Technip Life Sciences

TIANJIN
2009 International Forum Of Pharmaceutical Engineering And Generic Drugs R&D

Technip

Agenda

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2. **Regulatory issues to face**
3. **Technical Organisation to comply with these rules**
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   - B) DOUBLE DOOR Freeze Dryer
3. **Freeze Dryers Loading Unloading and vials Capping in Compliance with new GMP's requirements**
4. **Recommendations**

1. Introduction

- **Regulation authorities emitted February 2008 a new revision of cGMP Annex 1, dedicated to manufacturing of sterile products.**
  - **This Annex was put in application till March-01-2009, with an exception for the specific parts concerning the freeze dry product capping (the authorities gave one year more make existing facilities to be fully compliant)**
- **All the manufacturers of pharmaceutical sterile freeze dried products must be fully compliant March-01-2010, if they want to keep their cGMP agreement.**
  - **Pharmaceutical Inspection Convention /Scheme (PIC/S) cGMP has been updated on September 2009, including the new Annex 1 concerning sterile products recommendations. WHO organization follows PIC/S recommendations around the world.**

- **Manufacture of sterile medicinal products - Annex 1 (extract concerning Freeze dried products)**
  - **116. Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.**
  - **117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.**
  - **118. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.**
  - **119. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.**

- **Manufacture of sterile medicinal products - Annex 1 (extract concerning Finishing of sterile products)**

  - **120. Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.**

  - **121. Vials with 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 minimize microbial contamination**

  - **122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimizing direct human interventions into the capping operation.**

Annex 1 - Issues Application to Sterile Projects

- **All these new recommendations brings freeze dried producers to reconsider all their process,**
  Including capping operation into primary packaging process.

- **The continuous class A itinerary of the freeze dried vials bring to reconsider the position of the capping machine into the workshops, as close as possible to Freeze driers.**

- **The new capping workshop classification brings a reorganization in personal flow (new personnel airlocks (requirements) and in material flow (new caps sterilization equipment/Material air lock)**

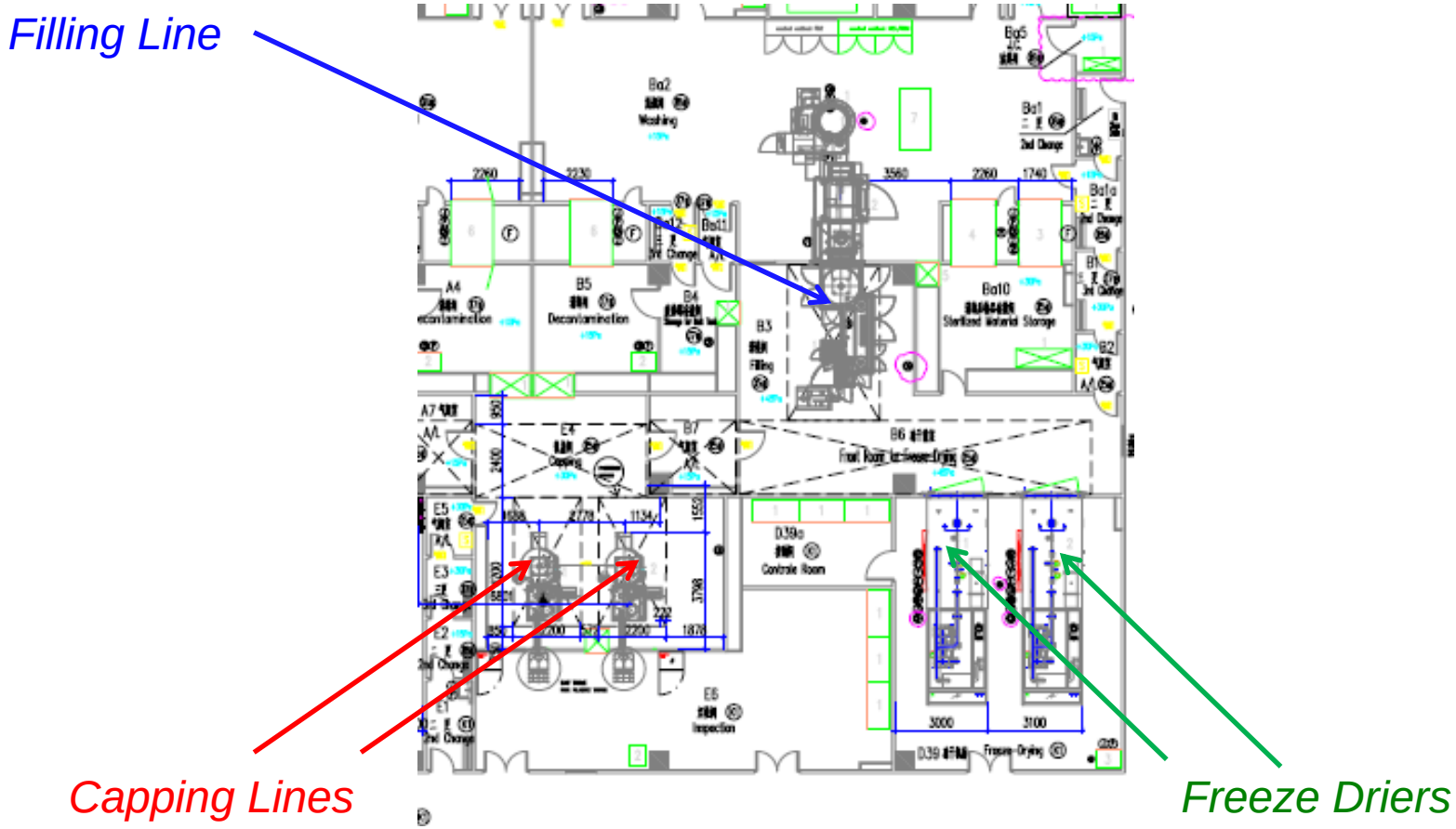
- **The new capping workshop classification may bring a reorganization in Freeze driers unloading area, including storage phases before capping.**

