# Generic Drug Product Quality Review Per Current IQA (Integrated Quality Assessment)

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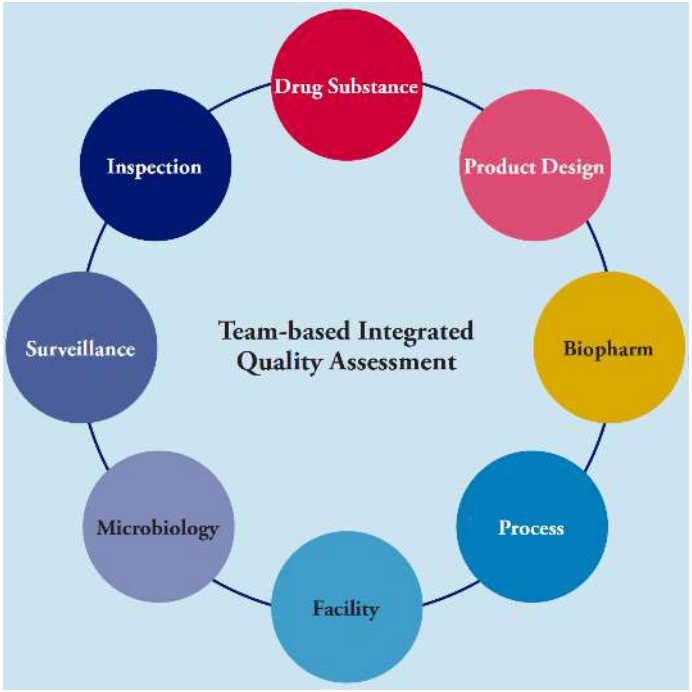
# Drug Product Quality Review per IQA

## What is IQA?




***What is IQA:*** Integrated Quality Assessment by a team of Subject-Matter Experts (SME)

## Why IQA?


***Why IQA:*** An IQA team of subject-matter experts (SME) will provide an aligned, patient-focused and risk-based drug product quality recommendations for an application, inclusive of drug substance, drug product, manufacturing, and facilities – To achieve the goal of "**One Quality Voice**"

# Drug Product Quality Review per IQA

## IQA Teams and Roles:

- **Application Technical Lead (ATL):**
  *Oversees the technical content (Branch Chief, QAL, or Senior CMC reviewer from OLDP)*
- **Regulatory Business Process Manager (RBPM):**
  *Manage overall review process and timeline and coordinates all review disciplines (OPRO staff)*
- **Discipline Reviewers**
  - **Drug product quality review** *(OLDP CMC review staff)*
    - *S.1-7. Drug substance in application (standalone document)*
    - *P.1., P.2-8. Drug product formulation, PD study, Control of excipient, Control of drug product, Reference standards, Container closure system, Stability*
  - **Drug product manufacturing process** *(OPF CMC review staff)*
    - *P.3. Manufacture (Drug product manufacturing process and process controls)*
  - **Microbiology** *(OPF Microbiology review staff)*
  - **Facility** *(OPF Facility review staff)*
  - **Biopharmaceutics** *(ONDP/DBPh Biopharm review staff)*
    - *Drug release/dissolution*
  - **Environmental Analysis** *(EA review staff)*
  - **Other technical advisors as needed** *(OTR Lab, OPPQ Policy, OS Surveillance, etc.)*
  - **Pre-Approval Inspection (PAI)** *(ORA Lead / SMEs participate)*

# Drug Product Quality Review per IQA

## Outline:

I. Drug Product Quality Reviewer's Role in IQA

II. Drug Product Quality Review Essentials

III. Common Deficiencies in Drug Product Quality Review

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# Drug Product Quality Review per IQA

## I. Drug Product Quality Reviewer's Role in IQA

To Assess the Adequacy of Parts of the Chemistry, Manufacturing and Controls (CMC) In an Application (NDA/ANDA)

