PDA Training Container Closure Systems

Setting of Specifications/ Submission Documentation

Content

- Technical/ Quality specification
- Regulatory specification
- Technical drawing
- Regulatory drawing
- DMF for US submission

Content of a specification for a packaging component
(Bilateral agreement between supplier and customer)

- Material specification – detailed description incl. material type
- All properties/ parameters tested with the respective testing standard
- DEL (standard or customized)
- Sampling plan (if not DEL)
- Compliance with regulatory standards incl. pharmacopoeias
- Compliance with technical standards (ISO, EN etc.)
- Requirements for change management
- Shipping instructions

Content of testing standard of packaging components

- Chemical identity testing of materials, e.g.
  - IR-spectroscopy of polymers
  - thermal analysis of polymers
  - hydrolytic resistance of glass
- Specific properties (e.g. light protection)
- Functional tests
- Dimensional testing

Defect Evaluation List

- Standardized sampling and testing of packaging components (incl. description of test methods)
- Standardized classification of known defects
- Jointly developed and agreed between packaging suppliers and users of the packaging components (e.g pharmaceutical industry)
- Widely used in Europe for quality assurance of packaging components
- Sampling for quality control testing
  - randomized according to pre-defined sampling tables
  - DIN/ISO 2859 or
  - as an agreement between supplier and customer

Defect Evaluation List

Sampling for quality control testing

- at the supplier as final quality control
- at the customer for release testing

alternatively

- sampling at the the supplier and shipment of the samples to the customer (tailgate sample)
- take over of quality testing results of the supplier by the customer after supplier qualification

Defect Evaluation List - Sample table **qualitative** testing

Batch size N	Test samples n	n/N (%)
≤ 500	N oder 80	16 - 100
501 - 1200	80	6,7 - 16
1201 - 3200	125	3,9 - 10,4
3201 - 10000	200	2 - 6,2
10001 - 35000	315	0,09 - 3,1
35001 - 150000	500	0,3 - 1,4
150001 - 500000	800	0,2 - 0,5
> 500000	1250	< 0.25

Defect Evaluation List - Sample table **quantitative** testing

Batch size N	Test samples n	n/N (%)
≤ 500	N oder 13	2,6 - 100
501 - 1200	20	1,7 - 4
1201 - 10000	32	0,3 - 2,7
10001 - 35000	50	0,14 - 0,5
35001 - 500000	80	0,02 - 0,23
> 500000	125	< 0.025

Defect Evaluation List - Predefined defect classes

- Defect class 1 (critical defects)
  - Packaging material not usable (e.g. wrong printing, deformation, breakage)

- Defect class 2a and 2b (Major defects)
  - Usability of packaging material markedly (2a) or moderately (2b) impaired (e.g. out of tolerance specification with major or moderate impact on manufacturing process)

- Defect class 3 (Minor defects)
  - Usability of packaging material slightly impaired (e.g. cosmetic defects)

Defect Evaluation List - Defect evaluation

AQL = Acceptable Quality Level

- The agreed AQL is the quality level at which a delivery or a batch will be accepted with high probability in accordance with sampling instructions
- It provides the supplier and the customer with valuable indications of the quality of the corresponding product and is also useful for quality management
- The AQL value is part of the random sampling tables

