

INSPECTION PROGRAM FOR FREEZE DRIED BIOLOGICALS

*Agence française
de sécurité sanitaire
des produits de santé*



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INTRODUCTION



- **Modified biological products**
- **Referentials**
- **GMP Annex 1 last modifications**
- **Freeze drying process**
 - Final bulk product (FBP) preparation
 - FBP sterilizing filtration through 0.22 μm
 - Aseptic filling and partially stoppering
 - Aseptic transporting and loading lyophilizer
 - Freeze drying and complete stoppering
 - Capping
 - Individual inspection
 - Finish product testing
 - Shipping
- **Examples of deviations observed in inspection**

BIOLOGICAL MEDICINAL PRODUCTS



- medicinal products derived from human blood or plasma
- **vaccines : bacterial, viral, recombinant**
- immune sera, purified or fractionated IgGs, monoclonal antibodies
- **allergens including named patient preparations**
- hormones, cytokines, enzymes
- **products from fermentation : whole cells, extracts, rDNA techniques**
- gene therapy products
- **non medicinal products : in contact with cells, tissues, organs**

REFERENTIALS



- **EU**
 - Directives : Marketing Authorisation, Qualified Person, Good Manufacturing Practices (new annexes 1 and 2)
 - European Pharmacopoeia
- **French**
 - Code de la santé publique
 - BPF / BPDG, AMM
- **Other referentials used**
 - Notes for guidance de l'EMA (quality of water for pharmaceutical use ...)
 - PIC/S (Validation of aseptic process, isolators ...)
 - WHO (GMP, TRS ...), PDA, ISO

DIRECTIVE 91/356

Article 5



« The manufacturers shall regularly review their manufacturing methods in the light of scientific and technical progress »

EudraLex

The Rules Governing Medicinal Products in the European Union



Volume 4

Good Manufacturing Practices

Medicinal Products for Human and Veterinary Use

Annex 1: Manufacture of Sterile Medicinal Products

- RELEASE FOR PUBLIC CONSULTATION November 2005
 - DEADLINE FOR COMMENTS April 2006
 - AGREED BY AD HOC GMP INSPECTION SERVICES GROUP June 2007
 - ADOPTED BY EUROPEAN COMMISSION **December 2007**
 - DEADLINE FOR COMING INTO OPERATION **January 2009**
- Capping grade A January 2010**

GMP to sterile medicinal products updated in 4 main areas :

- Classification table for environmental cleanliness of clean rooms and associated text
- Guidance on media simulations
- Guidance on bioburden monitoring
- Guidance on capping **of freeze-dried vials**

CLEAN ROOM CLASSIFICATION / MONITORING



• Classification

Grades	Maximum permitted number of particles per m ³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

« in operations » for normal and simulated operations

• Monitoring : in operations and at rest

- For grade A zones full duration of critical processing and continuous monitoring are expected
- Locations based on risk analysis
- $\geq 5 \mu\text{m}$ alert limit = 1 for grade A
- « At rest » after 15 to 20 min « clean up »

VALIDATION OF ASEPTIC PROCESSES



- Normally process simulation tests should be repeated twice a year per shift and process **A1.42**
→ one filling line and each associated lyophilizer
- The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch **A1.42**
- The target should be zero growth... **A1.42**

VALIDATION OF ASEPTIC PROCESSES

new Annex 1.69



...and the following should apply:

- When filling fewer than 5000 units, no contaminated units should be detected.
- When filling 5,000 to 10,000 units:
 - a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;
 - b) Two (2) contaminated units are considered cause for revalidation, following investigation.
- When filling more than 10,000 units:
 - a) One (1) contaminated unit should result in an investigation;
 - b) Two (2) contaminated units are considered cause for revalidation, following investigation.

