Modular Turnkey Concept for Pharmaceutical Sterile Formulation Facilities

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KEY WORDS
- Parenterals: sterile solutions and suspensions
- Formulation – Compounding of pharmaceutical drugs
- CIP/SIP (DIP included)
- Sterile Filtration
- Integrity testing
- Sterile containment
- Sterile RTP technology
ABSTRACT

Sterile parental drugs are produced or formulated in GMP critical batch processes. These automated process installations are submitted to a lot of regulations applying to the pharmaceutical industry. The formulation installations have moved away from being just utilities’ extensions and have become speciality installations requiring a high degree of technical skills but also knowledge about regulations and qualification/validation strategies.

As a result of this, specialised suppliers offer a turnkey approach for concept design, detailed engineering, realisation and qualification of these installations. Nowadays, there is a move towards modular skid concepts, allowing prefabrication and pre-qualification.

Driving forces for modularization are:

- On one side: the increasing level of requirements of the pharmaceutical industries under the economic as well as of the pharmaceutical regulations’ pressure.
- On the other hand: the need of the supplier to increase efficiency in manufacturing and provide proven performances in an international market.

As such the main advantages of the modular skid and turnkey concept for these batch systems are a high predictability of the project results and clear guarantees and responsibilities.

Economically a remarkable shortening of the time to market of the sterile drug is far more important than an eventual cost reduction in realisation.
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GLOSSARY

API: Active Potent Ingredient
CIP: Clean In Place
CST: Clean Steam
Det.: Detergent
DIP: Dry In Place
EC: European Community
EHEDG: European Hygienic Engineering & Design Group: testing and certifying of equipment on hygienic design
E&I: Electrical and Instrumentation
FAT: Factory Acceptance Test
IQ: Installation Qualification
LAF: Laminar Air Flow
OQ: Operational Qualification
PQ: Performance Qualification
PV: Process Validation
PW: Purified Water
RTP: Rapid Transfer Port
SAT: Site Acceptance Test
SOP: Standard Operating Procedure
SIP: Sterilisation In Place
S88: International standards for automated batch processes
WFI: Water For Injection
3A: US organism, certifying equipment on hygienic design
3.1.B: Material certificate, guaranteeing material composition
2.2: Declaration of material type by supplier
1. INTRODUCTION: DEFINITION OF THE SUBJECT

Type of drugs:

- Sterile drugs: parenterals or injectables
- Liquid products
- Powders: through lyophilization (freeze dried)
- Filled in ampoules, vials or syringes

Formulation or Compounding of sterile drugs means:

- Adding API to liquid (mainly WFI) and solid components to create a sterile drug with the right composition.
- The process has to be operated such that the end product is sterile.
- Therefore the process has to be executed under low bioburden conditions and from a certain stage onwards even under sterile circumstances
- Sterile solutions are obtained through sterile filtration.
- Sterile suspensions are obtained through a more complicated process: a combination of filtration, a dry sterilisation method and the use of isolator and RTP technology.
- Formulation actions are dosing, weighing, mixing, heating, cooling: they have to be accurate and in accordance with GMP requirements.
- In addition: the operator, for health reasons, often has to be protected from direct contact with the concentrated API: adding API under closed containment.
- Environmental conditions are important: room classification conditions to be guaranteed, because they can promote (cross) contamination to the product.
2. THE FORMULATION PROCESS

There are 2 main types of formulation installations:

- Fixed installations:
  - Larger volumes: typical capacities from 1000L onwards.
  - Limited range of products.
  - Fixed vessels and connections to filters and filling machines.

- Flexible installations:
  - Smaller volumes: range typical from 25 to 1000L.
  - Broad range of products and presentations: multipurpose.
  - Mobile vessels, flexible connections, RTP connection to filling lines.
Formulation process flow: example of a fixed installation:
Process steps:

- Preparing equipment for CIP.
- CIP (and DIP): Cleaning and Drying in Place of the equipment.
- Preparing equipment for SIP.
- SIP (and DIP): Sterilisation and Drying in Place of the equipment.
- Inline Integrity testing of sterilised filters.

