EDQM webinar

Sterilisation

Critical Quality Aspects – Assessor's viewpoint

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European Pharmacopoeia

- Ph.Eur. 5.1.1 Methods of preparation of sterile products
- Ph.Eur. 5.1.2 Biological indicators and releated microbial preparations used in the manufacture of sterile products
- Ph.Eur. 5.1.5 Application of the F_0 concept to steam sterilisation of aqueous preparations
- Ph.Eur. 2.6.1 Sterility
- Ph.Eur. 5.1.9 Guidelines for using the test for sterility

Guidance

- Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

- Use of ionizing radiation in the manufacture of medicinal products 3AQ4A

- ISO 11137 Sterilisation of health care products – radiation
- ISO 11135 Sterlisation of health care products – ethylene oxide

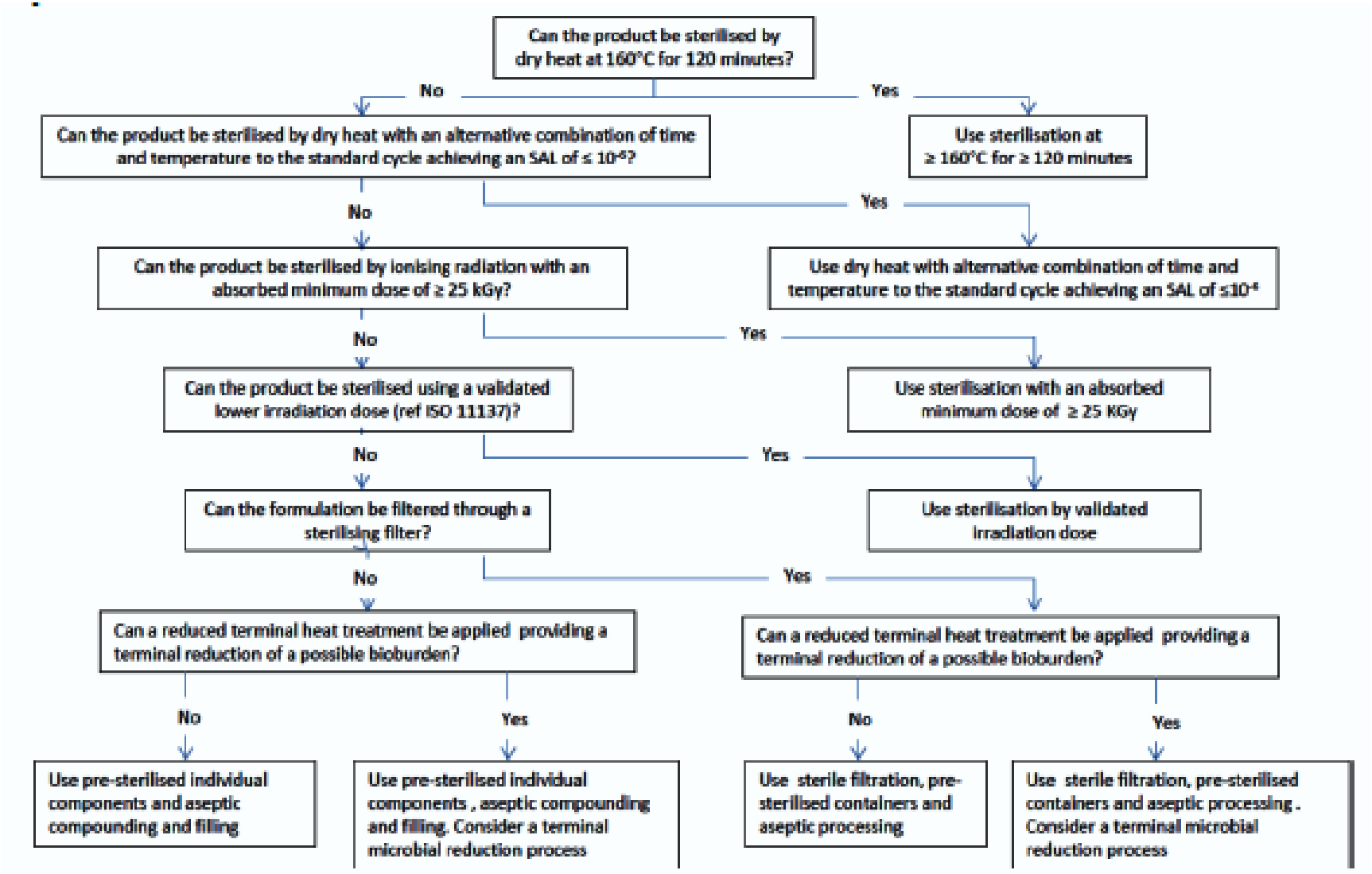
Sterility definition & terminology

- Assured by use of suitable and validated manufacturing process
- Cannot be tested for a batch of drug substance / product
- Testing for sterility: absence of viable microorganisms in the tested unit
- Dependent on factors
  - Bioburden of raw materials
  - Sterilisation procedure
  - Integrity of the container closure system
  - Use of aseptic techniques

Sterility terminology