- **The Freeze dryers are commonly used in two configurations:**
  - **Freeze dryers conception with one door for loading and unloading (the second door if existing is dedicated to maintenance)**
    - For such configurations, the condenser may take place on the right, on the left, on the back (if single door) or under the Freeze dryer chamber
  - **Pass through double door Freeze dryers, using one door for loading, and the other door for unloading.**
    - For such configurations, the condenser may take place on the left, on the right or more often under the Freeze dryer chamber

▶ SINGLE DOOR Freeze dryer

- **The Freeze dryer loading and unloading activities are made in the same area. To avoid cross contamination between batchs / products, filling and freeze dryer loading activities must not occur during freeze dryer unloading activity.**
- **Considering that freeze dried products are often stored in cold conditions, it will be very difficult to guaranty class A in a cold room. As a general rule, the unloading of the Freeze dryer and the capping must be done continuously, locking the filling/loading activity.**
- **The capping operation may be done in a dedicated area, with potential interfaces mutualization with filling area (Material and personnel air locks, autoclave, transfer isolator…).**
- **This Freeze dryer configuration is mainly used to produce small batchs.**
- **The loading and unloading of the product is mainly manual, vials are transferred from filling to freeze drying on trays.**
- **For small batchs, the Freeze dryer unloading may be done into mobile LAF, to reduce hold time of the filling and freeze drying workshops.**

▶ SINGLE DOOR Freeze dryer: Typical Organization No1



Sterile Freeze Dried Products and new Annex 1 PIC/S GMP
3. Technical Organization to comply with these rules

