Integrated Quality Assessment: Drug Product

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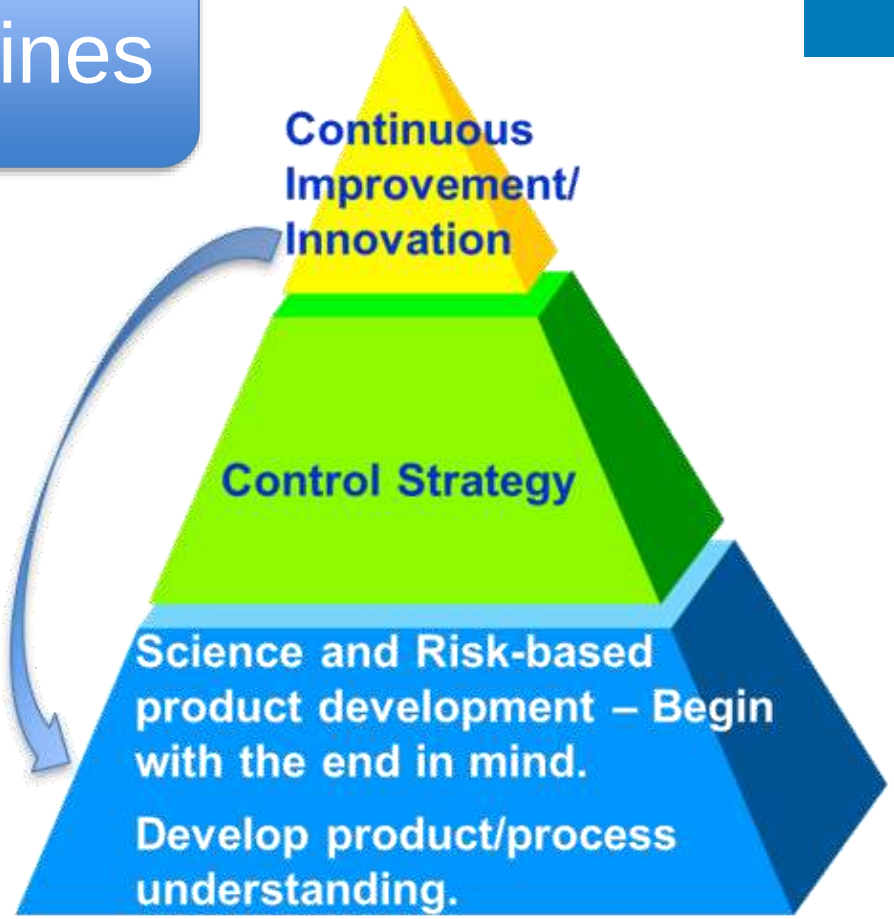
Learning Objectives

- Describe the functions of the drug product discipline within the IQA and outline critical aspects of ANDA assessment
- Identify common deficiencies and steps to avoid them
- Evaluate a case study to emphasize the importance of product knowledge and understanding

