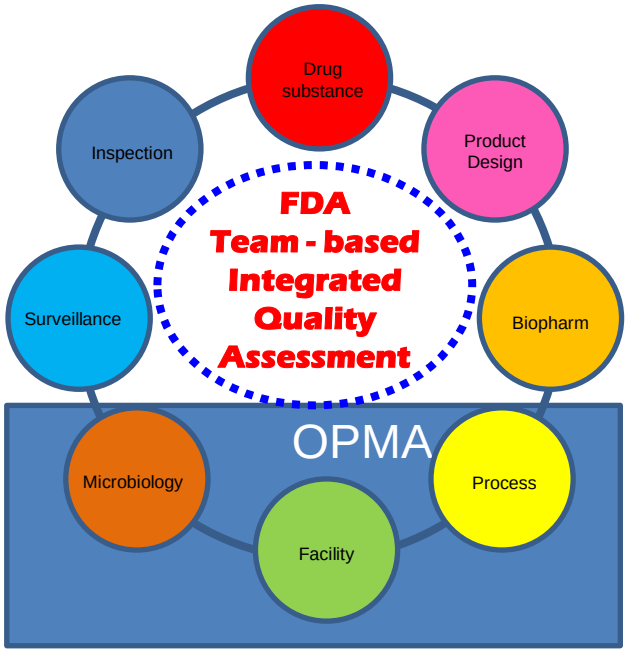
Vision:
OPQ will be a global benchmark for regulation of pharmaceutical quality.

Mission:
OPQ assures that quality medicines are available to the American public.



Office of Pharmaceutical Manufacturing Assessment (OPMA)

Mission: Ensure Quality is built into commercial manufacturing processes and facilities over product lifecycle



OPMA Purview

- Investigational New Drug Applications (IND)
- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Biologics License Application (BLA)

Pre-market & Post-market

- Manufacturing process
  - Oral dosage forms
  - Liquid dosage forms (sterile and non-sterile)
  - Other (e.g., MDI, TDDS, implants...)
- Facilities
  - Risk assessment of commercial manufacturing facilities
  - Pre-approval inspections
    - Paper-based assessments
    - Remote interactive assessment
- Microbiology (sterile products)

OPMA Putting OPQ's Attributes in Practice

AGILE

- Cross-training reviewers to assess complementary content from multiple disciplines as well as expand dosage form expertise
- Using remote assessments tools when appropriate to decrease PAI/PLIs

INFLUENTIAL

- Collaboration with ORA via NIPP to standardize data collection for risk-based inspection decisions
- Continuously striving for assessment consistency including via review guides and periodic 'self' audits.

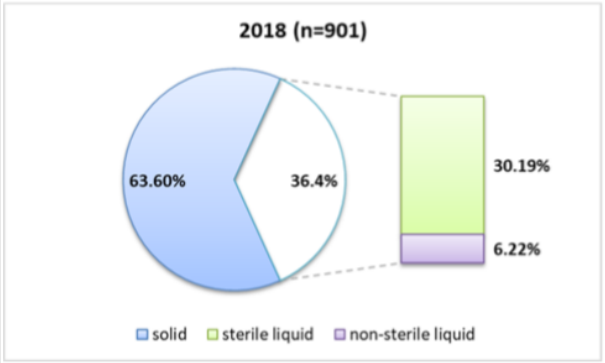
CONNECTED

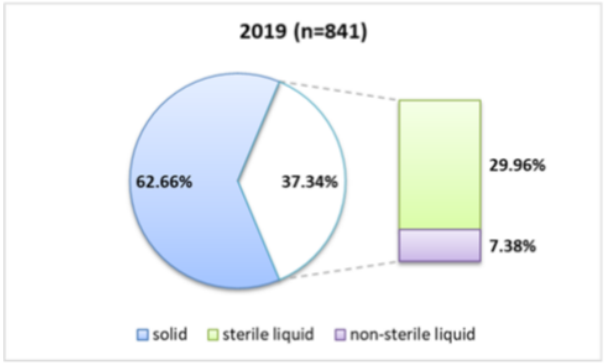
- Working cross-center and within center to prioritize meeting UFA commitments and avoid Drug Shortages.
- Expanding analytics capabilities via KASA, Facility Dashboards and building up PQ-CMC capabilities for longer term.