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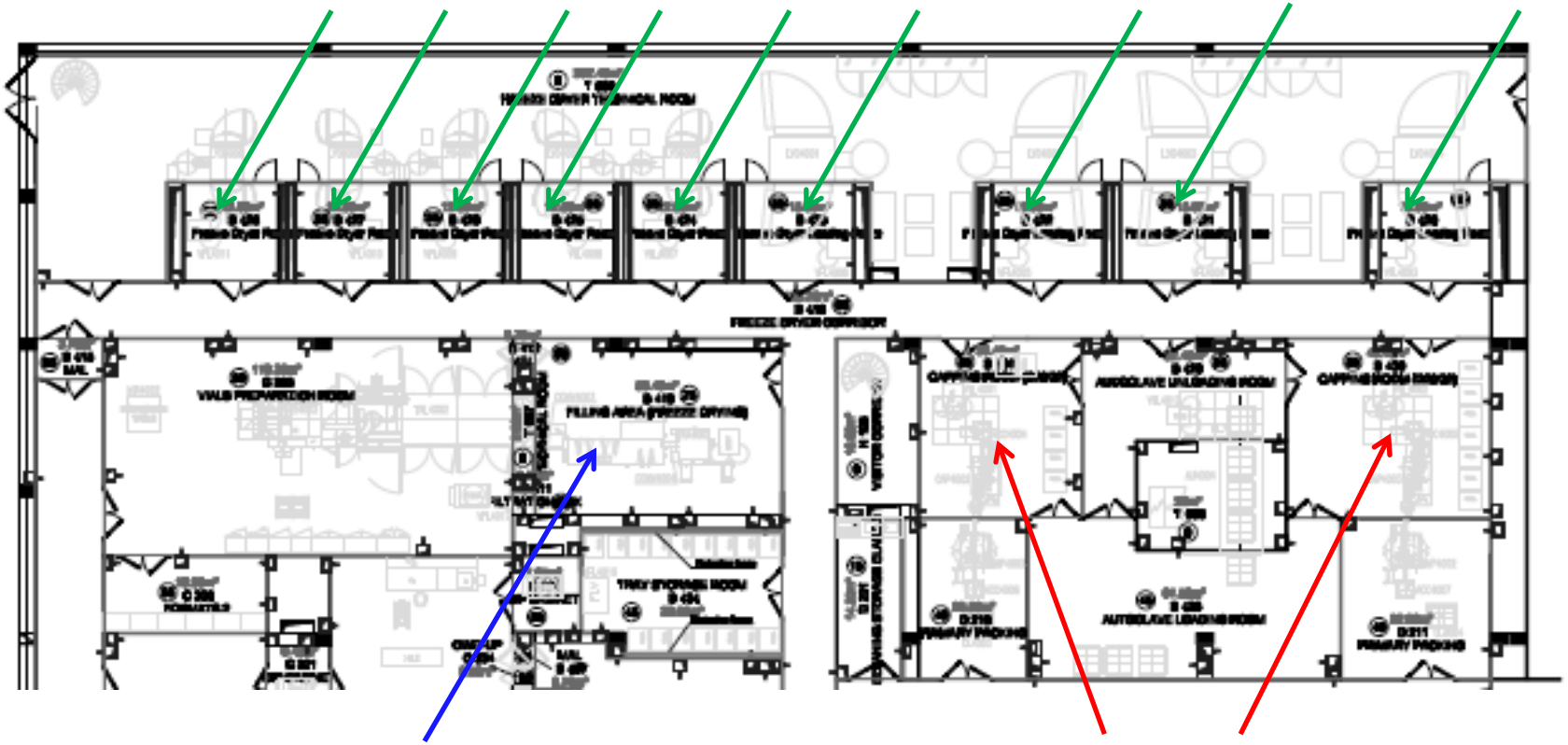
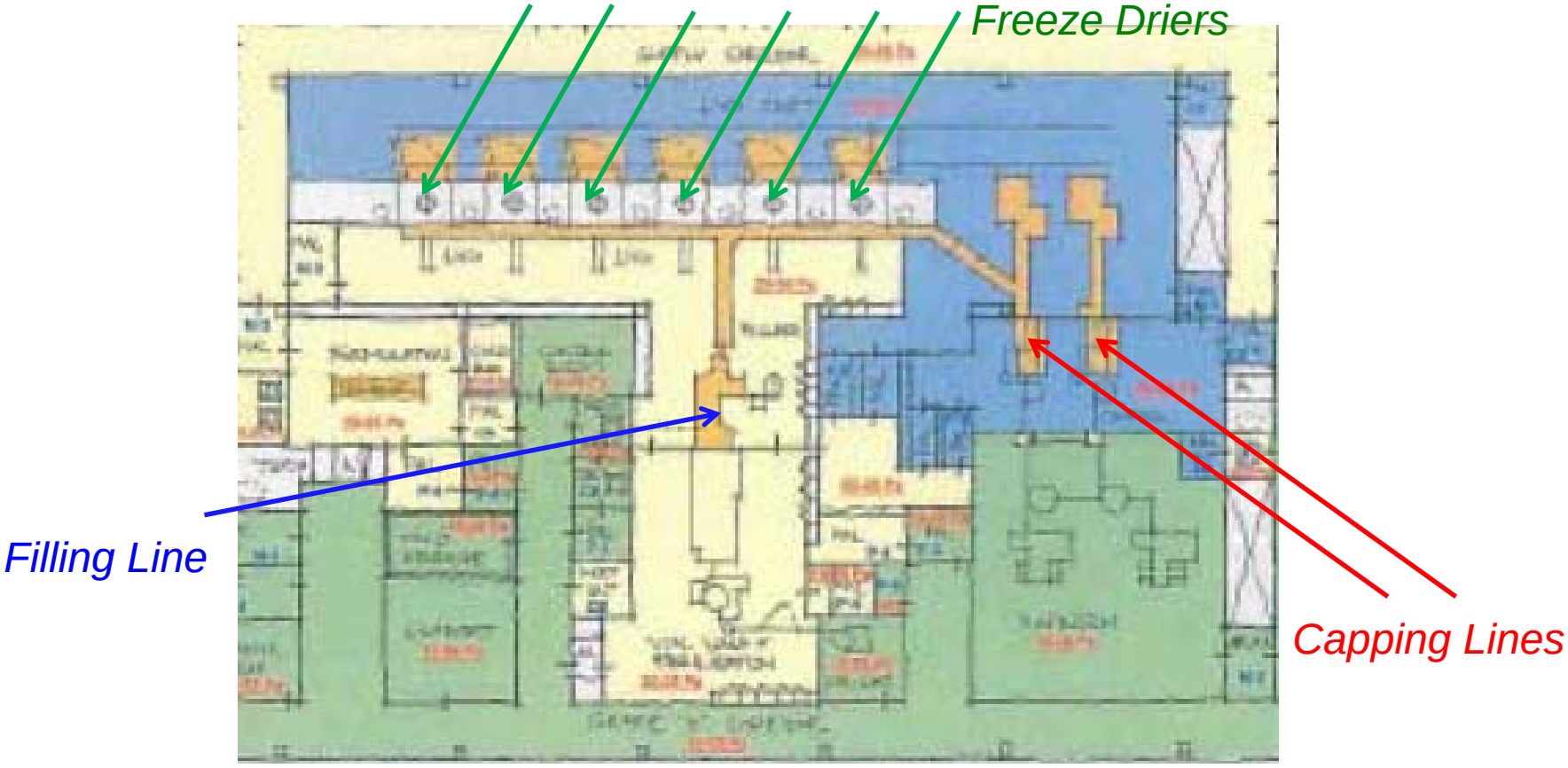
SINGLE DOOR Freeze dryer: Typical Organization No2



