3.1 Packaging: assessment and common issues

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Assessor

Packaging

- Packaging- definition- as a reminder
- Assessment focus
  - PQ requirements and assessment of packaging suitability
  - Quality control
- Examples of common issues and assessment tips

Packaging

- WHO TRS 902 Annex 9 defines packaging as ' *the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.*'

- US FDA defines container closure system as '*the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.*'

Assessment focus

- Proposed packaging (container closure system) should be supported by:
  - detailed description of materials of construction, appearance, dimensions, pack sizes etc.
  - data demonstrating suitability for the intended use
  - adequate control strategy (specification) to ensure/monitor suitability of all received lots

We assess, based on the submitted information/data, whether the proposed container is suitable for the product and whether the applicant has adequate specification to ensure quality of all future container lots

Composition/formulation of packaging materials, e.g. polymers

- The principal polymer
- Residues from polymerization, e.g. monomers, trapped solvents, catalysts, etc.
- Processing aids, such as lubricants and mould release agents,
- Additives such as plasticizers, fillers and extenders, heat stabilizers, colourants, whiteners, preservatives, etc…
  - For example, a PVC film or a rubber stopper from two different manufacturers may have different compositions
  - Depending on the actual composition, the protective performance of the containers may differ
  - Each of these substances may potentially be leaching to the product or may interact with the product

Packaging materials Suitability- General

Safety	Protection	Compatibility	Performance
Should be acceptable for use: should be made of materials regarded safe for human use and should not leach harmful or undesirable amounts of substances	Should have acceptable barrier properties against moisture, oxygen, light, microbes and contaminants	Should not interact with the product; should not adsorb/absorb the product components	Accompanying measuring devices should allow reproducible dose measurement

Suitability

- Specific requirements for a container closure system may vary depending on
  - The nature of the container – e.g., glass vs plastic
  - Product type/formulation- e.g., injectable vs orals; liquid vs solid,
  - Route of administration- e.g. inhalation vs IM/IV vs oral route
  - Duration of treatment- long term vs short term

Containers for solid orals

- Plastic containers, blisters or strips

	Requirements
Safety	Declarations as to compliance with appropriate food additive regulations (e.g. USFDA or EU regulations)
Protection	Water vapour permeation (WVTR) and light transmission (LT) rate for e.g. as per USP-671, on a case by case basis;
Compatibility	Stability data for the packaged FPP
Performance	Reproducibility for measuring devices e.g. for powders or granules

- Examples:
- HDPE bottle pack
- Al based sachets
- Al/PVC/PVDC
- Al/PVC
- Al/PVC/PE/Aclar

Containers for oral liquids

- Plastic bottles, glass bottles

	Requirements
Safety	Food grade declaration and tests as per USP 660/Ph.Eur 3.2.1 (Glass); USP 661/Ph.Eur.3.1.10 (Plastics)
Protection	Plastics: WVTR (weight loss) and on a case by case basis LT, as per USP 671
Compatibility	Stability data for the packaged FPP; leachables may also need to be considered for plastics for chronic treatment
Performance	*Appropriateness* and reproducibility for measuring devices for e.g. as per PhInt

- Examples
  - PET bottles
  - HDPE bottles
  - Type III , IV Glass bottles

Containers for injectables

- Glass, plastic

	Requirements
Safety	Glass as per USP 660 and USP 1660 Plastic as per USP 661/Ph.Eur. E.g., 3.1.7; 3.1.14;
Protection	Water loss for liquid large volume injectables in plastics; LT for glass/plastics on a case by case basis; Container integrity (microbial or dye ingress or other methods)
Compatibility	Glass: FPP stability data (solid products); delamination (USP1660) (for liquids) Plastics: extractable/leachables study; FPP stability data
Performance	Appropriateness, safety/compatibility and reproducibility of measuring devices that may be included in the product pack

- Examples
  - Type I, II, IS glass vials or ampoules
  - PE, PVC, PP bags
- Extractables: substances that may be released when the material is challenged with strong solvents and/or extracting conditions
- Leachables: substances that may be released to the FPP under normal storage conditions

Containers for injectables- contd

- Rubber stoppers

	Requirements
Safety	As per USP 381 (includes USP 87/88) or Ph.Eur 3.2.9 Composition of the rubber or at least declaration that the material is free from 2-mercaptobenzothiazole, nitrosamines.
Protection	USP 381/Ph.Eur 3.2.9; Container integrity testing together with the glass;
Compatibility	Extractables/leachables studies (on a case by case basis); accelerated and stability data
Performance	e.g. penetrability, resealing as per USP381/Ph.Eur 3.2.9

- Examples
  - Butyl rubber
  - Halobutyl rubbers

Specifications

- QA controlled specifications for the primary as well as for functional secondary packaging components should be maintained and submitted for review

- Assessment focus is in ensuring that at least the following tests as applicable are included
  - appropriate identification test for the material in immediate contact with the product
    - e.g. lacquers for Al foil (by IR), Al foil (chemical method), polymer layers (by IR) in immediate contact with the product
  - certain tests that relate to the protection performance of the container
    - e.g. thickness of Al foil, dimensions for rubber stopper/glass mouth, wall thickness
  - Containers for liquids/injectables
    - e.g. all relevant USP 660 tests for glass; USP 661 for plastics for liquids, USP 381 for rubber stoppers

Other aspects

- Washing and sterilization of components for sterile products
  - Should be supported by process validation data (reported as part of P.3.5)
- Sealing quality/integrity
  - Container integrity testing for sterile products
    - One time test reported as part of product development
    - Routine leak testing performed as part of the product manufacture
- Child-resistance, Tamper-proof/tamper evident, ability to open, anticounterfeit measures- these requirements vary depending on specific jurisdictions.