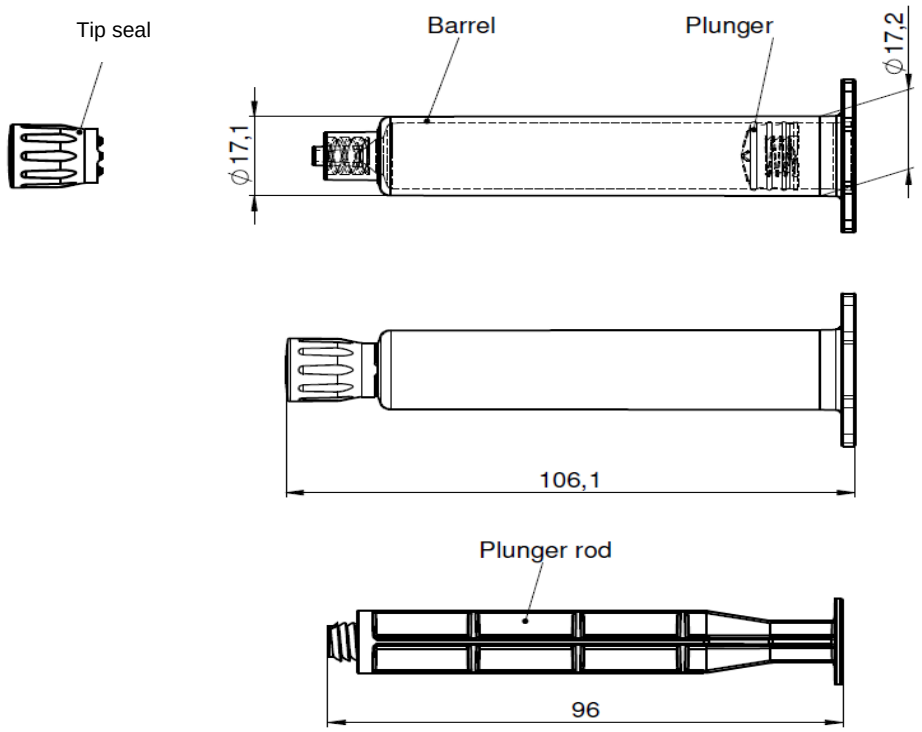
↳ The more critical a defect the lower is the AQL

Defect Evaluation List - Sample plan and AQL values of qualitative testing

Batch size N	n	AQL								
		0.1	0.25	0.4	0.65	1.0	1.5	2.5	4.0	6.5
up to 500	N or 80	0	1	1	1	2	3	4	6	9
501 – 1 200	80	0	1	1	1	2	3	4	6	9
1 201 – 3 200	125	0	1	2	2	3	4	6	8	12
3 201 – 10 000	200	1	1	2	3	4	6	8	12	18
10 001 – 35 000	315	1	2	3	4	6	8	12	18	27
35 001 – 150 000	500	1	3	5	6	9	12	18	27	44
150 001 – 500 000	800	2	4	6	9	13	17	27	41	63
over 500 000	1250	3	6	10	13	18	26	40	61	96

Fig. 15.1: Random sample basic table for qualitative tests (acceptance probability 95 %).

Barrel of pre-fillable plastic syringe – practical example



Barrel of pre-fillable plastic syringe – practical example

- Material description
  - Plastic barrel: Cycloolefin polymer (COP)
  - Sealing element: COP outer cover with thermoplastic elastomer (TPE) sealing element

- Material conformity
  - The COP plastic barrel with TPE tip seal complies with the following guidelines or regulations:
    - Ph.Eur. 3.2.2 Plastic containers and closures for pharmaceutical use
    - USP-NF <661> Containers – Plastics
    - JP General Tests, Processes and Apparatus - 7.02 Test Methods for Plastic Containers
    - EMEA/410/01 <Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal>
    - Commission Directive 94/62/EC <Heavy metals in packaging materials>

Barrel of pre-fillable plastic syringe – practical example

Test Specification

Test	Acceptance criterion	Method
Appearance - barrel	colorless, transparent	visual
Identity (IR) - tip seal	has to comply with reference spectrum	IR-spectroscopy
Identity (IR) - barrel	has to comply with reference spectrum	IR-spectroscopy

Barrel of pre-fillable plastic syringe – practical example

Test Procedure

- Appearance – barrel
  Conduct a visual inspection of the packaging component for e.g. its appearance and for obvious defects.
- Identity (IR) – tip seal
  Conduct the test procedure as per instructions and stipulations of Ph.Eur. 2.2.24 for example recording by attenuated total reflection.
- Identity (IR) – barrel
  Conduct the test procedure as per instructions and stipulations of Ph.Eur. 2.2.24 (recording by attenuated total reflection)
  or
  prepare a foil of the material (recommended conditions: 3.5 t at 240 °C for 1 min) and measure the IR-spectrum according to Ph.Eur. 2.2.24.