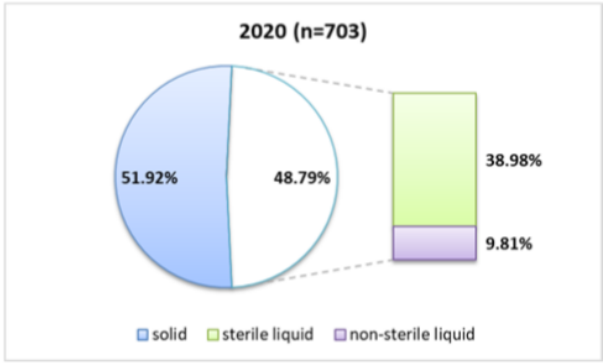
ANDA Deficiency Trends

Dosage form trends for ANDA applications

ANDA original applications received for evaluation (2018-2020)





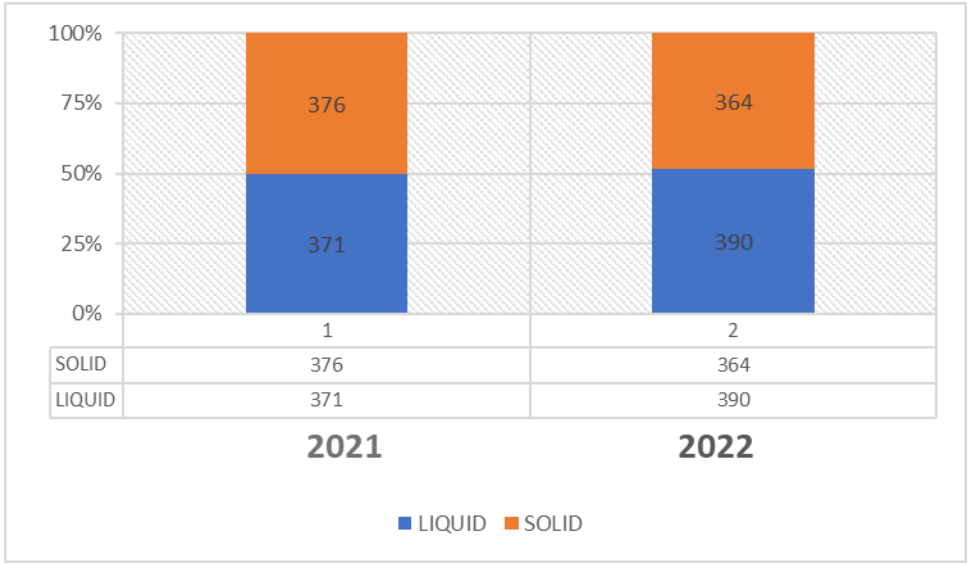


~8-10% of sterile liquid applications received per year: Lyophilized products

Courtesy: *LCDR Steve Rhieu, OPMA*

Dosage form trends for ANDA applications

ORIGINAL ANDA Applications (FY 2021 and 2022)



Trends Project Purpose

Analyze trends in process deficiencies to identify improvement opportunities

Aid assessor and applicant to deliver first cycle approvals

Liquid Products within study scope

- Injectables
  - IV, SC, IM
- Oral
  - Solutions, suspensions
- Topical
  - Gels, ointments, lotions, creams
- Insufflated
  - Inhaled, nasal

Methods

- Compilation of IQA reviews from Panorama
- Extraction of IRs
- Categorization of deficiencies
- Trends and analytics