Media fills should primarily validate aseptic operations :

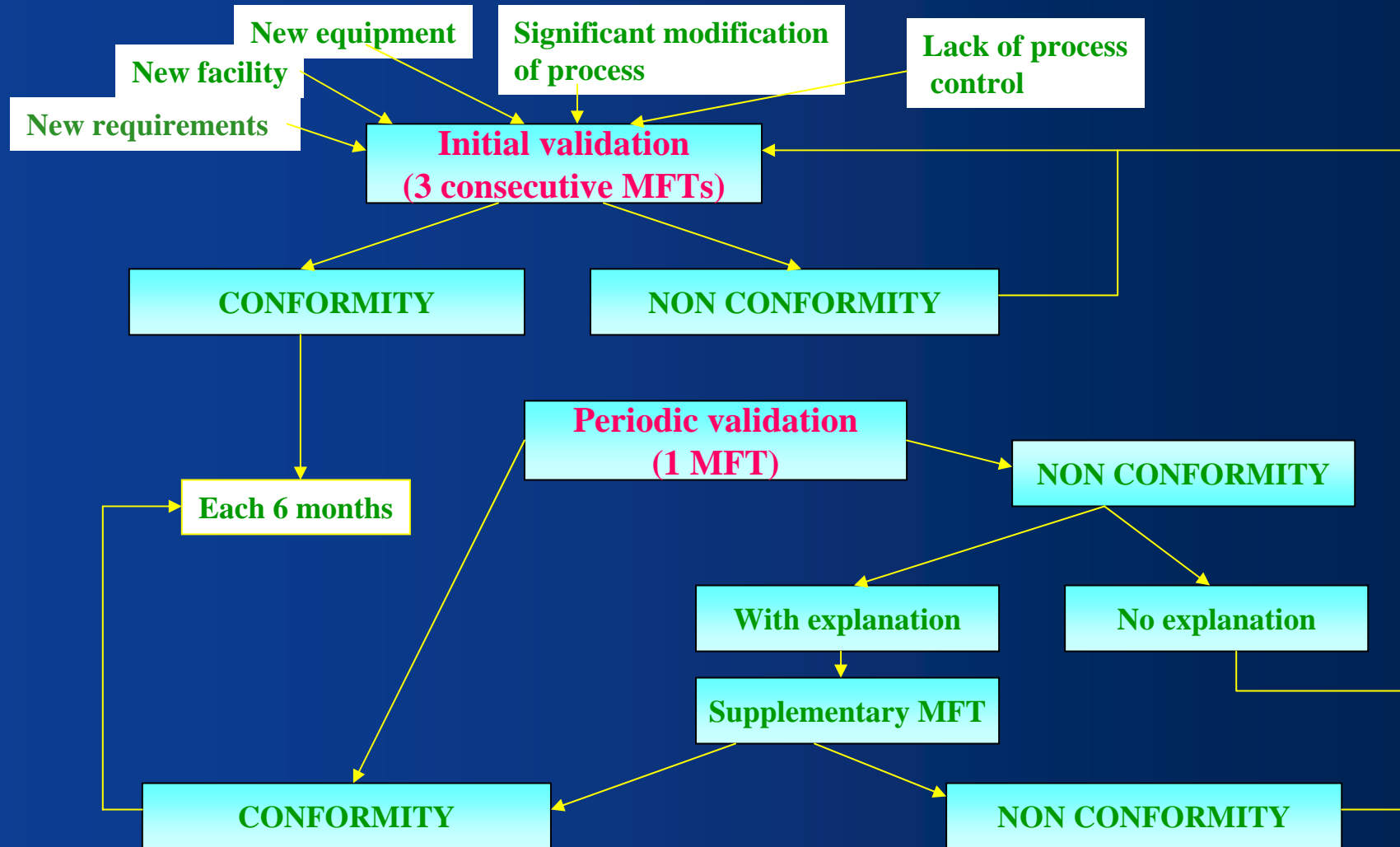
- filling
- transportation
- loading
- capping

→ no freezing, no vacuum, no gas flush...

