

Quality Assurance.

No detail left behind: A holistic approach to opening authorization in Sterile Manufacturing.

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The process of obtaining authorization to open a pharmaceutical site in France is governed by a standardized form issued by the ANSM. This form is structured into three main sections: the applicant's identity, detailed information about the future pharmaceutical site – including the name of the responsible pharmacist – and a technical note that precisely outlines all planned activities at the new location.

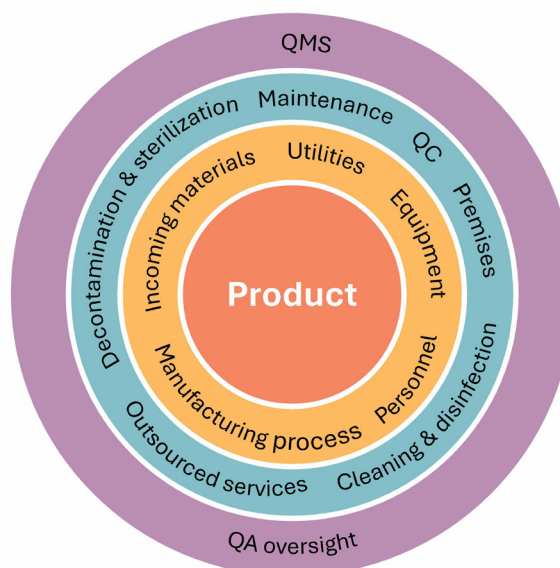
In the context of modifying an industrial site to accommodate a new sterile product manufacturing unit, any change to the pharmaceutical site must be reported to the health authorities. While the ANSM provides a formal framework, the structure and content of the modification request – particularly the description of its impact on existing operations – remain relatively flexible. The applicant is free to present the changes and their implications in the manner they consider most appropriate.

However, the responsibility for ensuring the completeness of the modification description lies entirely with the applicant. This task can be particularly challenging, as feedback from the authorities often resembles a detailed reminder of GMP. The goal of this article is to support pharmaceutical industrials in achieving a comprehensive submission by highlighting the key elements that should be described and included in the modification request. In some cases, the reminders provided in the various sections directly address specific expectations from health authorities.

The article outlines critical points to consider when submitting a request to modify the opening authorization of a pharmaceutical site. These points are organized into 12 sections, each corresponding to a specific activity or function within an industrial site.

All the sections discussed in this article aim to bring the product – positioned at the center of [Figure 1](#) – under control.

The first circle of elements to be put under control when initiating a change request in the regard of the obtained opening authorization. It includes those



↑ [Figure 1](#) : A quality product - the target of manufacturers

directly related to the product: incoming materials, utilities, equipment, personnel, and the manufacturing process. The following circle corresponds to support production activities, i.e. cleaning and disinfection, decontamination and sterilization, maintenance, QC, premises, and outsourced services. Finally, the QMS and QA oversight are intended to ensure the sustainability of processes to guarantee the overall product quality.

Section 1: Utilities

The sterile product manufacturing unit may follow a single-use approach, a conventional approach, or a hybrid of both, depending on the strategy chosen for the project. The utilities involved in such modifications are not always the same. In this case, we are addressing a

modification that requires the full range of utilities, namely various pharmaceutical-grade waters, clean steam, and process gases.

As part of this, the modification request must include a description of the creation and/or changes to the production/distribution systems for water, gases, and steam, along with the proposed design. The applicant must also justify the requirements for each utility involved (expected quality, point of use, use or not of terminal filtration). When filters are to be included in the installations, the control strategy for these filters must be detailed.

In certain cases, it may be relevant to describe the other utilities used – particularly when they are involved in controlling critical process parameters

When should you submit a modification request to the health authorities?

The list of modifications requiring a request to the ANSM is specified in Articles R5124-10 and R5124-10-1 of the Public Health Code :

- The manufacture or importation of a new category of products among medicinal products for human use, investigational medicinal products for human use, cannabis medicine, any system containing a radionuclide (generator, kit, precursor).
- The manufacture or importation of a new pharmaceutical form or a pharmaceutical product not covered by the current opening authorization.
- The implementation of a new

pharmaceutical operation related to manufacturing, importation, or exploitation.