- Sterility Assurance Level (SAL)
- Acceptable level of $\leq 10^{-6}$
- Probability that 1 in 1,000,000 units which has been subjected to sterilisation is not sterile (i.e. contains viable microorganisms)
- Only applicable to terminal sterilisation (e.g. moist heat and dry heat)
- Not applicable to aseptic processes

Decision tree - dry powder



1. Dry heat sterilisation

- Principle: heat transfer to containers & surfaces
- Use of dry heat oven in which temperature can be set
- Forced ventilation optional
- Standard conditions (according to Ph.Eur. 5.1.1): 2 hrs at 160 °C
- Standard conditions require no validation
- Other conditions (lower temperature or shorter times):
  - Load mapping (cold spots)
  - Lethality variability within load
- Suitable for dry powders

2. Ionization radiation

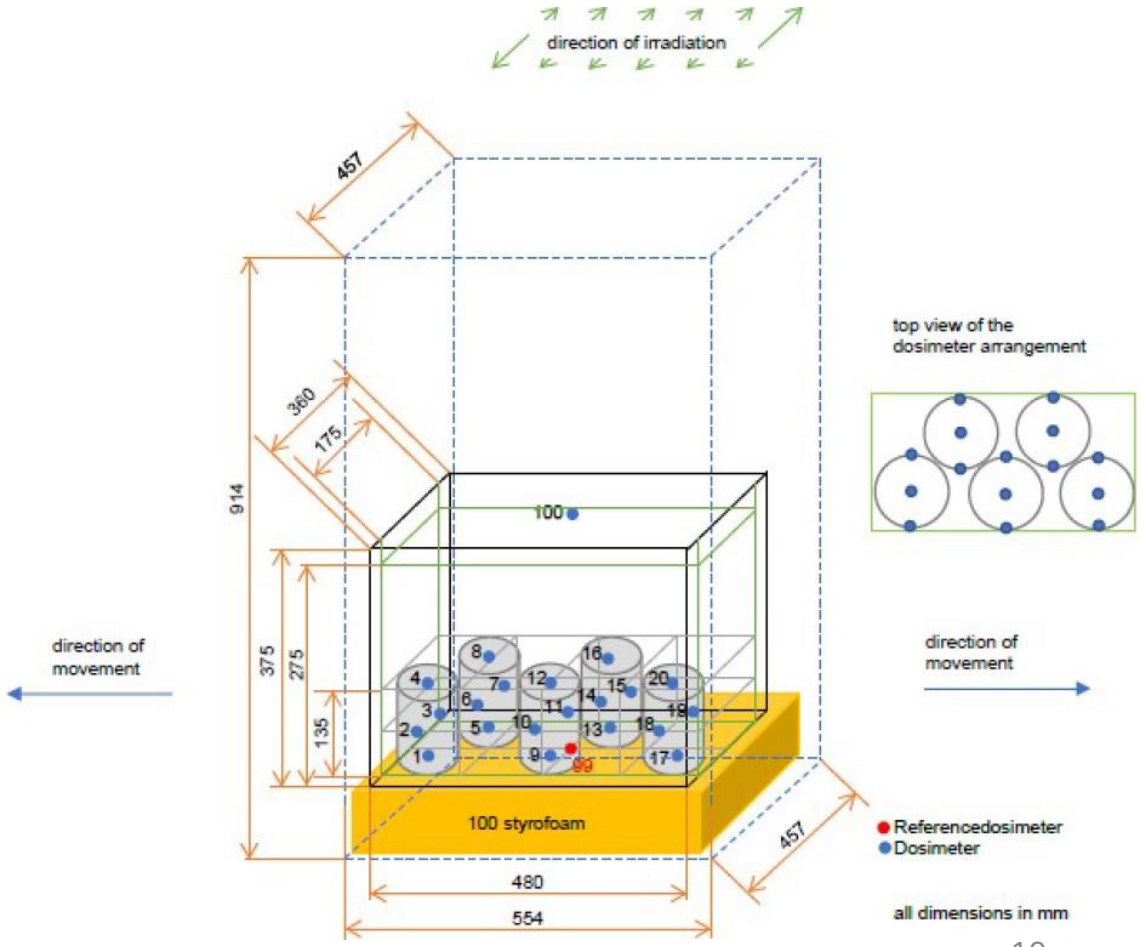
- Options:
  - gamma rays from a suitable isotopic source (e.g. Cobalt 60)
  - beam of electrons energised by a suitable electron accelerator
  - X-rays resulting from bombarding a suitable target with energised electrons
- Standard conditions: absorbed dose > 25 kGy
- Note for Guidance "*The use of Ionization Radiation in the Manufacture for Medicinal Products*"
- ISO 11137
- Ph. Eur. chapter 5.1.1
- Dedicated plant