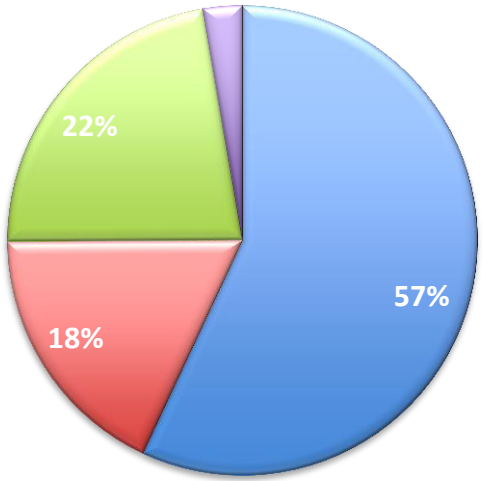
Data pool

976 IQA reviews

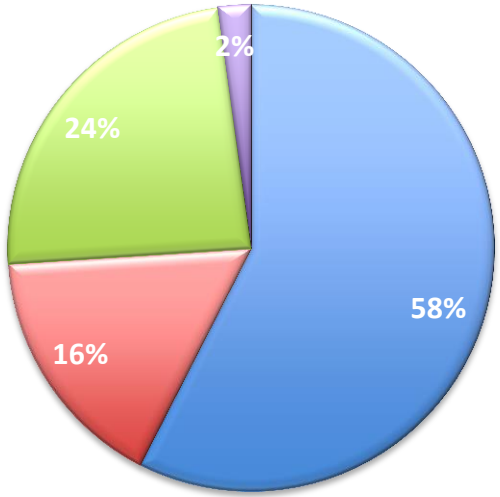
Jan 2019-Jun2022

5,652 Deficiency IR's

IQA Frequency

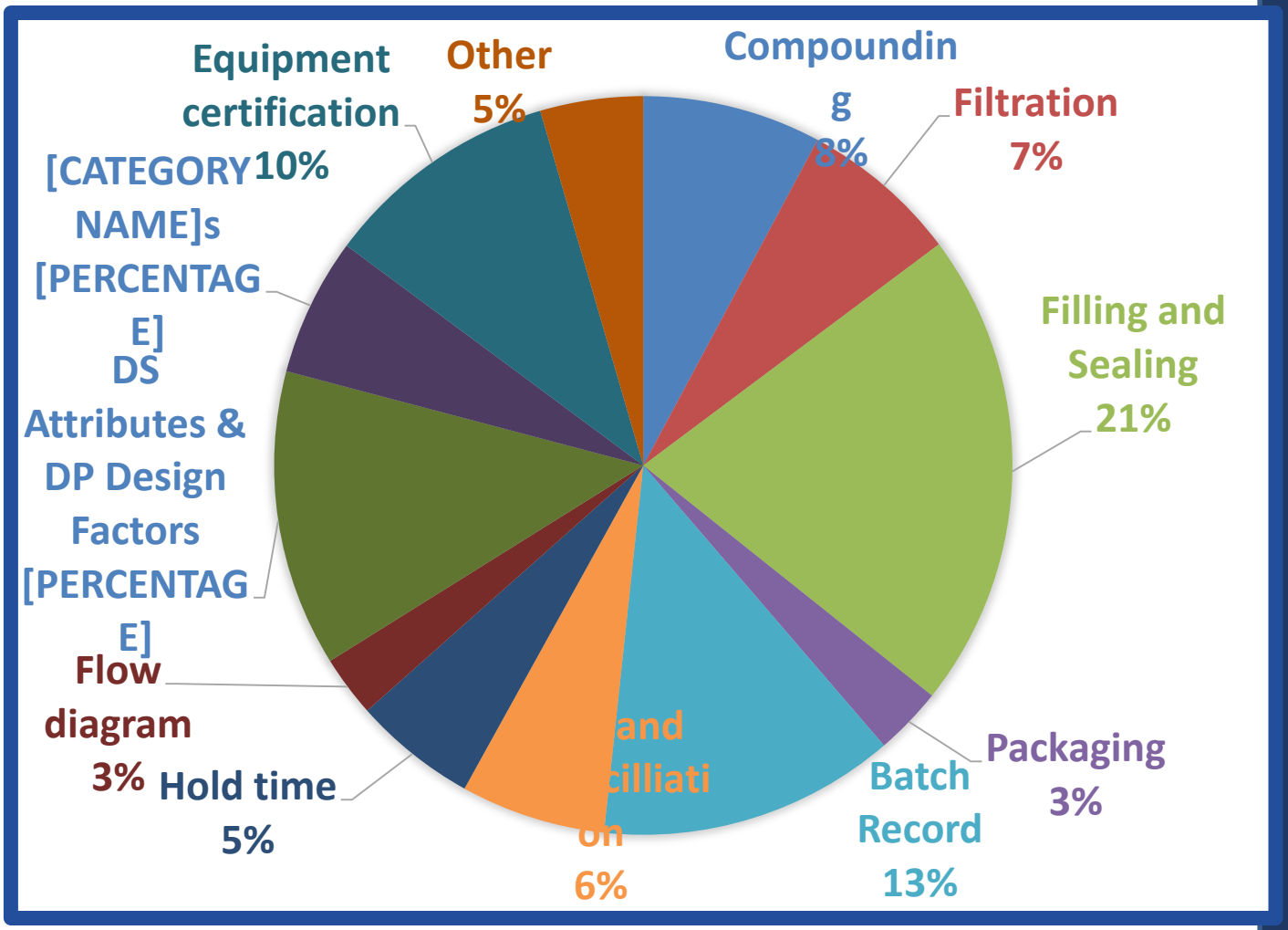


IR Frequency



Deficiency Categories

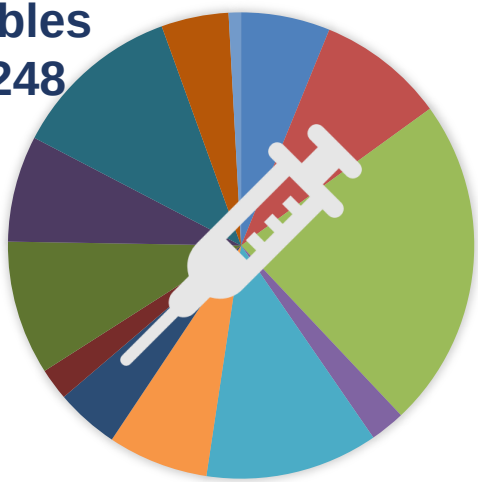
- Process flow diagram
- Drug substance (DS) attributes and drug product (DP) design factors
- Compound (mixing)
- Filtration
- Filling/sealing
- Equipment certification
- Extractables and leachables
- Packaging
- Batch records
