How to Select Pharmaceutical Packaging for Parenteral Drugs & Biologics

An introduction

Charbel Tengroth

CNPPA Suzhou Dialogue 2018-09-01

Outline

- Introduction to pharmaceutical packaging
- Primary packaging presentations for parenteral drugs: choices and selection criteria
- Common primary packaging issues
- Introduction to injection devices and impact on primary packaging
- Summary and questions/discussion

Pharmaceutical packaging

- Considered part of the drug product: therefore generally subject to same regulations as drug (e.g. GMP)
- Purpose of packaging is to preserve the stability and quality of medicinal products, and to protect them against all forms of spoilage and tampering

Pharmaceutical packaging

- Pharmaceutical packaging may consist of Primary Packaging, Secondary (Tertiary) Packaging, and Label and must:
  - Protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations;
  - Protect against biological contamination
  - Protect against physical damage
  - Carry the correct information and identification of the product

Pharmaceutical packaging

- Primary packaging components are in direct contact with the drug: must demonstrate compatibility:
  - The packaging itself does not have an adverse effect on the product (e.g. through chemical reactions, leaching of packaging materials or absorption)
  - The product does not have an adverse effect on the packaging, changing its properties or affecting its protective function
- Compatibility must be demonstrated through intended shelf life of the product (through acc. & real-time stability studies)

Parenteral drugs / Biologics

- Parenteral drugs are intended for injection
  - Intra-muscular
  - Intra-veneous (infusion)
  - Sub-cutaneous
- Many presentations
  - Bags
  - Vials
  - Syringes (luer fitting or staked needle)
  - Cartridges
  - Glass ampoules
- Dosage forms
  - Liquid for injection
  - Lyophilized powder (to use with diluent before administering)

General considerations for parenteral drug primary packaging

- Maintain sterility
  - Sterilized components
  - Aseptic filling/process
  - Hermetically sealed
- Particle free
  - Foreign matter
  - Aggregates / degraded product
  - Glass lamellae / rubber
- Inspectable
  - Transparent material
  - Label
  - Device

Consider the three P’s

- Product
  - Specific requirements, e.g. inert
- Process
  - Existing manufacturing lines
  - Low-waste process
- Patient
  - Needs, human factors
  - Setting for drug delivery (home, clinic, emergency)

Selection criteria

Concern	Glass vial	Plastic vial	Glass syringe	Plastic syringe	DCC glass	DCC plastic	Ampoule	Cartridge glass	Cartridge plastic	Custom glass	Custom plastic
Unstable solution											
Multi-dose											
Glass delamination										?	
Home use											
Metal exposure			?	?						?	?
E & L											
Gas permeation											
Cost											
Time											

Product value impact

Low value drug

- Vials
- Ampoules
- Bags
- Lyo powder, no co-packed diluent

High value drug

- Pre-fillable syringe
- Infusion kits
- Injection pens
- Auto-injector

Cost of overfill					
Injected Volume	**Overfill Volume**	**Units sold per year**	**At $100/ml**	**At $50/ml**	**At $25/ml**
0.5	0.5	100,000.00	$ 5,000,000	$ 2,500,000	$ 1,250,000
0.5	0.5	500,000.00	$ 25,000,000	$ 12,500,000	$ 6,250,000
0.5	0.5	1,000,000.00	$ 50,000,000	$ 25,000,000	$ 12,500,000
0.5	0.5	2,000,000.00	$ 100,000,000	$ 50,000,000	$ 25,000,000
0.5	0.5	20,000,000.00	$ 1,000,000,000	$ 500,000,000	$ 250,000,000

Use considerations

Frequent dosing (eg daily)

- Multi-dose, multi-use cartridge/pen with luer fitted needle
- (Multi-dose) vial with single use syringes
- Pre-filled syringe (no device)

Non-frequent dosing (weekly or reactive)

- Ampoules
- Multi- or single dose auto-injector
- Pre-filled syringe (staked needle)

Common issues with Primary packaging

- Extractables / leachables: rubber closure leaches harmful compounds or affects stability of drug
- Incompatible components causes issues with container closure integrity (during filling process or during shelf life)
- Silicone: excess silicone causes particle formation. Too little, or interaction with content causes difficulty to inject (syringes or cartridges)
- Glass: leaching chemicals (alkali metals) destabilizing drug. High-pH formulation causing pitting of glass and formation of glass particles / lamellae
- Insufficient washing / depyrogenization causes foreign matter in drug
- Insufficient sterilization causes biological contaminant
- Metal (tungsten) contamination from needle hub in syringe

How to handle risk with packaging?