Formulation

- WFI dosing: with or without temperature control of dispensed WFI.
- Adding powders and ingredients in liquid form: preweighed and possibly in closed containment when health risks for the operator.
- Mixing.
- Heating/cooling through vessel jacket.
- Sampling.

Sterile filtration.

- Integrity testing of product filter after filtration.
- Holding of sterile product under controlled vessel atmosphere.
- Filling at filling machine (straight or through sterile RTP technology).
- Integrity testing of vent filter after filling at filling line.
3. REALIZATION OF FORMULATION FACILITIES

A formulation installation is a combination of components and disciplines, mentioned hereafter.

The Process installation:

- Mechanical equipment and utilities:
  - Vessels: preparation or formulation vessels and holding vessels.
  - Mixers.
  - Vent filters (hydrophobic filters) tested with WIT, in line.
  - Product filter (hydrophilic filters): bubble point testing in line.
  - Filter integrity testing devices to be integrated in the process installation
  - Rapid Transfer Ports for sterile coupling to isolators
  - Heat exchangers: heating cooling CIP liquid, WFI, jackets of vessels
  - Pumps.
  - Laminar airflow above preparation vessel and connecting points (in case of mobile vessels).
  - Isolator: in case of sterile suspension.
  - Utilities: Sterile air, instrument air, Clean steam, Purified water, WFI, industrial steam or superheated water, cooling water, vacuum, N2.
  - All equipment should comply with GMP requirements concerning CIP and SIP.

- Instrumentation:
  - Control of dosing, heating, cooling, mixing, pressurising
  - Sufficient and accurate instruments to keep the process at all times under control.
  - Accurate logging and storing of critical parameters to be sure product meets requirements.
  - Malfunctioning of instruments or uncontrollable production parameters leads to rejection of the product.
  - Development of a calibration programs and calibration procedures and tools, adapted to the installation: to guarantee that the process is continuously under control.
Physical calibration on site must be possible: specific calibration facilities or tools to be developed and installed.

Automation, data collection, reporting:
- The automation and operation concept of the installation must be complementary to the manual handling of the operator: it must provide tools for normal production operations, and for calibration and maintenance operations.
- Data collection and storing and batch reports compliant with US CFR 21, part 11: electronic records and signatures.
- Software structure and realisation must be easy to validate, also after changes.

Building construction and area classification:
- Area classification: before starting the concept development the location for the formulation booth has to be divided into different areas in accordance to its function
- Technical area:
  - non classified
  - CIP/SIP utilities, most of utility technical equipment
  - Maintenance area
- Formulation area (production area):
  - Often grade C (class 100 000 in operation) with LAF (class 10 000 in operation) above critical zones
  - Only the main equipment for production are installed here: vessels, filters,
- Area classification and HVAC, air treatment system to be engineered such that no cross contamination is provoked
- Air flow pattern in Formulation area is important: supply and extraction air ducts to be developed with the process installation in mind, in order to prevent malfunctioning due to the process equipment.

Legislation and Regulations; standards and guidelines:
- Before the development of the concept is started a checklist about the legislation and regulations applicable to the installation should be made
- Good Manufacturing Practice:
- European legislation (EC):
  European Community GMP Guideline and Requirements; Annex 1, Manufacturing of sterile medicinal products
  - EC GMP Guide 3.42: Equipment labelling
- American legislation (US):

  **US CFR 21 part 211 subpart D-Equipment: Design, construction, cleaning, maintenance and automation**
  - US CFR 211.63: Equipment design and location
  - US CFR 211.65b: Equipment construction
  - US CFR 211.68a: Equipment calibration and maintenance
  - US CFR 211.105b: Equipment identification
  - US CFR 21 part 11: Electronic records, electronic signatures

