Notifications according to Article 41, MPLO

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1 Purpose and scope

Article 41 of the Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1) defines that all major changes to facilities, equipment, systems or procedures used in

- manufacturing (including testing),
- import or export of medicinal products (incl. active product ingredient and intermediates) or ATMP
- wholesale trading or trading abroad with medicinal products or ATMP
- brokerage or agency activities in connection with such products
- or collection of blood

which may have a quality relevant impact should be notified to Swissmedic by the establishment licence holder providing the respective required information.

This Technical Interpretation outlines the understanding of paragraph 2 of this article by the Swiss inspectorates. It is also intended to provide licence holders with information on which changes Swissmedic considers major in accordance to article 41, paragraph 2 of the MPLO and therefore to be reportable.

Note that this document is not aimed to instructing companies on their own, internal categorisation of changes, this being their sole responsibility, together with the GMP/GDP-compliant implementation of the associated required measures.

This Technical Interpretation applies to the Swiss inspectorates, which conduct inspections under the jurisdiction of Swissmedic (i.e., the Swissmedic inspectorate and the inspectorates of the cantons according to art. 60 TPA), subsequently referred to as inspectorates. It can be used by companies as a basis for assessing the need to notify to Swissmedic of major changes.

2 Basics

- Therapeutic Products Act (TPA; SR 812.21), Article 69
- Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1)
- Transplantation Act (TxA; SR 810.21)
- Ordinance on Fees Levied by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic; SR 812.214.5)

3 Definitions and abbreviations

ATMP	TpP/GT/GMO
ERP	Enterprise Resource Planning
LLM	Large Language Model
ML	Machine Learning
MPLO	Medicinal Products Licensing Ordinance (SR 812.212.1)
PQR	Product Quality Review
TPA	Therapeutic Products Act
TpP/GT/GMO	Transplant products/gene therapy products/genetically modified organisms

4 Notifiable changes per article 41, paragraph 2 of the MPLO

It is the responsibility of any licence holder to assess if a change falls within the scope of article 41, paragraph 1 of the MPLO and accordingly requires an application for the adaptation of the establishment licence, or if it needs to be notified according to article 41, paragraph 2.

A list of common examples of major changes within the context of article 41, paragraph 2 of the MPLO, requiring notification to Swissmedic, as described in chapter 5 of this Technical Interpretation, can be found in table 1. This list, which does not claim to be exhaustive, primarily applies to licence holders with manufacturing activities. However, those change types marked with an asterisk (*) may also pertain to companies operating in the GDP field (e.g., companies involved in distribution or wholesaler activities, etc.).

The notification of a major change per article 41, paragraph 2 of the MPLO must generally precede the implementation of the system, equipment, facility or procedure to which the change applies. Companies should submit the change notification with a reasonable margin of time before implementation, as the evaluation to be carried out by Swissmedic for the assessment and subsequent approval of the change may, depending on its nature and intended use, require time-consuming, in-depth evaluations and possibly an inspection. For example, in the case of a major technical modification, an extension of the plant or the start-up of a new manufacturing line, it is recommended that the corresponding change notification be submitted at least 6 months before the planned completion of the respective qualification activities or the first use for GMP purposes.

The timing of Swissmedic's formal decision may depend significantly on the nature of the notified change. In certain cases, it may be necessary for a company to begin implementing the change, and to use the affected plant, system, equipment, or process, before receiving the decision from Swissmedic that it has no objections. This may be required, for example, to generate the necessary supporting data and documentation.

It is therefore essential to emphasize that, in any case, the company must ensure, through robust, well-documented measures and effective change management, that the plant, system, equipment, or process affected by the notified change is only released for use once all applicable requirements have been fulfilled. If batches are produced during the course of the change realisation, these measures must also guarantee that such batches are not released for use in animals or humans until Swissmedic has confirmed that it has no objections to the change implementation.

Table 1: Major changes (art. 41, para. 2 MPLO) to be notified to Swissmedic

Area	Change
	Construction or revamping involving structural or technical measures of clean rooms used in manufacturing - of sterile active pharmaceutical ingredients or sterile products; - of low bioburden drug substances; - or of non-sterile products (incl. primary packaging).
	Construction of new buildings or lines used for secondary packaging of products (drug products).
	New production buildings or lines for the manufacture of chemically synthesized active ingredients.