- Start early!
  - Selection of primary packaging components must be done as part of pharmaceutical formulation development
- Be thorough!
  - Study market-specific regulations
  - Generate stability data early (part of development)
  - Don’t wait to do E&L study
- Be smart!
  - Think strategic
  - Re-use selection for family of drugs/formulations
  - Work with supplier (long lead time components)

Injection devices

- Injection pen
  - Multi- or single use
  - Cartridge
  - Uses pen needle
  - Multiple doses, fixed or variable
  - User pushes on the plunger to inject
  - Uses ISO standard cartridges
- Auto-injector
  - Multi- or single use
  - ISO standard Cartridge or pre-filled syringe
  - Pen needle or staked needle
  - Multiple or single dose, fixed or variable
  - Automated injection
  - Often uses automated safety features to protect needle
- On body injector
  - Large dose / long injection time / frequent dosing (insulin pump)
  - Automated features
  - Communicating

Growth driving factors of injection device market

- Diabetes: most people suffering from diabetes are not treated
  - New therapies under development (less frequent dosing)
- Allergy: Epinephrin injection devices a very large market and growing
  - Epipen an aging design, market ripe for disruptive change
- New therapies (mostly) based on biologic drugs
- Biosimilar drugs – Device typically chosen to mimic functions of innovator product

Primary packaging considerations for device products

- Siliconization process crucial for device performance
- Points of contact between primary package and device defined and controlled
  - Neck / shoulder
  - Syringe flange
  - Distance support point and needle point (will determine injection depth)
- Annealing and glass forming process – impact strength

Case study – Primary Packaging selection

- Drug is a mAb in a liquid stable formulation
- Oncology indication
- Intended for sub-cutaneous injection in clinic, or by caregiver
- Promising early clinical results
- High-value drug
  - Precise dosing required
- Phase 1 clinical trial completed
- Project ready to prepare for Phase 2 clinical manufacturing
- 1 ml long ISO standard syringe preferred by selected filling site

Will proceed with a ready-to fill syringe combination product!

Packaging selection – Early steps

Internal activities

- Start combination product development activities
  - Design & Development plan
  - User and Product req spec
  - Risk management activities
- Clinical manufacturing plan
  - Coordinate with packaging component deliveries for early stability screening studies
- Packaging compatibility study plan

External activities

- Prior knowledge search
  - Similar products / formulations
  - Patient / user needs through formative HF studies
  - Regulatory reqs
- Contact suppliers
  - Product offerings
  - Quality audits
  - Supply assurance and lead times, etc

Packaging selection – continued work

- Continue work following Design Control guidelines (DHF, RM, etc)
- Evaluate product comp screening studies
- Primary pack candidate selection (likely primary and back-up)
- Start E&L work
- Stability studies

- Requires dialogue with packaging component suppliers
  - Formulation: pH, surface active excipients, ionic strength, etc
  - Physical properties (extrusion forces)
  - Known leachates

Packaging selection – Closing out

- Finalize accelerated stability study
- Continued real-time stab studies
- Finalize design verification
- Close out E&L work – final selection of commercial packaging
- Plan for validation of combination product
- Plan for closing of DHF

- Timing for this is Drug Product process validation / Phase 3 clinical manufacture
  - Some work may have to carry on towards launch
- Do not want to risk Phase 3 clin manufacture

Summary

- Pharmaceutical packaging critical to product quality and patient safety
- Packaging selection process part of pharmaceutical development
  - Start early
  - Be thorough
  - Be smart
- Parenteral / biologic drugs have specific demands on packaging
- Devices require even more control on the packaging manufacture
- Drugs for parenteral administration expected to grow significantly over next ten years, driven by
  - Increased treatment of common conditions (diabetes, heart disease)
  - New therapies (specific conditions)
  - Biosimilars