2. Ionization radiation

- Description
  - Type of irradiation
  - Mode of operation (batch- or continous)
  - Material and dimensions
  - Bioburden
  - Loading pattern
  - Dosimeters
- Validation
  - Loading pattern
  - Changes to product or packaging as result of irradiation (radiolysis products)
  - Maximum dose determination

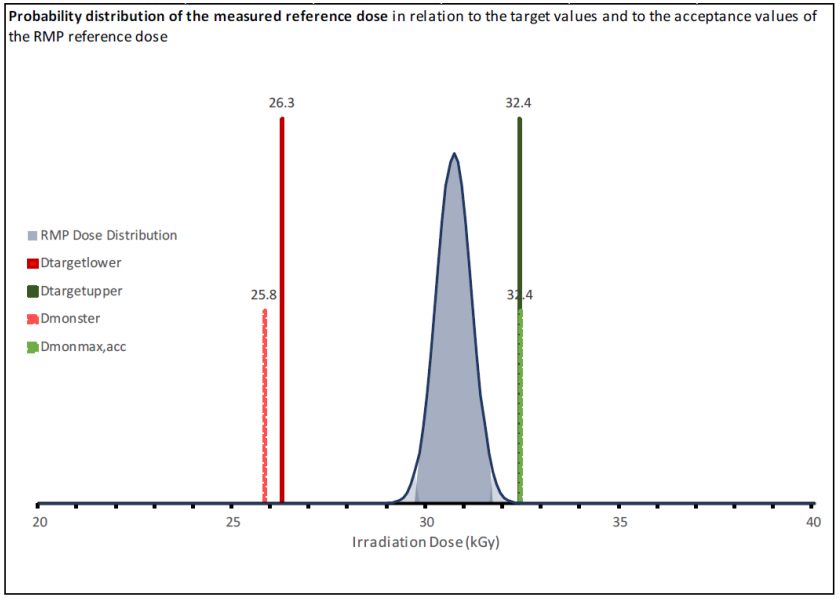
Example API-1

- API batch packaged in HDPE plastic bottles, inside LDPE foil, 6 bottles in styrofoam box
- Addition of dry ice prior to sterilisation, conditioning
- Dose mapping
- Requirements
  - Min 25 kGy
  - Max 34 kGy



Example API-1 Results dose mapping

	Dose in kGy		
Dosimeter No.	1. Irradiation	2. Irradiation	3. Irradiation
1	30.9	31.7	30.7
2	30.4	31.6	30.0
3	30.4	31.7	30.3
4	32.0	32.6	31.7
5	29.6	30.9	29.5
6	30.4	31.5	30.0
7	29.8	31.0	30.0
8	30.7	31.7	31.0
9	30.1	31.1	30.0
10	30.5	31.0	29.2
11	30.0	31.0	29.1
12	31.6	31.9	30.7
13	30.2	31.0	29.2
14	30.7	30.7	29.4
15	29.7	31.0	29.4
16	31.4	31.5	30.5
17	31.0	30.6	30.3
18	30.8	30.4	29.3
19	30.8	30.5	29.4
20	32.3	31.9	30.8
99 RMP	30.8	31.1	30.2
100	34.2	34.1	34.5