# Drug Product Quality Review per IQA

## I. Drug Product Quality Reviewer's Role in IQA

1. **Drug Substance (or API)**
   - ✓ Evaluation of sponsor's scientific knowledge and adequacy of controls of Drug Substance in ANDA (*standalone document from DMF*)
2. **Composition/Formulation**
   - ✓ Evaluation of Composition, Formulation and Product Development
3. **Control of Excipients**
4. **Control of Drug Product**
   - ✓ Evaluation of adequacy of Drug Product Controls including analytical methods and criteria
5. **Container Closure**
   - ✓ Evaluation of safety/suitability of Container Closure System
6. **Stability / Shelf-Life Analysis and Recommendations**

# Drug Product Quality Review per IQA

I. Drug Product Quality Reviewer's Role in IQA

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# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

### 1. Drug Substance (or API)-*Evaluation*

**Evaluation of DS will include the following:**

- ✓ Pharmaceutical Equivalence (*sameness to innovator product per regulatory expectations*)
- ✓ Adequacy of controls
- ✓ Impact on product quality, safety, manufacturability

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

### 1. Drug Substance (or API)-*Recommendation*

1) **Full description and complete information on physiochemical properties of drug substance**
2) **BCS classification demonstrated by data**
3) **Aqueous solubility as a function of pH**
4) **Polymorphism**

   Thermodynamic form of polymorphic form should be identified and its impact on DP manufacturability and performance be discussed

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

### 1. Drug Substance (or API)-*Recommendation*

#### 5) Adequacy of Controls

- ✓ Specifications in line with DMF or tighter as needed
- ✓ limits for general impurities in compliance with ICH Q3A (R2) IT/QT as per MDD and TDI to avoid the need for a toxicology consult
- ✓ Limits for Potential Genotoxic Impurities should be in line with ICH M7 or per a toxicology consult
- ✓ Additional tests needed to ensure uniform manufacturability/quality of DP (e.g. polymorphism, justified particle size, density, microbial tests etc.)

#### 6) Reference Standard for DS/DP

- ✓ In-house reference standard: sponsor needs to submit/interpret all spectral data to confirm structures and purity
- ✓ USP reference standard: IR comparison is sufficient

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 1. Drug Substance (or API)-*Recommendation*

### 7) Test Methods and Method Validation

- ✓ **In-house methods**: Full validation reports are needed -- refer to USP<1225>
- ✓ **Transferred methods** from DMF holder/outside lab: Method transfer reports and method verification data should be provided by ANDA sponsor -- refer to USP<1224>
- ✓ **Compendial methods**:
  - If compendial method is used: ANDA sponsor needs to provide Method Verification reports -- refer to USP <1226>
  - If modified/non-compendial method is used: ANDA sponsor needs to demonstrate Method Equivalency to the compendial method -- refer to USP<1225>

### 8) Retest Date

- ✓ NMT 12 months is generally accepted by the agency unless otherwise justified by in-house stability data at the DP manufacturing site under in-use conditions

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 2. Composition/Formulation-*Evaluation*

### Sponsor is expected to:

- **Assess proposed drug product formulation**: the use and amount of excipients (inactive ingredients) should be justified with respect to **IID** (Inactive Ingredients Database), comparison to **innovator** (per Reverse-engineering analysis of Reference Listed Drug) and **target population/expected dosing**
- Consider 21 CFR 314.94 expectations regarding dosage form and "exception" excipients *(particularly applicable to parenteral and transdermal products)*
- Consider design differences compared to innovator product *(as applicable)*
- Consider Size, Shape and Visual Differences compared to innovator product*

  * Refer to Guidance: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules: *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377938.pdf*

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 2. Composition/Formulation-*Evaluation*

### Sponsor has the Flexibility:

- in choice of inactive ingredients when developing a generic product in many dosage forms *(21 CFR 314.94 (a) (9) (ii) – Inactive ingredients)*
- in choice of drug substance and excipient sources and the choice of manufacturing process

### With such Flexibility comes Responsibility:

- "…*provided that* the applicant identifies and characterizes the differences and provides information demonstrating that the differences **do not** affect the **safety** of the proposed drug product." (21 CFR 314.94)
- The applicant should also understand/assess the **impact** on product **quality** and **performance**

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

### 3. Control of Excipients

- **Public/Compendial Tests:** Majority of excipients are in relation to public standards, e.g. National Formulary (NF) and United State Pharmacopeia (USP), and should comply with the public/compendial standards
- **Additional Tests** may be necessary based on product design, manufacturability, and performance (*detailed in PD study*)
  - ✓ Sometime review of Type IV Drug Master File is needed (e.g. colorant, flavorants etc.)