- Yield and reconciliation
- Hold time



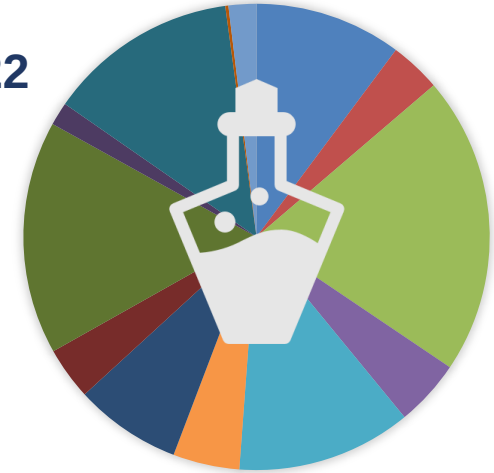
Deficiency Frequency By Category

N = 5,652

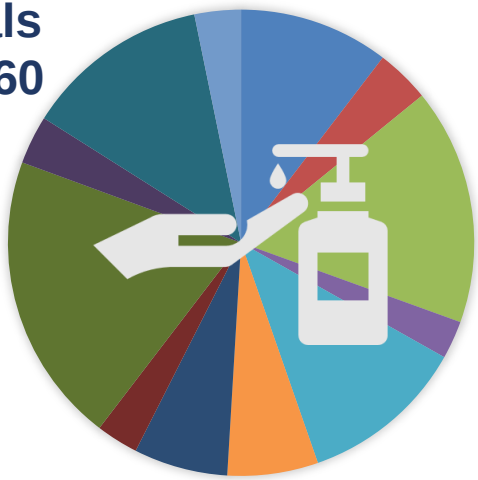
Injectables
N = 3248



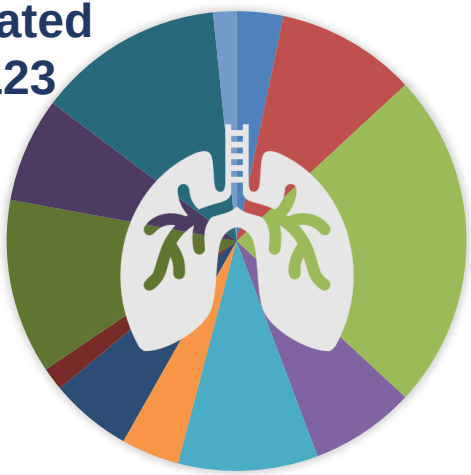
Oral
N = 922



Topicals
N = 1360



Insufflated
N = 123



- Compounding
- Filtration
- Filling and Sealing
- Packaging
- Batch Record
- Yield and Reconcilliation
- Hold time
- Flow diagram
- DS Attributes and Design Factors
- Extractables and Leachable
- Equipment certification
- Lyo
- Combination