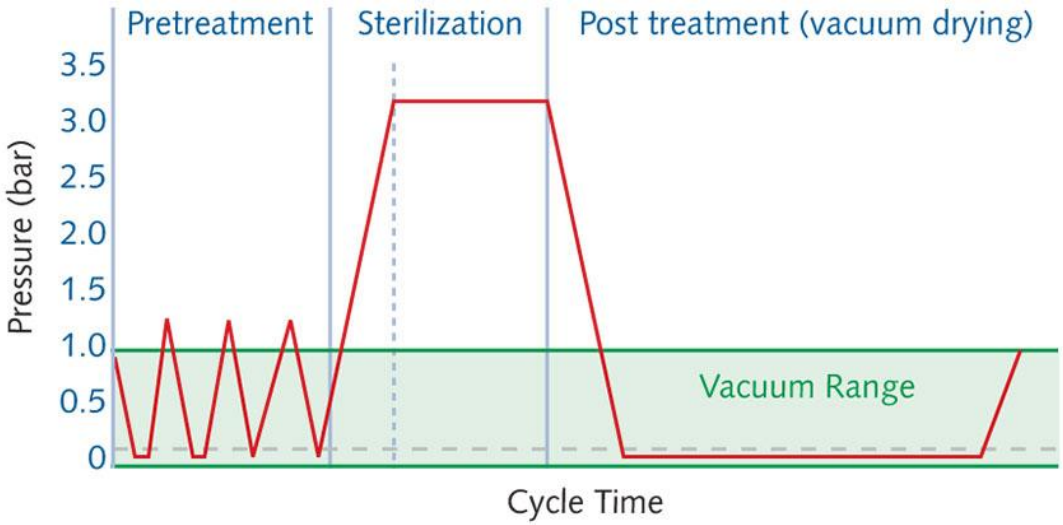
	Dose values in kGy				
Irradiation unit	1	2	3	Mean	sd
D_{mon} (Reference dose; RMP)	30.8	31.1	30.2	30.7	0.5
Calculation of the lower RMP dose limits					
Minimum position	5	18	11		
D_{min} (Minimum dose)	29.6	30.4	29.1		
AF_{min} (Correction factor)	0.961	0.977	0.964	0.967	0.009
D_{target}^{lower}	*25/(0.967-2*0.009)*			**26.3**	
D_{mon}^{ster}	*25/0.967*			25.8	
Calculation of the upper RMP dose limits					
Maximum position	20	4	4		
D_{max} (Maximum Dose)	32.3	32.6	31.7		
AF_{max} (Correction factor)	1.049	1.048	1.050	1.049	0.001
D_{target}^{upper}	*34/(1.049+2*0.001)*			**32.4**	
$D_{mon}^{max,acc}$	*34/1.049*			32.4	

3. Gas sterilisation

- Alkylating (ethylene oxide) or oxidising (hydrogen peroxide and peracetic acid) gas
- EtO: acts directly on DNA
- Low temperatures (30-60 °C)
- Penetrates porous materials
- Not corrosive
- Toxic gas, flamable and explosive
- Dedicated plants

3. Gas sterilisation

- Process developed and validated according to ISO 11135
- Pre-conditioning
  - Moisture (steam)
  - Time and temperature
- EtO
  - 300-800 mg/L
  - Pressure
  - Time
  - temperature
- Aeration to remove EtO
  - Active aeration
  - Passive aeration
  - Time (min 24 hrs)
  - Pressure changes

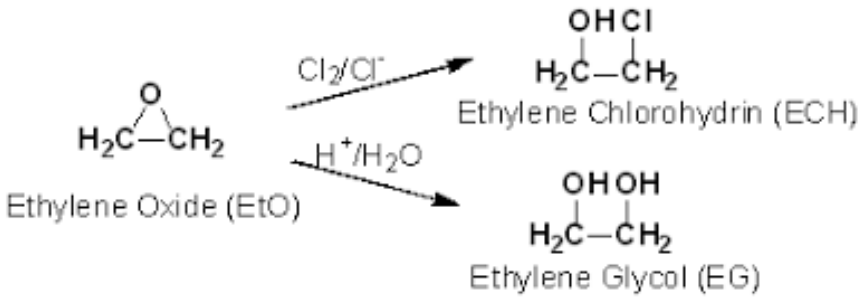


3. Gas sterilisation

- Process control:
  - Temperature (2 places)
  - Pressure
  - Concentration EtO
  - Time
  - Biological indicators (ISO 11138-2)
  - Chemical indicators (ISO 1140-1)
- Validation details to be included in dossier