- ISPE Baseline guides are a good and practical help to make the right interpretation of the EC and US GMP regulations. They provide practical guidelines to do the right things during the realisation and qualification of the installation: f.i.
  - Baseline guide for Sterile Manufacturing facilities
  - Baseline guide for Water and Steam Systems
  - Baseline guide for Commissioning and Qualification
  - GAMP

- Safety regulations: for Europe:
  - EC machine directive
  - PED (pressure equipment directive)

**Validation, qualification:**

- The combination of the above mentioned equipment, instrumentation, automation, and the realisation of the environmental conditions (the building) all in compliance with the regulations has to result into a validated production process.
- The qualification/validation process starts at the beginning or even before the project and runs parallel with the realisation of the installation:
  - Check EU and US GMP compliance of the equipment and building
  - Qualification of the system during DQ, IQ and OQ: from design to installation and operational tests: based on a test plan, test procedures,
test protocols and test results (all these most of the time to be supplied by the system builder)

- Process validation:
  - cleaning validation
  - thermal validation
  - microbiological validation
  - process product validation

- Certification: to be sure that the equipment is compliant to the GMP or to specific requirements most of the time certificates are asked to be delivered by the suppliers:
  - 3.1B or 2.2: material certificates: for stainless steel equipment
  - Material surface treatment certificates (Ra values)
  - 3A certificate: about the feasibility to clean the equipment
  - EHEDG: same as but more stringent than 3A certificate
4. EVOLUTION OF THE FORMULATION TECHNOLOGY TO STANDARDISED AND MODULAR CONCEPTS

History of formulation in a nutshell:

- Originally a formulation installation was only an extension of the utilities in a clean room area.
- A lot of the production process was based on manual operations.
- All these manual operations (including dressing of the operator, cleaning of equipment, …) to be covered by SOP’s.
- The performance of the process was highly dependent on the skills and seriousness of the operator.
- A 100 % guarantee on sterility and product quality with full traceability was impossible to realise, but this was accepted.
- Today, with evolution of the technology and the higher level of the requirements a sterile formulation installation is a very specific installation including:
  - CIP/SIP
  - Sterile containment technology
  - Sophisticated instrumentation
  - High degree of automation with batch application
  - Recipe driven process
  - Full traceability on installation history (from realisation onwards)
  - Full traceability of parameters of each produced batch (including CIP and SIP parameters)
  - High degree of communication with other installations or building management systems.
- To realise this, specific technical skills are needed. In addition to these a good knowledge of the pharmaceutical legislation and regulations is necessary to build an installation which can be qualified and validated in an acceptable time frame.
- Without validation, no commercial production is allowed.
Driving forces towards turn-key modular systems:

On the pharmaceutical clients side:

- Formulation and compounding installations have become speciality installations, engineered, realised and qualified by specialised suppliers.
- The pharmaceutical clients need guarantees about the performance, cleanability, sterility, product composition and the ease to validate the installation: a turnkey supplier for the whole installation can take full responsibility.
- Most formulation processes have the same process flow and the same type of equipment, (as described before) so standardisation and modularization is possible.
- Standardisation has to be combined with modularization: this way flexible solutions to the needs of the client can be realised.
- Testing and qualification of automated systems has become a very time consuming effort: standardised and modular concepts allow pre-tested and pre-validated equipment and software, thus reducing testing and qualification time.
- No interference of building construction with the construction of the process installation, this causes often delays in realisation time of the process installation, thus retarding the already time consuming qualification and validation. Process construction and testing runs parallel with building construction thus reducing overall project time.
- The client has the possibility to evaluate the installation, based on operational tests in the workshop, improvements can be made and tested in the workshop.
- Reduced time to commercial production due to reduced construction and qualification time.
- Predictability of the result, due to experience of supplier
- Easier to control project planning and budget due to experience of supplier
On the suppliers side:

- When involved in early stage: valorisation of specific knowledge and skills from the beginning of the project onwards
- Reduced engineering time.
- Reduced software realisation time: software configuration instead of software development.
- Standard testing and qualification procedures and protocols: no time consuming development of these documents.
- More efficient construction work in workshop: reduced construction time
- Suited for an international market: reduced construction and qualification time on site.
- Because of a standardised solution, easier to give guarantees about performances, sterility and ease of validation.
- Independent of the building construction and delays during the construction: instead of a sequential project planning a parallel planning is possible, thus reducing construction time
5. TRADITIONAL PROJECT CONCEPT VERSUS MODULAR SKID CONCEPT

See project time schedule of 2 formulation installations on next page.

- Both projects are similar installations: sterile compounding with mobile vessels
- Both projects are realised by a turn-key supplier (Egemin NV) from concept till operational qualification.
- Project value is similar: about 2.25 million Euro.
- In the case of detailed engineering being executed by an engineering contractor, project continuity would have been interrupted for a tendering and purchasing stage.

- Traditional project concept:
  - All mechanical and E&I construction works on site.
  - Construction on site started after building construction is almost finished.
  - All operational testing started after completion of mechanical and E&I works on site.
  - Operational testing had a lot of implications on the software, so software changes were necessary and FAT of the software was to be redone.
  - A lot of paperwork was done to justify the software changes.

- Modular and skid concept
  - Construction in workshop began at the same time that building construction was started.
  - Operational testing was started in workshop before official FAT: results of testing were integrated in software before commissioning (pre-SAT)
  - Installation was done on site before the building constructions on the formulation booth were finished, even the utilities were not installed yet.
  - After connection of utilities commissioning on site started.

**Time schedule:**

- The project time for the modular skid concept was about 6 to 7 months shorter.
- Because of more complex building works in the project with the prefabricated modular skids, a traditional on site construction only would have started about 4 to 6 months after the finishing of the skids in the workshop.
In this case the project would have been finished even later than the first traditional project, and this only because of the building construction.

Costs:
- The Modular skid concept gave some extra costs due to:
  - The construction of a temporary platform: simulation of site circumstances
  - Packing and transport
  - The overall assembly to be done twice: in workshop and on site
  - Some tests to be done twice: in workshop and on site
- On the other hand, due to shorter engineering and realisation time there was a cut down on cost for these activities
- The modular skid concept was an international project whereas the traditional on site project was in Belgium
- Construction and testing time on site was shorter than in the traditional project, thus limiting personnel travel and living costs.

Predictability of project results:
- The standardised and modular skid concept had some advantages on the predictability of:
  - Process performances
  - Time schedule for the realisation of the project was lined out accurately
  - Time to qualification
  - Budget control
### Project time schedule: comparison traditional versus modular project concept

<table>
<thead>
<tr>
<th>Task description</th>
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<th>Year 2</th>
<th>Year 3</th>
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<td>Mechanical works on site</td>
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<td>Operational FAT workshop (IQ)</td>
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<td>E&amp;I works on site</td>
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<td>Time reduction modular versus traditional</td>
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Remark: x due to changes to the WFI loop the operational SAT for the WFI loop had to be repeated.
Case study: a modular turn-key formulation installation

- **Concept engineering**

  The process equipment, the process operation and automation system, the utilities, the building, and the air treatment system were integrated in a modular concept with following modules:

  - CIP skid
  - SIP skid with vacuum unit
  - Compressed air and Nitrogen reduction station
  - Secondary cooling skid, WFI cooling included
  - CIP collector
  - 5 Works stations with integrated clean room walls and air ducts
  - 4 mobile vessels
  - Electrical cabinet and operator PC

*Modular Workstation with integrated clean room wall*
CIP skid: 3D model
Mechanical construction

Standardized Units, Equipment modules, Common Resources, integration of air ducts and SS clean room walls in the workstation modules. Assembly of all modular skids in workshop as it will be installed on site: temporary platform was built to realize real site circumstances.