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 4. Control of Drug Product -- *Evaluation*

**To Confirm Product Quality and Performance**

- Review staff would assess the tests and acceptance criteria used for routine product release and shelf life (Stability) testing
- Controls generally include (but not limited to) the following *tests*:
  - ✓ Visual description *(color, shape, engraving, scoring, and size/dimensions)**
  - ✓ Identification *(2 discriminative ID methods are usually recommended)*
  - ✓ Water Content *(especially when hygroscopic ingredients and wet granulation are involved)*
  - ✓ Uniformity of Dosage Units per <905> *(release only)*
  - ✓ Dissolution or Drug Release
  - ✓ Assay *(content/potency of API, preservative, and antioxidants)*
  - ✓ Impurities *(Degradants: identified, specified, individual unknown, and total)*
  - ✓ Residual solvents *(per <467> option 1 or 2)*
  - ✓ Microbial tests (per USP <61>/<62>, <1111>)

* *Refer to Guidance: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules*

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 4. Control of Drug Product – *Challenging Area*

### 1) Identification of Process Impurities

- ✓ Process impurities are carryover impurities from Drug Substance manufacturing process, which can be defined per **consulting DMF holder** or by **chemical structures** (*It's not necessary to include process impurities in DP specification*)

### 2) Identification of Degradation Products

- ✓ Degradation products are formed during manufacturing/storage of drug product due to **chemical degradation** of drug substance and/or **interaction** with environment, other components, and container, etc. (*per ICH Q3B(R2)/M7*)

### 3) Identification of Other Impurities:

- ✓ Impurities in Excipients
- ✓ Residual Solvents (*per ICH Q3C(R6)*)
- ✓ Elemental Impurities (Residual Metals) (*ICH Q3D*)

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 4. Control of Drug Product – *Challenging Area*

### 4) Qualification of Common Impurities:

- Limits for **Common Impurities:** ICH Q3B(R2) Qualification Threshold (QT) as per MDD are generally accepted *(but not always, due to known toxicity or quality concerns)*
- Limits for **Compendial Impurities:** Compendial limits are generally accepted *(but not always, due to known toxicity or quality concerns)*
- **Comparison to the Reference Listed Drug** (*often the NDA innovator drug*)
  - ✓ *Justification by data of comparison using the same method of analysis*
- **Significant Human Metabolite**
  - ✓ *Justification may not be acceptable in all cases (e.g. quality impact)*
  - ✓ *May still need a clinical consult*

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 4. Control of Drug Product – *Challenging Area*

### 5) Qualification of Genotoxic/Carcinogenic Impurities:

- **Generally Acceptable: TTC = 1.5 µg/day**
  - ✓ *TTC = Threshold of Toxicological Concern. MDI of impurity controlled at 1.5 µg/day is generally considered acceptable (or considered to be protective for a lifetime of daily exposure)*
- **Toxicity Studies**
  - ✓ *Would require consult to clinical divisions to assess impact based on dosing, level, population, etc.*

*For more details, refer to M7 and M7(R1) Addendum:*
*https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf*
*https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464285.pdf*

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 4. Control of Drug Product – *Challenging Area*

### 6) Drug Release/Dissolution:

- **Dissolution/Drug Release**
  - ✓ For Solid Orals Products (tablets, capsules) as well as some others, performance is measured by Dissolution/Drug Release
- **Product Design**
  - ✓ Challenging based on product design differences and differences in material characteristics (e.g., solubility, solid state form, etc.)
- **Comparison with** Reference Listed Drug (**RLD)**
  - ✓ Assess performance as compared to RLD
- **Pharmaceutical Development (PD) Studies etc.**
  - ✓ Linkage to development studies and bioequivalence studies