- The creation of premises where pharmaceutical operations such as manufacturing, importation, wholesale distribution, or storage are carried out.
- The removal of premises where production and quality control operations are performed, or any removal of premises (including the change of holder of part of the authorization to open a pharmaceutical site).
- Changes to the storage conditions of drugs classified as narcotics.
- Modification of the distribution territory mentioned (for distributors).
- Relocation within the same site of a pharmaceutical site holding the

manufacturer status or the importer status, when their activities are limited to batch release.

- For manufacturers of medical gases, the addition of a storage room for packaged gases.
- Administrative change such as change in the legal form of the company, change in the corporate name of the company, appointment of a new responsible pharmacist, transfer of the registered office, change in the wording of the address of a pharmaceutical site, discontinuation of an activity or pharmaceutical operation (see Article R5124-10-1).

All other modification should be mentioned in the annual state declaration.

or clean utilities. For example, if temperature maintenance is required for critical process steps, it is appropriate to describe the technical elements used to control temperature (description of the planned monofluid system, such as glycol water, industrial steam, chilled water, silicone oils, liquid nitrogen).

Section 2 : Equipment

The new Annex 1 of the GMP guidelines emphasizes barrier technologies over conventional filling line configurations. It is the responsibility of the manufacturer to demonstrate the relevance of its technical choices. The operating principles of the newly implemented equipment must be explained, along with the proposed qualification approaches. Particular attention is expected regarding flow management, especially when barrier technologies are introduced on a site that previously did not have them.

In the modification request form, it is advisable to list the main equipment added, including their planned location, function, and operating principles. Depending on the case, this may include:

- Preparation area (weighing of raw materials, formulation tanks, storage tanks, filtration)
- Filling line (washing machine / depyrogenation tunnel / filling machine / capping machine / labelling machine / RABS / isolator)
- H₂O₂ airlocks / transfer isolators / autoclaves / RTP transfers / stopper preparation
- Freeze-dryer (including loading/unloading and tray handling if applicable)
- CIP/SIP systems for all equipment
- Packaging equipment

Special attention must be paid to the material flow into the cleanrooms. The transfer of materials through airlocks and cleanrooms must be described in detail, including the specific requirements related to transfer between different cleanroom classifications and any class breaks.

This section must also include the qualification principles for the equipment, specifying the parameters to be studied based on the equipment involved.

Finally, if the unit is to be equipped with a RABS or an isolator, the modification request must provide sufficient information on its design, airflow management and first air strategy, disinfection, integrity testing methodology and glove replacement, as well as cleaning and decontamination inside the barrier system.

Section 3: Personnel

Any request of opening authorization modification requires an assessment of human resource needs, both in terms of staffing and skills. New practices must be identified particularly if the asepsis mindset isn't yet implemented.

The planned production capacity, particularly the number of batches, may justify the adequacy of current or future resources with the introduction of new activities. A structured training plan must be established, including qualification, authorization, and disqualification procedures for personnel.

In the case of new technologies or pharmaceutical forms being introduced, specific strategies for microbiological monitoring and training must be implemented and described – particularly for operators, QC, and maintenance teams. The technical note must indicate – if the new unit requires additional resources in terms of skills or staffing – which departments are impacted by the change.

It is essential to justify this by specifying the expected capacity of the new unit in terms of the number of batches produced. The objective is to demonstrate that the resources available now or in the future will be aligned with the needs for implementing the new pharmaceutical activities.

The technical note must describe the training process planned for the new activities. It may also outline the procedures already in place for qualifying and authorizing personnel for their roles, or for temporarily disqualifying them depending on the context.

In the context of the new activity – especially if it involves the introduction of a new technology (e.g., barrier technology) – a strategy for microbiological monitoring of operators must be described in the technical note. The asepsis mindset is essential and should be outlined (major procedures like gloves management, aseptic behavior). If parenteral products – which by definition require sterility assurance – are introduced on site, all production and QC personnel must be trained not only in sterility sampling and testing procedures, but also in environmental and product microbiological control.

The personnel section in the request form should not only focus on the resources involved in the manufacturing or control of new products, but also on the entire chain of personnel involved, up to the release of the new products.

In particular, if the new activity involves a new pharmaceutical form (e.g., lyophilized product, vaccine, etc.), the staff responsible for certifying the finished product must be trained for the new product type or new process steps.