ORISE

FDA

Top 10

10. N = 164
- Particle Size Distribution

9. N = 167
- Filling and Sealing Interruption

8. N = 170
- Filling Critical Process Parameters

7. N = 172
- Extractables and Leachables

6. N = 180
- Filling and Sealing Limits

Top 10

5. Yield & Reconciliation Limits

N = 194

Top 10

4. Product Uniformity

FDA

N = 202

Top 10

3. Batch Records

N = 339

Top 10

2. Filling and Sealing in-process controls

N = 388

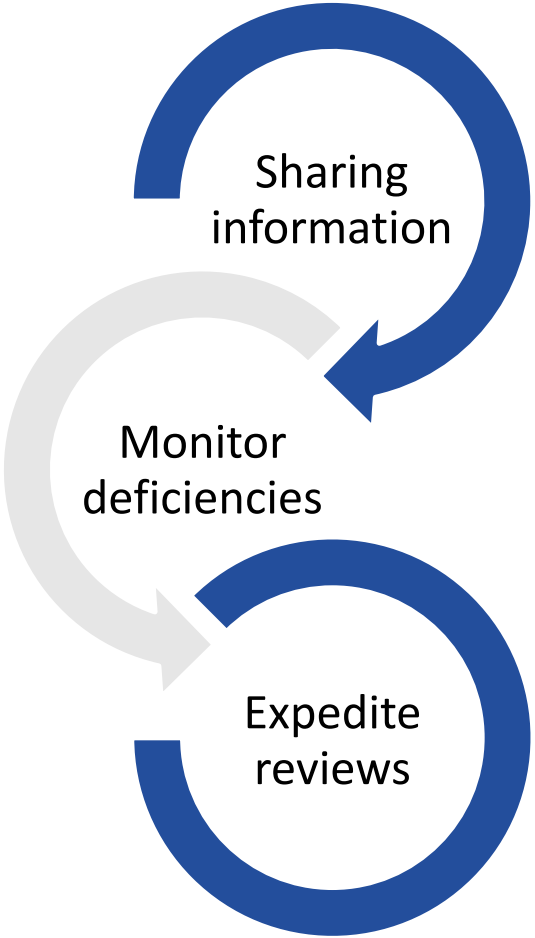
Top 10

1. Equipment Certification

FDA

N = 509

Future Direction



Points to Consider

Drivers for scrutiny

- **Regulatory changes**

❑ New Guidance's and/or MaPPs

Example:

- MAPP 5019.1 Rev 1 Allowable Excess Volume/Content in Injectable Drug and Biological Products (Jan 2022)
- MAPP 5019.2 Rev 1 Assessment of the Appropriate Net Container Content for Injectable Drug and Biological Products (Jun 2022)

❑ Updates to Pharmacopeia (USP, EP), including general chapters

Example:

- USP<1663>, USP<1664> for extractables leachables assessment
- USP<771> Ophthalmic Product-Quality Tests

- **Review concerns raised by application information**

Scenarios:

- Inconsistent information within application
- Missing controls that are needed to manage product quality

How can you assist?

- Be aware of upcoming changes and proactively plan to adopt
- Leverage your learnings on applications across your portfolio
- Avail of opportunities to engage early and across review cycle
- Justify your approach, however unique, with clear explanations and supporting data
- Know your product and process! Continue to monitor quality through product reviews to ensure consistency and identify lifecycle management opportunities.

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- Derek Smith, Ph.D.

FDA Resources

Office of Pharmaceutical Quality (OPQ) Annual Report (Feb 2022)

GDUFA III Resources

Manufacturing, Supply Chain, and Drug Inspections, including COVID-19 resources

- Q&A related to inspection, supply chain changes as well as related regulatory operations and policy.

CDER Manual of Policies & Procedures | MAPP

CDER Guidances (Drug) Newly Added Guidance Documents

2021 OPQ Annual Report (PDF - 4 MB)

Q&A

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