



FROM BIOMANUFACTURING TO THE FIRST INJECTABLE CLINICAL BATCHES : TECHNICAL AND REGULATORY ASPECTS OF INDUSTRIAL SCALE-UP

French CMO for parenterals

DBi - Overview



DBi, a French pharmaceutical company (F08/276), is a dedicated small-scale production site to provide up to 10 000 vials, for pre-commercial batches of liquid or lyophilized drug products considered highly active or subject to specific considerations.

DBi meets international standards and guidelines:

- GMP facility
- Highly qualified team
- Efficient scale up
- Documentation conforming to the IMPD format and Product Specification File

Capacity:

- Aseptic filling of vials up to 100ml: Batch size 10 000 vials (3m² in the lyo)
- Liquid or freeze dried drug product
- Aseptic filling of syringes up to 30.000 syringes
- Terminal sterilization

Key points for a successful scale up



Make a real identification of final needs

Make a real inventory of data available

Make a real Quality Control inventory

Make a real identification of critical parameters

Anticipate the scale up: industrialization and GMP compliance

Make a real regulatory review

Make a real Quality Assurance review

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Identification of final needs



Technical batches for stability, toxicity, feasibility, quality control, validation: number, batch size?

Clinical batches: number, batch size?

Regulatory aspect: contract, validations

Planning

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Inventory of data available



Process: flow chart, specifications

API: available in sufficient quantity and produced under GMP conditions

Raw materials: available, GMP

Packaging components: available, GMP, compatibility study with the product

Sterilization solution: available, GMP, validated

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Quality Control inventory



Specifications of API, raw materials, packaging components, IPC, finished product available and accurately defined

Corresponding analytical methods available, well defined and validated

Corresponding microbiological methods available, well defined and validated

For information, you need:

- Validation of all the analytical methods
 - Validation of all the microbiological methods: bioburden, sterility
 - IPC as short as possible with “common” and robust method
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Risk assessment for critical parameters: control and monitoring

Ex.:

- for a solubilization, is the visual aspect sufficient or is it better to have analytical control (osmolarity, pH) ?
- Adjustment: temperature, pH
- Sterilization: filters, autoclave cycle

Special attention should be paid to “historical” stage

Ex: at the beginning of the development, filling under nitrogen due to a specific raw materials. Change of raw materials but we still have nitrogen

Raw materials from pharmacopea

Pharma Grade packaging components, particularly for stoppers (ex: it's difficult to write “penicillin stoppers” in a IMPD and you need compatibility study with this stoppers)

Industrial process, particularly for dissolution (ex: when it's possible, it's better to have a stirrer instead of ultrasonic for dissolution)

Secure process (ex: it's not so secure to heat 100 liters of pure ethanol till 80°C with a flame)

Minimizing the aseptic operation (ex: when it's possible, it's better to have lyophilisation instead of diafiltration for concentrate a protein solution)

Pharma Grade filters for sterile filtration (ex: it's difficult to validate a sterile filtration with a filter media for HPLC solvent purification)

Contract with the different partner

GMP facilities

IMPD

QP for the release

Clinical labeling

The partner's Quality Assurance system must be Audited

You need a GMP compliance (including Annex 13 and biological product) of the partner

The documentation must be sufficient to be included in an IMPD

The Quality Assurance system of the partner must be presentable and auditable by a third party (ex: your future partner for the commercialization or for the licensing of the product)

Partnership

Risk assessment

Critical parameters

Industrialization

Quality Control

Validation

DBI

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