It is strongly recommended to specify that training plans will be updated specifically to incorporate this new pharmaceutical form – for all relevant roles: production, QC, and maintenance in particular.

Section 4: Manufacturing process including holding times, visual inspection

To facilitate the evaluation and approval of the request for modification, the process and all planned operations should be described. The proposed validation aspects must be outlined and explained, covering not only the manufacturing and filtration processes but also the filling steps and all auxiliary processes.

The description of the process and planned operations may be presented in the form of a flowchart to ensure easy understanding and to provide a comprehensive overview for the authorities.

The validation aspects of the new process must be detailed in the technical note, and should include but not limited to the following:

- Validation of the aseptic process, including the definition of critical operations and process times through a risk analysis,
- Validation of CIP processes, specifying the intended method,
- Validation of SIP processes,
- Depyrogenation validation,
- Validation of the overall process (concerning the new unit).

It is important to specify that the various critical durations introduced by the modification will be verified as part of these validation activities. The durations to be considered in the technical note include, among others: time between the start of manufacturing and sterile filtration, filtration duration, filling duration, loading time of a freeze-dryer (between sterile filtration and lyophilization), time out of refrigeration if applicable, as well as dirty holding time, sterile holding time, clean holding time.

Additional elements must be included, notably the flow between the exit of the fill & finish area and the visual inspection zone. Linked to the visual inspection activities holding times, monitoring of

time out of refrigeration, description of the intermediate storage area, time since terminal sterilization should be described.

The new Annex 1 of GMP also places significant emphasis on the filtration process and its associated requirements. Therefore, the product filtration modalities must be described, particularly the position of the filter relative to the filling point. The technical note must specify the validation strategy for the product sterilizing filter.

Section 5: Incoming materials (i.e. raw materials, components, single-use systems, consumables)

The opening of a new manufacturing unit is often accompanied by the introduction of a new product at the site in question. New product means new incoming materials, with supply conditions that may be more or less standardized. The addition of the handling of these raw materials, components, and consumables required for the production of the new product – and their impact on existing flows – must be assessed in relation to current material flows.

It is therefore essential to declare all new raw materials and consumables, particularly any new active substances. These changes must be subject to an impact assessment with respect to existing flows to ensure full control over the risk of cross-contamination. In particular, the management of any GMOs introduced as a result of the modification must be specified.

This section may also describe the implementation of SUS, where applicable.

Section 6: Premises

The addition of a sterile manufacturing unit can be implemented in several ways, e.g. by extending an existing building, integrating it into an active production area, or building an entirely new facility. Regardless of the approach, such a project inevitably alters the site's infrastructure.

When referring to infrastructure, this includes both the structural elements (e.g., building shell) and the production environment, with particular attention to confinement and air handling systems. Beyond these structural components, it is essential to provide a detailed description of all anticipated flows within the new manufacturing unit.

A comprehensive flow description should encompass product/intermediates movement, sample handling, personnel circulation, all types of materials, raw materials (including weighed materials), and waste management. The more holistic and detailed flow mapping, the better it supports regulatory expectations.

Additionally, the implementation of infrastructure control systems – such as an EMS – must be clearly described to demonstrate how the environment will be monitored and maintained under control.

The construction of the structural works mainly involves the provision of site layout drawings and building drawings.

The finishing works must include the basic technical characteristics of the materials and technical principles used (e.g., confinement & glazing, doors, floors, ceilings, airlocks). Details must be provided regarding the management of piping and drainage systems planned in the cleanrooms, particularly concerning

cleanability, maintenance, and disinfection aspects. Measures planned for the visualization of activities in Grade A/B areas must be described, and the area drawings should allow identification of glazed surfaces.

Air treatment systems are one of the key elements ensuring the sterility of manufactured products. Therefore, any request for modification must emphasize all related elements. Drawings showing cleanroom classifications, pressures, temperatures, and humidity levels (when controlled) must be attached to the request. When specific products such as plasmids or viral vectors are expected in the area, the specificities related to the nature of those products must be presented.