Plunger of pre-fillable plastic syringe – practical example

- Material description
  - Plunger: Bromobutyl gray cross-linked silicone coated

- Material conformity
  - The plunger complies with the following guidelines or regulations:
    - Ph.Eur. 3.2.9 Rubber closures for aqueous parenteral preparations, for powders and for freeze-dried powders
    - USP-NF <381> Elastomeric closures for injections
    - JP General Tests, Processes and Apparatus - 7.03 Test for Rubber Closures for Aqueous Infusions
    - EMEA/410/01 <Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal>
    - Commission Directive 94/62/EC <Heavy metals in packaging materials>

Plunger of pre-fillable plastic syringe – practical example

Test Specification

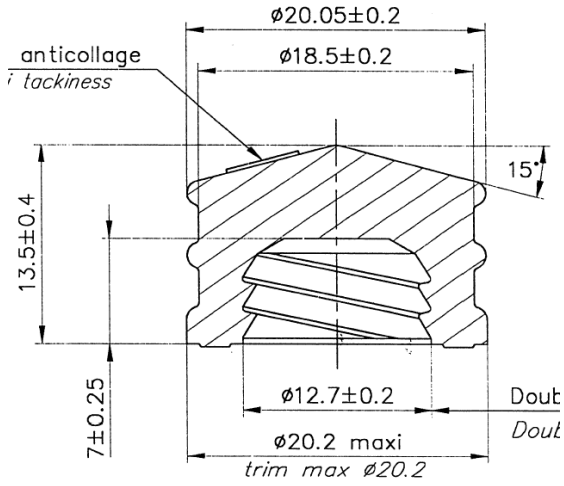
Test	Acceptance criterion	Method
Appearance	gray	visual
Identity (IR)	has to comply with reference spectrum	IR-spectroscopy
Total ash	44.0 - 48.0 %	gravimetric

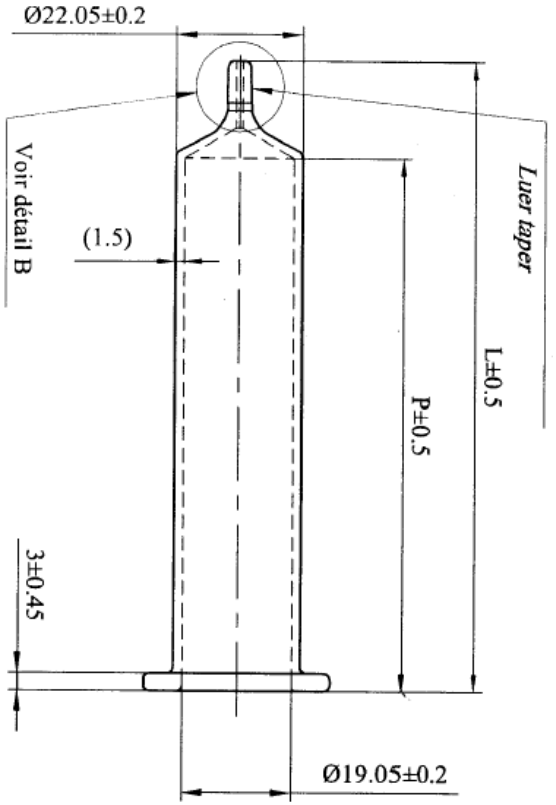
Plunger of pre-fillable plastic syringe – practical example

Test Procedure

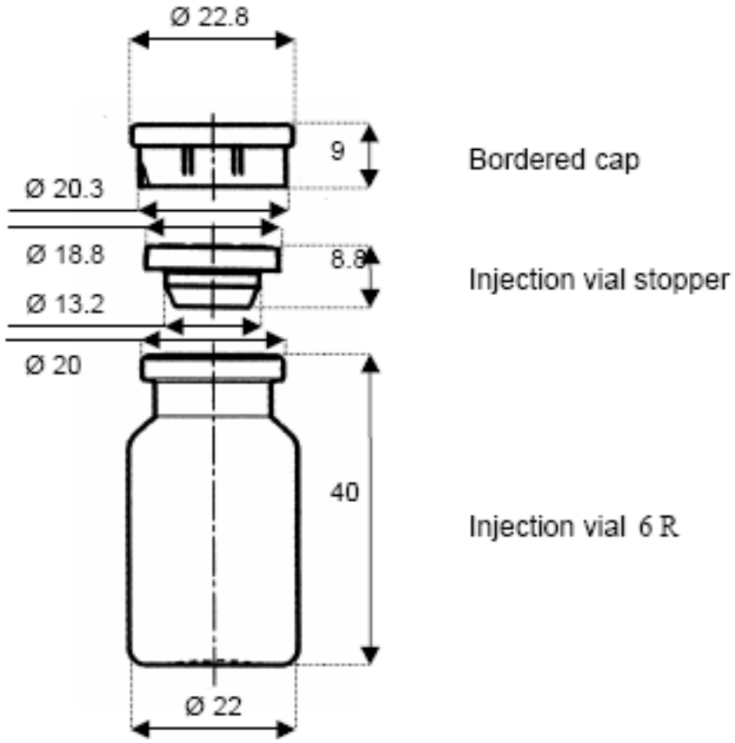
- Appearance
  Conduct a visual inspection of the packaging component for e.g. its appearance and for obvious defects.
- Identity (IR)
  Conduct the test procedure as per instructions and stipulations of Ph.Eur. 3.2.9 and 2.2.24 for example recording by attenuated total reflection.
- Total ash
  Conduct the test procedure as per instructions and stipulations of Ph.Eur. 3.2.9 and 2.4.16.