→ incubation of MFTs recommended at

20-25°C AND 30-35°C

VALIDATION OF ASEPTIC PROCESSES LOGIGRAMME



FBP PREPARATION



- Grade C environment for solutions filtered, if not filtered A/B **current Annex 1.12**
 - Components after washing at least in grade D **A1.12**
 - Components and starting materials not sterilised or filtered, handling and filling of aseptically prepared products A/B **A1.12**
- for alumin adjuvanted vaccines FBP is prepared in sealed tanks in A/B.

FBP STERILIZING FILTRATION



- Sterile filtration through 0.22 μm (or less) **A1.82**
- A second filtration immediately prior to filling may be advisable **A1.82**
- Final sterile filtration as close as possible to the filling point **A1.83** → **time and distance**
- Integrity test before and immediately after use **A1.85**
→ **integrity test in line after sterilisation just before use**
- Time and pressure difference determined during process validation **A1.85**
→ **validation of sterile filtration with *Brevundimonas diminuta* at least $10^7/\text{cm}^2$ of effective filtration surface.**
- Integrity of critical air gas / air vent filters after use **A1.85**

BIOBURDEN MONITORING

Current annex 1.52 **New annex 1.80**



- The bioburden should be monitored before sterilisation. There should be limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used.
- Bioburden assay should be performed on each batch for both aseptically filled products and terminally sterilised products.
 - Bioburden should be performed before prefiltration with the testing of at least 100 ml.
- Where appropriate the level of endotoxin should be performed.
 - Holding time limits should be established on the basis of real time experimental data for each biological product.

ASEPTIC FILLING AND PARTIALLY STOPPERING (1)



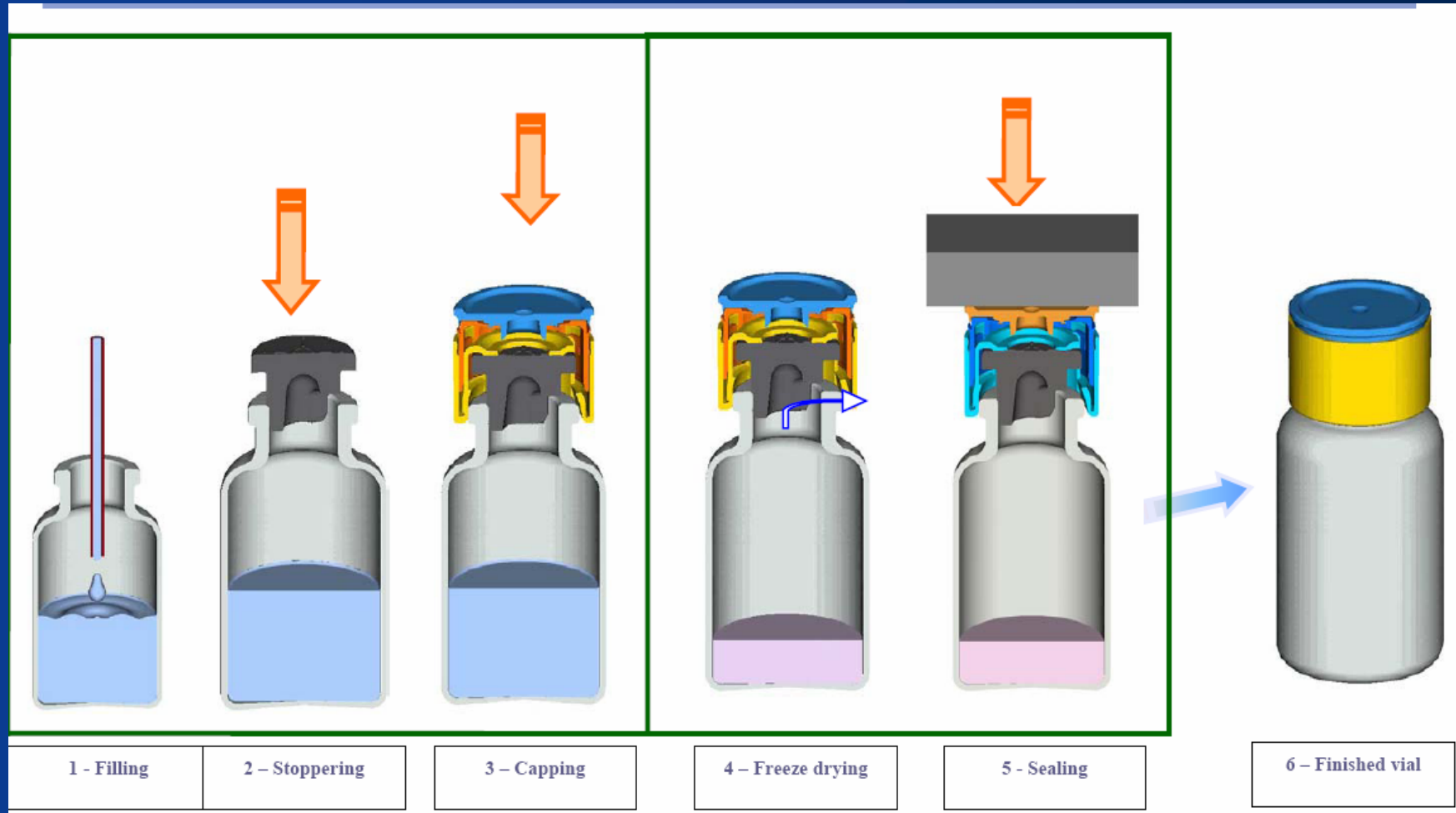
- **Introduction of the vials**
 - Washing process and final rinse with WFI
 - Depyrogenation tunnel : annual qualification with endotoxin challenges, cooling exit grade A, critical parameters and any breakage event registered,
- **Filling (1)**
 - Validation of filling operations
 - Annual qualification of the grade A/B filling zone including airlocks
 - Qualification of operators
 - Assurance of fill volume : monitoring throughout the filling operation to avoid low fill not apparent after lyophilization
 - SOP for broken vials

