

Combination Product Assessment for ANDAs

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CDER | US FDA

Pharmaceutical Quality



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



Pharmaceutical Quality



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



Drugs are no different.



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



Pharmaceutical quality is
assuring *every* dose is safe and
effective, free of contamination
and defects.



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

Purpose/Importance?

To ensure generic form is **therapeutically equivalent** to its reference listed drug (RLD):

- Produces the same clinical effect and safety profile as the RLD
- Under the conditions specified in the product labeling and can be freely substituted for its RLD.

Objectives:

Discuss various aspects of quality assessment of a generic combination drug-device product



ANDA applicants are better equipped to submit quality information



Reduce assessment time and in turn will lead to *faster approval of generic parenteral drug products*

Combination Products

- Combination products are defined in 21 CFR 3.2(e).
- Combination of two or more regulated components: drug-device, biological-device, drug-biological, drug-device-biological.
- This presentation: Combination product with drug-device constituent parts.
- Primary mode of action (PMOA) is that of a drug → CDER is assigned as the Lead Center.

Combination Product Types

Three types of Drug-Device Combination Product:

- Pre-filled with the drug
- Co-packaged with the drug product, or
- Separately distributed but labeled for use together

ANDA Assessment:

- Assessment of CDER-led Combination Product ANDA:
 - Quality
 - Labeling
 - Bioequivalence
 - Division of Clinical Review (DCR) - Comparative Analyses.
- Labeling, Bioequivalence, DCR → Office of Generic Drugs (OGD)
- Quality → Office of Pharmaceutical Quality (OPQ).

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Quality Assessment of Combination Drug Products:



- Quality assessment of a drug device combination product can be divided into two parts:
 - CDER/OPQ Assessment:
 - **Quality attributes** pertaining to drug substance, drug product, microbiology, manufacturing process, and facilities.
 - CDRH/OPEQ¹ Assessment:
 - OPQ Assessor (OLDP²): Intercenter Consult Request (ICCR) to CDRH; evaluate **functional attributes** → Performance testing
 - OPQ Assessor (OPMA³): ICCR to CDRH → *Device Quality Systems/ Facilities Assessment (21 CFR 820)*

¹CDRH/OPEQ = Center for Devices and Radiological Health/ Office of Product Evaluation and Quality

²OLDP = Office of Lifecycle Drug Products

³OPMA = Office of Pharmaceutical Manufacturing Assessment

Drug Product Quality Assessment



- Drug Substance
 - Physicochemical properties: Description, pH, solubility, chirality, hygroscopicity, etc.
 - Impurities: Organic, Inorganic, Residual Solvents
 - Specifications (Type II DMF or USP, as applicable).

Drug Product Quality Assessment



- Combination Drug Product = Drug + Device
 - Drug
 - Critical Quality Attributes
 - Device
 - Functional Attributes/ Performance Testing

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Drug Product Quality Assessment



Drug Product

Product Quality Tests, Universal USP<1>	
Description	
Identification	
Assay	
Impurities	
Container Content	USP <697>
Container-Closure Integrity	
Particulate Matter in Injection,	USP <788> and Visible Particulates in Injections, USP <790>
Sterility	USP <71>
Bacterial Endotoxins Tests,	USP <85> or Pyrogen Test, USP <151>
Residual Solvents,	USP <467>
Other tests (as applicable): pH, Osmolality, Viscosity	
Conformance to USP <1>, USP<232>/ ICHQ3D	
Packaging -	USP<381>, USP<659>, <660>, <661>, <661.1>, <661.2>, <1663>, <1664>

Reference:
- USP<1> Injections and Implanted Drug Products (Parenterals) –Product Quality Tests

Drug Product Quality Assessment



Drug Product

Product Quality Tests for Specific Parenteral Dosage Forms USP<1>	
Injection Solutions	For Prefilled Syringes: Glide Force; Break Loose Force For Multiple-Dose Containers: Antimicrobial preservatives
Sterile Powders (Lyo or Powder Fill) for Injections	<ul style="list-style-type: none">▪ Uniformity of Dosage Units, USP <905>▪ Completeness and Clarity of Solution▪ Water or Solvent Content▪ Reconstitution Time
Injection Suspensions	<ul style="list-style-type: none">▪ Uniformity of Dosage Units, USP <905>▪ Particle Size Distribution▪ Dissolution▪ Resuspendability▪ Sedimentation Rate and Volume▪ Syringeability
Injection Emulsions	<ul style="list-style-type: none">▪ Globule Size Distribution in Lipid injectable Emulsions, USP <729>

Drug Product Quality Assessment



- Packaging System:
 - Sterility/ Container Closure Integrity Testing (CCIT) of Primary CCS
 - Qualification of CCS: USP <381>, USP <660>, USP <661>
 - Glass Delamination
 - Extractables and Leachables – All applicable information included in submission:
 - Risk based approach during assessment

Drug Product Quality Assessment

In general, Low risk - Extractables and Leachables

- Most sterile powders for Injections
- Simple aqueous solutions
- When vial-stopper presentation comprises of Film coated rubber stoppers



For low risk parenteral belonging to above categories, USP qualification tests (<381>, <87>, <88>) for the rubber stopper may be sufficient.

Important: Information stated above is not prescriptive.

Drug Product Quality Assessment



High risk - Extractables and Leachables

- USP <1663> and USP<1664>
- AET calculation
- If any extractable > AET, leachable study should be provided
- If any leachable > AET, supporting tox studies should be provided to deem the risk as low



Drug Product Quality Assessment



- Combination Drug Product = Drug + Device
 - Drug
 - Critical Quality Attributes
 - Device
 - Functional Attributes/ Performance Testing



CDRH Assessment

- Evaluation of Device Constituent part of the Combination Product:
 - ***Performance Testing:*** Dose Accuracy (expelled volume – USP<697>), Break loose Force, Glide Force → Comparable to RLD

CDRH Assessment

- Performance Testing:



Contains Nonbinding Recommendations

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CDRH Assessment



- Need for Device Quality Systems/ Facilities assessment
- CGMP requirements → 21 CFR part 4

Challenge Question

- Which of the following is an example of a drug device combination product?
 - Pre-filled with the drug
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 - All of the above

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Conclusion:

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Thank you !!