Scope – Solid Oral Dosage Forms

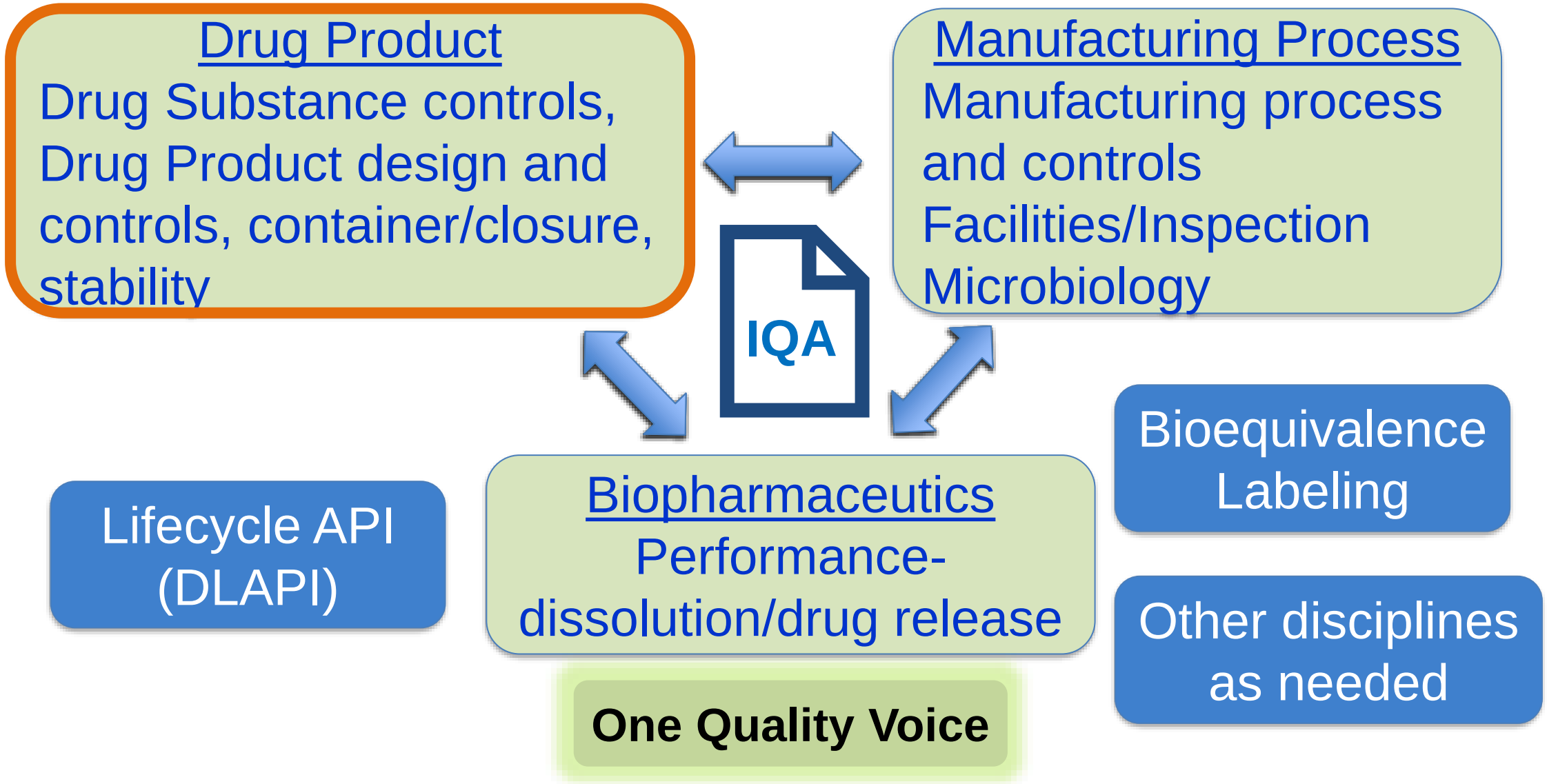
Patient Access to High-Quality Medicines

How do we get there?



- The Pharmaceutical industry manufactures high-quality drugs
- The FDA provides the necessary regulatory oversight to ensure safe, effective and high-quality drugs are available to the patient

OPQ's Integrated Quality Assessment



Drug Substance

- Reference to Drug Master File (DMF)
- Drug substance assessment in the IQA includes the evaluation of critical aspects of the API

ANDA submission should reflect a risk-based approach through clear understanding of the drug substance attributes that can have an impact on the quality, safety and manufacturability of the finished drug product.

Drug Substance Controls

- Complies with the USP monograph as a minimum requirement
- Additional tests established based on a risk-based approach and in consultation with the DMF holder (e.g., water, polymorph, particle size, impurities)
- Impurities classified as process and/or degradation products; controlled per ICH Q3A
- Genotoxic impurities controlled per M7
  - Azide impurities in at-risk ARBs (Valsartan, Irbesartan, Losartan, Olmesartan, Candesartan)

Drug Substance Controls

- Method verification per USP <1226> or full validation per USP <1225>; ICH Q2

- Reference standard:
  - USP reference standard – Lot number and certificate of analysis (COA)

  - Non-USP reference standard - COAs and copies of structural elucidation and characterizations (FT-IR, NMR, MS, UV, elemental analysis, etc.)