Overall assembly of skids: 3D model
Construction of temporary platform in workshop

WS Skids assembly seen from the back
Automation

Modularity was realized at the mechanical and E&I level as well as at the automation level. The modular concept was developed according to S88 standards (standards for batch processes);

Standardized and pre-qualified operation phases are linked to the mechanical Units and the Common resources.

Out of these modular phases recipes are composed for operation of CIP, SIP, formulation, filtration, vessel pressure control.

For automation purposes the installation was split up in following units. Each unit has it's own configured operation phases:

- CIP unit: mechanical unit
- Cooling installation: mechanical unit
- Heating installation: mechanical unit
- Vacuum unit: mechanical unit
- WS (docking stations): mechanical unit
- SIP collector: common resource (a common resource links utilities to mechanical units, and/or units to units)
- CIP collector: common resource

See Modular Skid Concept below.
Modular Skid Concept

Utilities

- CIP preparation
- COOLING installation
- HEATING installation
- VACUUM unit

CIP Collector

SIP Collector

Docking station

VESSEL

EQUIPMENT

Utilities

PW

WFI

CST

SIP

CIP

...
- Testing and Qualification (IQ) of separate units in workshop
  Mechanical and E&I FAT in workshop, following standardized test plans, test procedures and test protocols

*WS with mobile vessel during FAT*
Testing and pre-qualification (commissioning) of the assembly
Operational tests with software of the assembly in the workshop.
Test utilities in workshop: demin water, steam, cooling water, compressed air.
Commissioning in workshop (pre-SAT or pre-qualification) of configured software.

Assembly ready for commissioning (pre-qualification) in workshop
Shipping and installation on site

The installation is followed by an assembly check and mechanical and E&I SAT (IQ) of the re-assembled installation.

After IQ is finished: commissioning on site with connected utilities and improved software.

Out of this the last changes are made to the software before the official FAT (qualification) of the software takes place, according to standardized test plan, procedures and protocols

Packing for transport
- **Operational Qualification on site**
  Qualified software is loaded into the installation, from now onwards all software changes have to be justified on paper.
  OQ: Operational Testing and operational qualification of the assembly with all utilities on site.

- **PQ and Process Validation (PV)**

  *View of Operational Qualification and Process Validation Activities*
6. GENERAL CONCLUSIONS

Automated formulation installations have moved away from being just utilities’ extensions and have become specialty installations requiring a high degree of technical skills but also knowledge about regulations and qualification/validation strategies.

As a result of this, specialized suppliers offer a turnkey approach for concept design, detailed engineering, realization and qualification of these installations. Nowadays, there is a move towards modular skid concepts, allowing prefabrication and pre-qualification.

Driving forces for modularization are:

- On one side: the increasing level of requirements of the pharmaceutical industries under the economic as well as of the pharmaceutical regulations’ pressure.
- On the other hand: the need of the supplier to increase efficiency in manufacturing and provide proven performances in an international market.

Profits of modular skid mounted turnkey projects:

- Reduced realization time.
- Reduced qualification and validation time.
- All this resulting in a reduced time to market of the drug (very important in case of a new drug).
- Predictability of the result: leading to strong guarantees, better budget estimation and better budget control
- Clear Responsibility.
- Easy to operate on an international market.
- Certain cost reductions, due to time reductions and standardization.
- Repeatability: same staff to engineer and construct the skids
On the other hand extra costs are involved due to:

- Simulation of site circumstances and utilities in the workshop (temporary platforms, supporting frames, ...).
- Dismantling, Packing, transportation and re-assembly of the skids on site.
- Some operational tests will be executed twice (in workshop and on site).

As such the main advantages of the modular skid and turnkey concept are a high predictability of the project results and clear guarantees and responsibilities. Economically a remarkable shortening of the time to market of the sterile drug is far more important than an eventual cost reduction in realization.