Detailed technical drawing with all critical dimensions incl. acceptable tolerances contributing to the suitability of a final packaging system



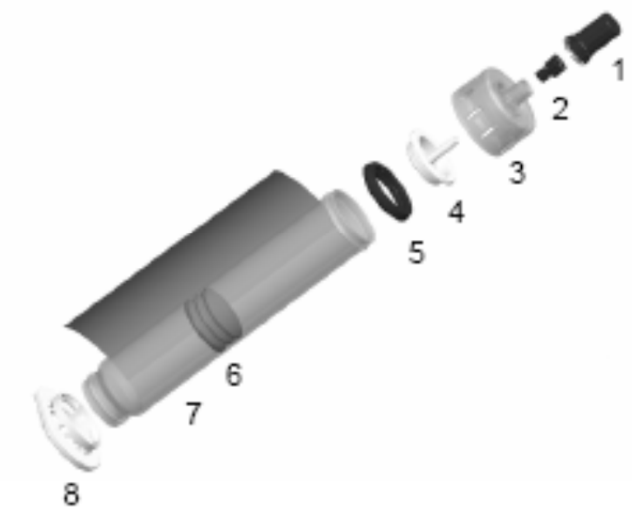


For regulatory purpose the grade of detail of the technical drawing is reduced, otherwise even slight dimensional changes require a full change management



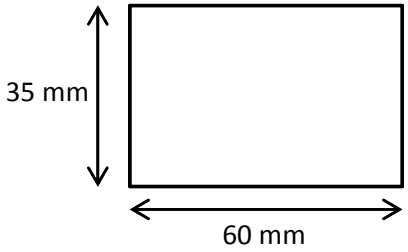
Regulatory drawing

Components	Dimensions
1. Screw cap	26 x 17 mm
2. Tip cap	15 x 10 mm
3. PC cap	36 x 43 mm
4. Luer lid	25 x 35 mm
5. Gasket	7 x 37 mm
6. Plunger	17 x 33 mm
7. Glass barrel	181 x 36 mm
8. Flange	∅ 53 mm



Regulatory Drawing

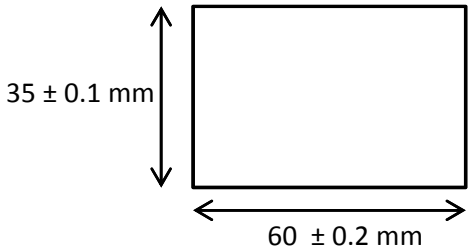
Submission
("contract" with authorities)



Variation

Technical Drawing

Quality Assurance Agreement
(contract with supplier)



Change Control

Change

Drug Master Files (21 CFR 314.420)

A Drug Master File (DMF) ….

- is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs
- the submission of a DMF is not required by law or FDA regulation
- a DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of a drug submission.

Drug Master Files (21 CFR 314.420)

Type I
- Manufacturing Site, Facilities, Operating Procedures, and Personnel

Type II
- Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III
- Packaging Material

Type IV
- Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Type V
- FDA Accepted Reference Information

Drug Master Files (21 CFR 314.420)

Reference is made via a Letter of authorization (LoA)

Each packaging material should be identified by

- the intended use
- components
- composition
- controls for its release
- the names of the suppliers or fabricators of the components used in preparing the packaging material
- the acceptance specifications
- data supporting the acceptability of the packaging material for ist intended use
- toxicological data on the materials

Thank you very much for your attention!!