DOUBLE DOOR Freeze dryer

- **The Freeze dryer loading and unloading activities are made in different areas to avoid cross contamination between batchs / products. Filling and Freeze dryer loading activities can be done during Freeze dryer unloading and capping activities.**
- **Considering that freeze dried products are often stored in cold conditions, it will be very difficult to guaranty class A in a cold room. So, the unloading of the Freeze dryer and the capping must be done continuously.**
- **The capping operation may be done in a dedicated area, with potential equipment mutualization with filling area (autoclave, transfer isolator…)**
- **This Freeze dryer configuration is mainly used to produce large batchs, and will require the use of automatic loading and unloading systems**
- **The product must be freeze dried directly on the shelves.**

▶ DOUBLE DOOR Freeze dryer: Typical Organization



Sterile Freeze Dried Products and new Annex 1 PIC/S GMP
4. Freeze dryers loading unloading and vials capping in compliance with new GMP's requirements

- **The sterile freeze dried drug products Manufacturers must take in account the environmental conditions upgrade concerning the unloading of Freeze dryers and capping.**

- **Considering the difficulty in maintaining Grade A with human activities under laminar flow, the major suppliers developed automatic systems to load and unload Freeze dryers without human operations in critical area.**

Sterile Freeze Dried Products and new Annex 1 PIC/S GMP
4. Freeze dryers loading unloading and vials capping in compliance with new GMP's requirements

- **These systems have been designed to be included into isolator or RABS (Automatic fixed loading system), or use mobile shuttle moving under Grade A laminar flow (Automatic mobile loading and unloading shuttle systems)**

- **The automatic mobile loading shuttle system allows to feed one or more capping machines equipped with laminar flow and RABS, installed in a separate Grade B room, with specific extraction to remove the high level of particles generated during crimping.**

Sterile Freeze Dried Products and new Annex 1 PIC/S GMP

5. Recommendations

- **It's very important to keep in mind that there is not only one solution to override your needs and to reach PIC/S recommendations. The target and the associated technologies are not the same if you want to produce 1 millions of vials per year or 200 millions of vials per year, always saving money and reaching the highest level in sterility insurance.**
- **For grass roots projects, there are always technical solutions for all requirements. The key point is not to transfer problems using a technical solution and to manage constraints.**
- **For revamping projects, the solution will be chosen considering the constraints around the new design of unloading and capping area.**
- **If possible, try to remove operators activities from critical Grade A areas in order to reach the quality level required by PIC/S and GMP Annex 1.**