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 4. Control of Drug Product – *Challenging Area*

### 7) Analytical Methods:

- **Purpose**: Evaluating the testing used to confirm product quality and performance
- **Methods**: Analytical method must be discriminating and stability indicating
  - ✓ *This directly relates to Drug Substance, Manufacturing and Drug Product analyses*
- **Validation**: Validation recommendations are available in FDA/ICH guidances and USP and are confirmed during CMC review

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

### 5. Container Closure

- Evaluation of container function and controls which includes the following aspects
  - ✓ Safety
  - ✓ Function
  - ✓ Performance (where applicable
  - ✓ Compatibility
- Delivery devices: May need a consult with CDRH for design review and device site inspections
- New packaging materials: Generally not recommended (May require review of Type III Drug Master file)

# Drug Product Quality Review per IQA

## II. Drug Product Quality Review Essentials

## 6. Stability/Shelf-Life Analysis and Recommendations

Evaluation of initial and long-term studies to propose and demonstrate quality and performance over the product's shelf-life

- ✓ **Controlled Room Temperature (CRT)/Stress Stability Study**: Sponsor provides CRT and stress (Intermediate/Accelerated) stability studies on multiple batches packaged in proposed marketing containers as a surrogate for long-term storage
- ✓ **Forced Degradation Study:** Sponsors also provide additional studies such as forced degradation (used to demonstrate analytical method adequacy ) as well as other storage conditions (time, temperature and humidity)
- ✓ **Initial stability data** for shelf-life (labeled) conditions are provided
- ✓ **Expiry Date**: Evaluate proposed expiry date and testing needed over shelf life along with proposed plan (protocol) for ongoing stability studies

# Drug Product Quality Review per IQA

I. Drug Product Quality Reviewer's Role in IQA

II. Drug Product Quality Review Essentials

**III. Common Deficiencies in Drug Product Quality Review**

# Drug Product Quality Review per IQA

## List of IQA Deficiencies

- Drug Substance Deficiencies
- Drug Product Deficiencies
- Process Deficiencies
- Microbiology Deficiencies
- Facilities Deficiencies
- Biopharmaceutics Deficiencies
- Labeling Deficiencies
- Environmental Analysis Deficiencies

# Drug Product Quality Review per IQA

## Major Deficiencies

- Unqualified impurity levels if toxicology studies are required for qualification
- New source of API is needed
- New site of the finished dosage form (FDF) manufacture is needed
- Unacceptable physical properties
- Need for full-term stability to establish expiration dating because of failing accelerated and intermediate data
- New packaging system is needed when system is not properly delivering the proper dose
- New analytical methods are needed because method is not stability indicating or is not sensitive enough, and significant method changes are necessary
- Critical quality attributes are not identified or controlled
- Environmental assessment is not provided for plant-derived products

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

### 1. Drug Substance (or API)-*Common Deficiencies*

- ✓ Failure to provide complete list of physiochemical properties of drug substance
- ✓ Inadequacy of information (details in polymorphism, aqueous solubility, etc.)
- ✓ Inadequacy of control of drug substance (polymorphism, stereochemistry, particle size etc.)
- ✓ Failure to provide adequate justification for specifications (impurities, particle size, assay for counter ion etc.)
- ✓ Failure to justify potential genotoxic impurities
- ✓ Failure to control compendial impurities
- ✓ Failure to provide equivalency studies between in-house method and USP method
- ✓ Failure to provide sufficient information on reference standards (identified impurities)
- ✓ Failure to demonstrate stability indicating ability of methods
- ✓ Failure to justify retest date of drug substance > 12 months