Common issues

Light transmission

- Data on LT missing
  - API/Product shown to be photostable- no further information required
  - Product shown to be or API known to be unstable- LT data should be requested depending on the nature of the proposed container
  - Some of the container components are not expected to be light protective, e.g., clear PVC with no UV deterrents
    - Product shown to be photo stable- no further information required
    - Product/API known to be unstable- the outer carton is considered functional
      - Storage statement on labels should include " Store in the original container to protect from light"

Moisture permeation

- Data on WVTR (water vapour transmission rate) missing
  - One or more of the product components may be of hygroscopic nature,
  - Moisture may affect not only chemical degradation but also general table/capsule characteristics, polymorph form etc…
  - Highly important for liquid formulations (water loss)
  - WVTR also serves as a reference value to support future changes
  - Therefore, at least one time data for the proposed container should be submitted
    - However, for Al/Al based blisters, strips or sachets, data may not be pursued provided that there is good in-process control of seal quality

Permeability values for common container components

GENERIC POLYMER NAME	WATER BARRIER	OXYGEN BARRIER
LOW DENSITY POLYETHYLENE (LDPE)	4	200
HIGH DENSITY POLYETHYLENE (HDPE)	2	25
POLYPROPYLENE HOMOPOLYMER (PP)	2.5	60
POLYPROPYLENE COPOLYMER	3.0	80
POLY VINYL CHLORIDE (PVC)	18	1
PLASTICISED (PVC)	80	100
POLY VINYLIDINE CHLORIDE (PVdC) (COATINGS)	0.1	0.5
CELLULOSE ACETATE (CA)	750	80
ETHYLENE VINYL ACETATE COPOLYMER (EVA)	40	600
POLYTETRAFLUORO ETHYLENE (PTFE)	0.4	1
POLYMONOCHOR TRIFLUORO ETHYLENE (PCTFE)	0.01	1

In $g/m^2/day$

- Known values for certain container components may not necessarily reflect the performance of a given container system. Performance also depends on
  - Thickness
  - Method sealing (e.g. induction sealing)
  - Applied torque, etc.
  - Therefore, MVTR and LT as necessary should be established for the specific proposed container system

Extractables/leachables data for injectables

- Absence of data on extractables/leachables profile on rubber stopper/plastic containers
  - When potential for interactions with product are expected to be low, e.g., powders packaged in rubber stoppered glass, or certain aqueous based injectable products with no surfactant or other agents that may promote extraction
    - No additional extractability study other than the standard tests included in USP 381 (including biological reactivity tests) may be pursued.
    - Accelerated and long term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as sorption
  - When the potential for interaction is expected to be high, e.g., products with high surfactant concentration, high ionic strength or low/high pH etc…
    - Extractables as well as leachables (e.g. on stability samples of the FPP) as tested with validated sensitive analytical methods such as LC/MS, GC/MC should be pursued.

Container vs Shelf life

- Proposals to support/extrapolate a shelf life for a product packaged, for example in Al/Al blister based on available stability data on batches packaged with HDPE bottle.
  - The proposed Al/Al blister may not necessarily be as protective as the HDPE bottle
  - Therefore, shelf life should be supported either
    - by demonstrating that the Al/Al is at least as protective as the HDPE bottle pack (i.e., by submission of comparative WVTR data) or
    - based on adequate stability data on batches packaged with the Al/Al (i.e. irrespective of the data in HDPE bottle pack)

Measuring device

- Proposed measuring device may be inappropriate for the intended use, examples
  - proposing a10ml oral syringe for doses less than 1ml
  - proposing measuring cap for low volume doses
    - Presents difficulties to health care worker/patient in withdrawing accurate doses
  - inappropriate shape/size of cups for measuring coated granules

Cup vs 10ml vs 1ml oral syringe consider doses of 3ml and 0.6ml

Measuring cap accuracy and reproducibility

- Consider a dose of 4gm of oral coated granules
- Reproducibility result (uniformity of mass of delivered dose):
  - all 20 individual measured mass were within 15% variation compared to the average mass of the 20 measurements
- Assessors also noted that 7 out of the 20 individual results were below 85% of the target dose
- Reproducible?
- What about dosing accuracy?

Summary

- Assessment of packaging focuses on
  - suitability of proposed container and
  - proposed controls for routine monitoring of suitability
- Suitability requirements vary depending on nature of container, product type, formulation, route of administration and duration of treatment

Useful references

- WHO Quality guideline (WHO TRS 970, Annex 4)
- Guidelines on packaging for pharmaceutical products (WHO TRS 902, Annex 9)
- Container closure systems for packaging human drugs and biologics (FDA Guidance for Industry, May 1999)
- Guideline on Plastic immediate packaging materials - EMEA/CVMP/205/04
- ICH quality guidelines
- USP /Ph. Eur.
- Previous talk on packaging by Chemolow A, available on PQ website

- Thank you for your attention