Drug Substance

Common Deficiencies:

- Aqueous solubility as a function of pH is not included and dose/solubility volume is not determined (BCS solubility)
- The API is said to not exhibit polymorphism when the literature reports indicate otherwise, and polymorph characterization is incomplete or not provided
- Forced degradation studies with under/over degradation and/or mass balance not established
- Impurity structures are not of high resolution, are inaccurate with missing chirality, and cannot be used to populate the KASA database

Drug Product Assessment

- Formulation
- Drug product controls (release/stability)
- Container/Closure
- Stability

Formulation

- Drug Substance
  - In general overages are not a recommended practice.
- Excipients
  - Excipient compatibility studies: chemical reactivity of excipients (or impurities in excipients), ratio of excipient to API per formula
  - Grade and level of excipients are justified based on formulation development/performance testing
  - The use of stabilization agents is justified
  - Compendial excipients are controlled based on current USP/NF

Drug Product Controls (release/stability)

- Compendial products should comply with the USP monograph as a minimum requirement
- Additional control strategies are established based on a risk-based approach with supporting data in product development studies (e.g., water content, polymorph, impurities, microbial testing)
- Dissolution profile for exhibit batches – to support changes to dissolution specifications without a new batch
- Analytical methods and method validation are suitable for the intended regulatory purpose
  - Method verification per USP <1226> or full validation per USP <1225>; ICH Q2

Drug Product Controls-Impurities

- Organic impurities – compliance with ICH Q3B, MAPP 5017.2
  - Process impurities
  - Degradation products
- Genotoxic impurities – compliance with ICH M7
- Residual solvents – compliance with USP <467>/ICH Q3C
- Elemental impurities – compliance with ICH Q3D
- Nitrosamine impurities - *Control of Nitrosamine Impurities in Human Drugs Guidance for Industry*

Container Closure

- Container closure (including bulk containers) should provide adequate protection over the proposed shelf-life
- Compliance with USP <661> and <671> demonstrated
- Certificates of compliance with applicable 21 CFR for indirect food additives should be included
- Combination drug product (drug/device) may require a consult

Stability

- Six months accelerated and long-term stability data at submission (three drug product lots with two lots of API)
- Stability data for bulk packs when intended for re-packagers
- In-use stability data for drug products intended for alternative administration (e.g., tablets dispersed in liquids, capsules contents (pellets, beads, granules) sprinkled on soft foods) or based on a risk-based approach
- Expiration date should be justified per ICH Q1E (6 months accelerated; 12 months long-term data)
- Expiration date extension requested in a supplement for products approved with reduced expiry due to failures on accelerated conditions

ANDAs: Stability Testing of Drug Substances and Products
Guidance for Industry; Questions and Answers

Drug Product Assessment

Common Deficiencies:

- Compatibility studies do not reflect the chemical stability of the API in the formulation (i.e., testing for impurities is not performed, ratio of excipient to API is inadequate)
- Water content limit proposed is not supported by data
- Evaluation of data trends and investigation of data failures not provided
- Evaluation of assay and impurities shows lack of mass balance
- New batch required due to lack of supporting dissolution data

Drug Product Assessment

Common Deficiencies:

- Failure to use a risk-based approach to establish the need for in-use stability
- Stability protocol and stability commitment fail to include accelerated testing of validation lots when a scale-up is proposed
- Final approval request of tentatively approved applications fails to:
  - Outline updates (location and justification)
  - Include confirmation of compliance with “current” regulatory requirements (e.g., current USP, ICH Q3D, nitrosamines)

Case Study

Challenge

The API is a mixture of polymorphs (I, II) with distinct solubilities, so the ratio is critical for acceptable bioequivalence.

Findings and resolution

- Polymorph I is stable and II exists at a specific water content and it is known to interconvert to other forms
- Formulation development studies show specific polymorph ratios failed to achieve bioequivalence
- Limit water content to prevent interconversion of form II
- Monitor polymorph ratio in the finished drug product with limit supported by formulation studies

Challenge Question

Which statement is NOT TRUE?

A. Pharmaceutical Quality assures every dose is safe and effective, free of contamination and defects.

B. OPQ quality assessment is a multidisciplinary task and employs science and risk-based policies and standards.

C. Product development studies to generate the needed product knowledge and understanding are critical for a high-quality submission.

D. Data trends on stability do not need to be evaluated.

Summary

- Industry and the regulatory Agency must work together to ensure high-quality drug products
- Described the IQA as a multidisciplinary approach to ANDA assessment
- Described the ANDA assessment by the drug product discipline
- Identified some of the most common deficiencies encountered by the drug product discipline and provided strategies to reduce ANDA review issues and time to approval based on product knowledge and understanding

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Questions?

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