3. Gas sterilisation

- Not suitable for dry powders unless these are prepared under aseptic conditions
- ETO carcinogenic gas: direct impact on DNA
- Removal of toxic gas residues to acceptable level (ICH M7, EN 10993-7 for test methods)
  - EtO
  - Halogenated ethylenehydrines (e.g. ethylene chlorhydrin)



Example API-2

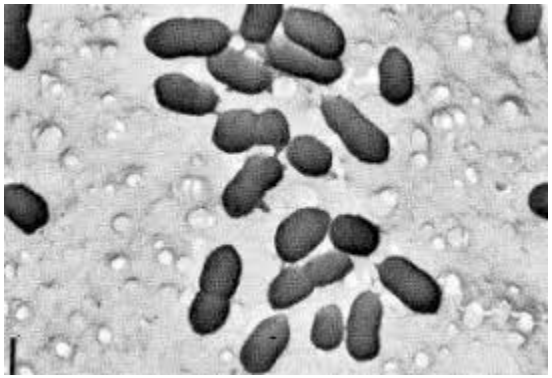
Parameter	Criteria
Pre-conditioning	Ambient conditions regarding pressure. 100° F (corresponding to about 38° C) – 120° F (corresponding to about 49° C), 45 – 80% RH (target 60% RH), 12 – 24 hrs.
Initial Pre-vacuum	20 minutes (minimum time) (1.5 – 2.5 “HgA range)
Humidity	1 “HgA rise (a 1 “HgA rise in pressure results in 30% RH @ 120° F -corresponding to about 49°C) -1.25 “HgA maximum (36.5% RH) 2.5-3.5 “HgA range 60 minute minimum (70 minutes maximum)
Gas Exposure	(an 11.2 “HgA rise after completion of humidity dwell results in approximately 620 mg/L EtO) 13.6 -14.8 “HgA range 109° F (corresponding to about 43° C) -131° F (corresponding to about 55° C) range 8.0 hrs minimum (8 hrs 10 minutes maximum). Chamber temperature 43-55 C
Aeration	Using air, 32-54 C, for 72-80 hrs.

4. Sterile filtration

- Removal of microbial load
- Filter pore size 0.22 µm renders solutions sterile (standard pore size)
- Other pore size (0.45 µm) reduce bacterial load
- Integrity of filter (IPC)
  - Before use (optional)
  - After use (mandatory)
- Performed as close as possible to final filling (GMP)

4. Sterile filtration

- Type of filter (material) listed in dossier
- Extractables and leachables studied
- Solution compatibility
  - Adsorption of active ingredients
- Bacterial retention capacity (*B. diminuta*)
- Bioburden of solution (<10 CFU/100 ml) as IPC



4. Sterile filtration

- Need information on filters in dossier
  - See table in guideline on Sterilisation
- Need information on processing times / holding times
  - 24 hrs, unless otherwise justified
  - Based on media fill data
- Media fill results are GMP
  - Check if media fill is performed on same / similar container closure
  - Check if time / amount of material covers proposed commercial batch size / processing time

Example – API 3

- aseptic filtration using a series of filters: 1.2µ, 0.2µ and 0.2µ
- 0.2µ filter (CVGL filter): Hydrophilic filter made of Polyvinylidene fluoride (PVDF), area of 2.07 m^2
- Bubble point test, min. 50 psi either API solution or purified water, also after prolonged contact (600 hrs)
- Bacterial retention study
  - 1 x 10^7 CFU/cm2 *B. diminuta*, 0 CFU in filtrate, bubble point 50.4 psi
  - 1 x 10^7 CFU/cm2 *B. diminuta*, To Numerous To Count (TNTC) in filtrate, bubble point 23.1 psi
- Extractables
  - Aqeuous solution, pH 5.0-6.2 hence model solvent is water at pH 2
  - Non-volatile residue, total organic carbon, HPLC

Conclusion

- Follow flow chart for selection of sterilisation
- Details of sterilisation conditions in CEP-dossier
- Validation data required for non-pharmacopoeial conditions