ASEPTIC FILLING AND PARTIALLY STOPPERING (2)



- **Filling (2)**
 - Environmental program
 - Non viable particulates continuous monitoring (**new A1**)
 - Viable particulates monitoring : air sample cfu/m³ with biocollector, sedimentation with settle plates, surfaces with contact plates, gloves (**current annex 1**) **gowns monitoring recommended**
 - Alert and action limits (**A1.6**), trend analyses (**6.9**)
- **Stoppering**
 - Vials partially stoppered by machine
 - No hand-stoppering operations, even with sterile forceps
 - **Vials partially stoppered + cap by machine and crimped in the freeze dryer : a new concept**

NEW CAPPING SYSTEM



TRANSPORTING AND LOADING LYOPHILIZER



- Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment (A1.12, new A1.34).
 - The filling line as close as possible to the lyophilizer with a primary barrier with laminar flows extending from the filling line to the lyophilizer. Monitoring should be performed in the filling line and near the door of the lyophilizer and between if necessary depending on the distance.
 - Closed grade A laminar flow cart to transport the vials from the filling line to the lyophilizer is acceptable. Airflow velocity and turbulence during operations should be evaluated.

FREEZE-DRYING AND COMPLETE STOPPERING : STERILISATION (1)



- CIP and SIP for new equipment.
- Sterilization with moist steam under pressure should parallel that of an autoclave.
 - Chemical treatment or gaseous ethylene oxide difficult to validate for inaccessible associated piping.
 - For EtO homogeneous humidification and absence of residue make this system objectionable.
- Hydrogene peroxyde vapour more acceptable alternate
- Sterilisation should include the chamber, the condenser, vapour and vacuum lines, valves, gauges and vent filters.