It is important to specify which AHUs will be newly installed or modified, as well as the list of rooms served by each AHU. The airflow principles applied to prevent any contamination (cross, particulate, or microbiological) must be described – for example, the use of low-level air intakes, implementation of sufficient air change rates, use of fresh or recirculated air, and the intended use of air extraction systems. Finally, the general operating principles of the air handling units, including during airborne decontamination phases, must be explained.

Nota bene: *If an H₂O₂ airlock is used and if it is considered as an equipment instead of a room, the airlock must appear on drawings. It is strongly recommended to specify the classification of the airlock.*

Furthermore, the qualification procedures for rooms and airflow (airflow visualization studies at rest and in operation) must be documented, along with the methods for defining the number of people per room.

Best Practices for Managing Flows

Numerous flows must be brought under control in a pharmaceutical manufacturing facility. They are interconnected and, in some cases, may intersect or occur simultaneously.

The main flows concerned are as follows:

- Semi-finished product / sample flow
- Personnel flow
- Waste flow
- Consumables flow
- Sterile equipment flow
- Clean equipment flow

- Dirty equipment flow
- Raw material flow
- Weighed material flow

As part of a request for modification of opening authorization, it is essential to apply the core principles described in GMP during the design of production areas.

Although personnel are by definition central to the management of flows – most often being responsible for moving materials from point A to point B – special attention must be paid to the handling of waste and dirty equipment.

Preservation measures must be

implemented, such as the temporal or physical segregation of flows (e.g., separation of material, personnel, and waste airlocks).



Cleanroom monitoring is generally ensured by EMS in which alert and action thresholds are defined, with appropriate delays depending on the criticality of the alert or action. The type of alarm reported (pressure, temperature, humidity) and the principle for defining alarms based on room types where alerts are triggered (e.g., airlocks but not Grade D areas) must be defined.

Another measure to control contamination risks is the management of flows both in the routine and during project, in case the production site is modified. All flows must be described, and should include but not limited to the following: personnel, raw materials, packaging items, consumables, bulk and semi-finished products, finished products, samples, dirty, clean, and sterile equipment, waste, and rejected units. In manufacturing unit designs which include Grade A and B areas, incoming and outgoing items must be managed with distinct unidirectional processes (either temporally or physically), meaning that entry and exit airlocks must be different. If such a design is not possible, the movement management of each type of item must be described in the technical note. Measures to prevent potential contamination of incoming items must be clearly specified. Measures planned to prevent cross-contamination must be described, and include a mandatory risk analysis detailing the means to protect the product, i.e. separation of flows in space or time, use of specific equipment such as BSCs, and application of personnel, material, and product flow rules.

If a modification is made in an active part of the building, it is recommended to carry out a risk assessment and define containment measures to ensure that the building works (risk of contamination, vibrations, dust, heat) and access by external personnel will not impact production areas near the new area in construction.

Finally, the arrangements for managing storage areas and associated environmental conditions must be described in detail.

Section 7: Maintenance

Maintenance activities must take into account the introduction of new technologies such as a RABS, an isolator, or an automatic freeze-dryer loading system. The specificity of these interventions requires the development of appropriate maintenance procedures.

These procedures must consider the scenarios for introducing tools into the aseptic environment, whether through the use of RTP (Rapid Transfer Ports), or through a strategy involving the permanent presence of tools within the isolator or RABS. These procedures must be challenged and validated during APS exercises.

Section 8: Quality control

When establishing a new area, the health authorities expect that new finished products – and therefore their associated controls – will be introduced, requiring analytical validation.

In addition, an in-process and finished product sampling plan must be outlined. Within this framework, sterility testing for each product must also be mentioned.

Section 9: Cleaning & disinfection

The planned measures for contamination control through the cleaning and disinfection of premises and equipment must be specified, even if such practices are already in place on site. The overarching principles for validating these processes must also be documented.

This section should describe the cleaning of premises, including the nature of the products used (disinfectants, sporicides, process-specific agents such as virucides, fungicides, biocides for plasmid removal). The cleaning of equipment – detailing the strategy for product-contact surfaces and, similarly to premises, the external surfaces and indirect product-contact parts of the equipment should also be described.

In the case of SUS, any remaining product-contact surfaces requiring cleaning must be clearly identified in the change request.