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

## 2. Composition / Formulation – *Common Deficiencies*

- **Overage**: Failure to fully justify the use of overage
  - ✓ *Justification by analysis of RLD, literature, PD study, etc.. Any use of overage of drug substance to compensate for Process loss, degradation or to extend shelf life is highly discouraged (refer to ICH Q8(R2))*
- **Exceeding IID**: Failure to justify the amount of excipients that exceeds IID
  - ✓ *The MDI of excipients should be calculated based on MDD and dosage forms of all strengths*
- **Antioxidant/Preservative**: Lack of justification for the use of antioxidant or preservative which is not used in other FDA approved drug products
- **Dose Dumping**: Lack of control (mainly MR product, reformation needed)
- **Large Tablet/Capsule Size**: Tablet/capsule size is significantly larger than RLD which potentially causes medication difficulty
  - ✓ *Refer to Guidance for Industry "Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation": https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf*

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

## 2. Composition / Formulation – *Common Deficiencies*

- ✓ Failure to provide justification for the use of an ingredient not listed in IID
- ✓ Failure to justify the use of ingredients that are known to cause potential allergic reaction (requiring declaration/warning) to a specific population (such as FD&C Yellow No. 5 and/or FD&C Yellow No. 6, Phenylalanine, Sulfite etc., refer to 21 CFR 201.20-22 and CFR 202.20)
- ✓ Failure to justify the accumulative amount of iron > 5 mg/day resulted from multiple Fe-containing ingredients
- ✓ Failure to provide quantitative composition of colorants and/or DMF #/LOA
- ✓ Failure to address potential medication error due to similar color, shape, weight, and size of dosage forms with different strengths

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

### 3. Control of Excipients – *Common Deficiencies*

- Missing COA acquired by sponsor
- Failure to comply with compendial standards
- Failure to justify the cumulative amount of residual solvents from multiple excipients

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

## 4. Control of Drug Product – *Common Deficiencies*

- Inadequate ID testing – single or non-discriminative ID tests
- Lack of testing on split tablets
  (Refer to Guidance for industry: "Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation"
  *https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269921.pdf)*
- Lack of justification for exclusion of microbial limit tests (susceptible to microbial contamination due to intrinsic hygroscopicity of DP, moisture content, manufacturing process-wet granulation, etc.)
- Lack of justification for proposed limits for identified and total impurities (per ICH, compendial standards, comparison with RLD using the same method of analysis)
- Lack of scientific rationale for definition of process/degradation impurities
- Elevated limit for process impurities without justification

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

## 4. Control of Drug Product – *Common Deficiencies*

- Lack of control of known degradation products (per other approved drug products, literature or scientific reports etc.)
- Failure to provide sufficient information on reference standards for degradation products
- Analytical methods are incapable of quantitating particular degradation products or non-stability indicating
- Analytical method for impurities is not properly validated (RRT/RF/LOQ of each identified impurity should be provided. Also, method validation should cover the appropriate range, e.g. lower limit, LOQ)
- Failure to submit reference standard data for impurities (Sponsor should make all efforts to acquire or synthesize and characterize impurity reference standards)

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

## 5. Container Closure – *Common Deficiencies*

- Lack of leak test for blister packs
- Failure to demonstrate compliance with USP<661> (materials) and/or <671> (performance) requirements
- Insufficient data for extractables for injection DP

# Drug Product Quality Review per IQA

## III. Common Deficiencies in DP Quality Review

## 6. Stability/Shelf-Life Analysis – *Common Deficiencies*

- Failure to update stability protocol to reflect the up-to-date specifications
- Failure to provide data to demonstrate compliance with revised specifications (e.g. dissolution test etc.)
- Failure to provide sufficient data to justify proposed bulk packing
- Failure to provide sufficient data under in-use conditions to justify the use of large containers (larger than RLD) for DP which is known to be hygroscopic and susceptible to oxidation/hydrolysis due to frequent exposure to air
- Failure to provide justification for observed TRENDS (decreasing dissolution, increasing degradants, etc.). Lack of root cause analysis and/or risk mitigation strategy for such trends
- Lack of mass balance in stability data

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*Thank you!*

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