FREEZE-DRYING AND COMPLETE STOPPERING : STERILISATION (2)



- Sterilisation before every run.
- Less frequency for part-stoppered vials must be justified by suitable microbiological data.
- Steam sterilisation :
 - High quality dry and saturated steam at required temperature. Condensate should comply with WFI.
 - Dead legs avoided wherever possible.
 - Ports for temperatures, vacuum devices, CIP systems and stoppering mechanisms are particular problem areas.
 - Condensate removal, steam traps and steam sterilisation of membrane filters are problems to address.

LYOPHILIZATION CYCLE



- **Instrumentation to control and record the key process parameters : shelf temperature, product temperature, condenser temperature, chamber pressure and condenser pressure.**
- **Computer controlled lyophilization : validation of the software program.**
- **Leak rate testing at a frequency determined from the data generated during validation.**
- **Review of preventive maintenance logs, discrepancy and investigation reports**
- **Double doors lyophilizer : interlocked, both in Grade A**

CAPPING new annex 1.118 to 122



- The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vials. Crimping of the cap should therefore be performed as soon as possible after stopper insertion **A1.118**
- Vial capping aseptic process or clean process outside the aseptic core → vials in Grade A air supply until cap has been crimped **A.1.120**
- Vials missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination **A1.121**
- Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising human interventions into the capping operation **A1.122**

INDIVIDUAL INSPECTION



Annex 1.90. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

- Automatic inspection of freeze dried products ? After filling ?
- Visual inspection : initial and periodic qualification of operators, conditions (illumination, background) and speed, specifications for each type of defect.
- Statistical analysis : satisfactory quality levels depending on the criticality of the defect. **Glass and metal particles critical (5.48, Annex 1.49)**

FINISH PRODUCT TESTING (1)



- dose uniformity, moisture testing
- sterility testing : The sterility test applied to the finished should only be regarded as the last in a series of control measures by which sterility is assured **Annex 1.91**.
- container closure integrity testing : Samples of other containers (e.g. not closed by fusion) should be checked for integrity according to appropriate procedures **Annex 1.88**.
- maintenance of vacuum : Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period **Annex 1.89**.

Stability:

Biological products involve frequently in the manufacturing process many intermediates with different shelf lives

- **Stability studies of each intermediate and of FP**
- **Stability studies of FP manufactured with intermediates just before expiry dates: worst case or cumulative stability studies if the shelf lives are based on loss of potency.**

SHIPPING



- Biological products stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.
- Time Out Refrigeration (TOR) should be recorded during capping, individual inspection and packaging.
- Validations including containers and methods.
- Contract manufacturing steps for the partially processed materials and the validated processes are followed and documented.
- Shipper assure proper temperature shipment maintained and recorded.
- Freezing of biologicals often dramatic.

DEVIATIONS (1)



- **VALIDATION OF ASEPTIC PROCESS**

➤ **MD** « Validation tests of aseptic preparation of final bulk products are not incubated at 30-35°C but only at ambient temperature. Thus, these tests are not able to detect the microbial contaminations of human origin which are the most important contaminants identified in environmental monitoring of this building. The tank is filled at 1/3 during the validation instead of 2/3 during the manufacturing process (GMP annex 1.42)»

DEVIATIONS (2)



- **VALIDATION OF ASEPTIC PROCESS**

- The same filling machine is used for different lyophilizers but all lyophilizers are not involved in the validation process each 6 months (GMP annex 1.42).

- The media fill tests program is not based on the principle that each filling machine and each format is tested twice a year, since it has been considered that the three filling machines are identical (GMP annex 1.42).

DEVIATIONS (3)



- **STORAGE – STABILITY - SHIPPING**

- During the individual observation of the vials and for the packaging, the control of the time out of the recommended storage temperature has not been set up (.GMP 5.36).
- Stability data of the final product support a shelf life of 36 months. Stability data on bulk products support a shelf life of 66 months at – 35°C. The new stability study in a worst condition (cumulative stability study) is not Completed (GMP 1.2.viii).
- The validation of packaging for shipment is not completed (GMP 1.2.viii, 5.60, 6.14).