Section 10: Decontamination & sterilization

Since decontamination and sterilization are parts of contamination control in sterile product manufacturing areas, the request for modification of opening authorization must outline the planned approach. In particular, the technical note must present how critical elements will be controlled. It should mention the definition of the equipment concerned, the establishment of detailed loading patterns, and the acceptance parameters for the various cycles. The validation approach must be documented.

A list of materials to be decontaminated in the H₂O₂ airlock or autoclaved for introduction into Grade B areas must be provided. It is also necessary to announce the creation (or the update) of procedures detailing the loading configuration for the airlock, autoclaves, isolator, or RABS, to ensure complete surface decontamination or sterilization.

Acceptance parameters for H₂O₂ cycles (relative humidity / temperature / H₂O₂ quantity) or autoclave cycles (pressure / temperature) used in routine must be provided.

The strategy implemented for components in indirect contact with the product at the filling machine level, including washing, autoclaving procedures, and control measures for hidden surfaces or those exposing the first air must be presented.

Concerning validation/qualification aspects:

- H₂O₂ decontamination validation should include but not limited to residue measurement and the use of biological indicators.
- Sterilization processes must also be supported by biological indicators results.
- Processes combining sterilization and surface/air disinfection of equipment in indirect contact with the product must also be described and validated.

In any case, those exercises must be supported by a risk analysis.

Section 11: Outsourced service

When submitting a request for opening authorization modification, although no specific documentation is formally required by the authorities, it is important to recall that all outsourced activities must be governed by a written contract with clearly defined responsibilities. This applies even if the outsourced activities are not directly impacted by the project.

Furthermore, the contracting organization retains ultimate responsibility for the review and evaluation of records and results provided by the subcontractor.

Section 12: Quality Management System & QA oversight

The existing quality system is, in principle, applicable even in the context of new projects. Any necessary adaptations of the system for the new facility must be clearly described and must take into account aseptic control aspects.

The organization set up to ensure sterility assurance level should be described. The contamination control strategy planned should document means to ensure effective monitoring of the newly introduced aseptic process.

It is recommended that the CCS be established concurrently with the submission of the modification request. Quality Assurance oversight should be defined based on the CCS elements, in connection with the monitoring of the various activities.

Conclusion

This article has provided an overview of the key expectations when submitting a request for opening authorization modification. This exercise should not be underestimated, as it plays a crucial role in building confidence with regulatory authorities and demonstrating technical mastery of the new operations. A well-prepared submission facilitates both the approval process and the successful launch of the new manufacturing area.

To achieve this, several critical domains must be brought under control and clearly described:

- **Premises:** Layout, zoning, and classification of cleanrooms.
- **Utilities:** HVAC systems, water and clean steam systems, compressed gases.
- **Equipment:** Qualification status, integration of new technologies (e.g., isolators, RABS, automated systems), flow managements.
- **Incoming Materials:** Control strategies for raw materials, packaging components, consumables, and single-use systems (SUS).
- **Manufacturing Process:** Description of the process flow, critical steps and aseptic operations, validation aspects.
- **Personnel:** Staffing, skills, training plans, qualification and disqualification procedures.
- **Maintenance:** Adapted maintenance plans for new technologies and aseptic environments.
- **Cleaning & Disinfection:** Procedures, agents used, and validation strategies for both premises and equipment.
- **Decontamination & Sterilization:** Control of critical parameters, loading patterns, and validation of H₂O₂ and autoclave cycles.
- **Outsourced Services:** Contracts, responsibilities, and oversight of subcontracted activities.

- **Quality Control:** Analytical validation, in-process and finished product sampling plans, including sterility testing.
- **Quality Management System & QA Oversight:** Adaptations to the existing system, integration of the CCS, and QA involvement across all activities.

By addressing each of these items comprehensively, the submission will reflect a robust and proactive approach to quality and compliance, aligned with authorities expectations and industry best practices.

Glossary

AHU	Air Handling Unit
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
APS	Aseptic Process Simulation
BSC	BioSafety Cabinet
CCS	Contamination Control Strategy
CIP	Cleaning In Place
EMS	Environmental Monitoring System
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practices
HVAC	Heat, Ventilation and Air Conditioning
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
RABS	Restricted Access Barrier System
RTP	Rapid Transfer Port
SIP	Sterilization In Place
SUS	Single Use System