Area	Change
	Construction or extension of temperature-controlled storage area* (e.g., climate chamber/rooms for controlled room temp./cold or cool storage, high rack storage area) for medicinal products, active substances, intermediates or ATMPs. Not included are stand-alone equipment like refrigerators, storage area for raw materials (incl. excipients), cell banks, packaging materials, stability and QC samples.
	Construction of rooms for collecting and processing of blood donations.
	Construction of new QC buildings or laboratory areas for the testing of medicinal products, active ingredients, intermediates, ATMP, in-process control samples or stability study samples, or relocation of the above-mentioned analytical activities into rooms of another building or area (incl. other floors of same building).
	Changes in the zone concept and/or classification of established clean room areas, incl. transfer of defined manufacturing activities into area with lower clean room requirements and adaptation of the pressure cascade strategy (e.g., reversal of pressure differences or provision of pressure sinks).
Clean Utilities	New system or upgrade of existing system for the generation, storage or distribution of water for injection (WFI), purified water (PW) and clean steam used in manufacturing.
	Introduction of new systems for the generation or distribution of process gases used in the manufacture of sterile medical products, sterile active ingredients or of low bioburden drug substances, or ATMPs.
Equipment / systems	Installation of new major processing equipment for sterile products manufacturing (e.g., filling line, RABS, isolator, freeze dryer, or depyrogenation tunnel), incl. equipment used for the terminal sterilization of products (e.g., autoclave).
	Introduction of new complex major computerized systems* used for the purpose of process control in manufacturing (incl. automation systems, manufacturing execution system) or material management systems (e.g., ERP system). Not included are software updates of the above-mentioned reportable computerized systems. Reportable is also the replacement or supplementation of paper-based manufacturing batch records or laboratory testing records by electronic record systems. Not reportable is the introduction of computerized systems used to manage personnel data (incl. learning management systems), SOPs or GMP records such as deviations, changes, complaints, audits or qualification documentation.
	Introduction or replacement of computerized system software with Artificial Intelligence/Machine Learning software* for use in manufacturing or supply (e.g., LLM for managing complaints, adverse drug reaction notification, PQRs, batch record review; ML applied to downstream processing to increase yield, or for automated visual inspection, etc.).
	Introduction of solvent recycling plants.
	Introduction of a new technology in production incl. new technology used for control strategies (e.g., continuous manufacturing, new type of major manufacturing equipment, new approach for container closure integrity testing or visual control of parenterals, 3D printing processes).

Area	Change
	Introduction of a new technology in quality control (e.g., introduction of rapid microbiological methods or methods using chemometric statistics), of new applications using artificial intelligence systems or introduction of process analytical technology (PAT) for process control, real-time release testing or parametric release strategy. The introduction of new analytical devices available on the market as standard and whose application is described in pharmacopoeias or comparable regulations (e.g., new HPLCs, Fourier-transform infrared spectrometer, GC-MS, etc.) does not require notification.
Product(s)	Change from a dedicated to multi-product manufacturing line/facility.
	Introduction of an organism of higher biosafety level or new type of genetically modified organism (incl. pathogenic or alien organisms that have been genetically modified) into an established manufacturing facility/building.

* Changes which may be relevant for companies with manufacturing activities and for those operating in the GDP field

5 Notification procedure

The change notifications with the corresponding relevant documentation, must be submitted in electronic form only using the “licences – major changes” eGov service. This will guarantee secure data communication between companies and Swissmedic.

To be able to use the “licences – major changes” eGov service, companies must request access to the eGov portal. More information is available on the Swissmedic Webpage https://www.swissmedic.ch/swissmedic/de/home/services/egov-services/licences-major-changes.html.

The planned changes should be notified using the form provided for this purpose and together with any relevant supporting documents as PDF via the eGov service. The notification form must be signed by the respective responsible person, either by hand or electronically. If the major change concerns various establishment licences (e.g., establishment licence for medicinal products and for TpP/GT/GMO), a change notification form must be submitted for each establishment licence.

The information to be provided includes, in addition to a description of the change, details of the planned realisation timelines, a list of the operational sites impacted, an overview of the planned measures and, if applicable, of individual main phases of the change implementation briefly summarized and, where appropriate, supplemented with supporting documents (e.g., change control, layout, project plan and/or qualification documentation).

The documentation will be assessed and the company will be informed whether additional information or time is required or if an inspection needs to take place before approval of the change. Any objections will be communicated in written form within 30 days after receipt of the notification. Fees are charged at cost.

Changes that have an impact on the establishment licence (art. 41, para. 1 MPLO) should be submitted only as a change request of the establishment licence.

Changes affecting the market authorisation of commercial products or investigational medicinal applications should additionally be submitted in accordance with the respective applicable procedure.

6 Changes to the previous version

- Chapter 1: clarification of the areas or activities per the establishment licence for which art. 41 paragraph 2 MPLO applies
- Chapter 4: addition of more detailed instructions regarding the timing for reporting major changes and the information to be provided when notifying a change; revision of table 1
- Various editorial adjustments