Legal requirements and mandatory due diligence by Mäkler* and Agents* acting in distributing of medicinal products on behalf of pharmaceutical companies

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Approval	Date:	Signature:
Author:	08.05.2023	Rosmarie Neeser
Technical verification:	08.05.2023	Federico Cimini
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1 Purpose and scope

Within the framework of the trade in medicinal products Mäkler[1] and Agents acting on behalf of pharmaceutical companies can play a key role by firms trading with medicinal products. In order to reduce the risks inherent to falsified medicines and to guarantee the safe supply of medicinal products to patients, it is also important for such a business model to ensure that it is always possible to prove that the quality of the medicines being traded is guaranteed throughout the entire distribution and supply chain.

In Switzerland this type of business activity is mandatory to be licensed due to the implementation of the Medicrime Convention (https://www.coe.int/en/web/medicrime) into Swiss legislation by the revision of the TPA and the MPLO by 01.01.2019. Mäkler* and Agents* are not the owner of the commissioned medicines, nevertheless Mäkler* and Agents* require an establishment licence granted by Swissmedic in accordance with Swiss legislation on therapeutic products and are regularly inspected.

This technical interpretation outlines in more details the legal requirements and due diligence for holder of an establishment licence for Mäkler* and Agents*.

2 Basics

- Therapeutic Products Act (TPA; SR 812.21)
- Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1)
- I-SMI.RL.02 Description, harmonisation and steering of the Swiss GMP/GDP inspection system for medicinal products

3 Interpretation

3.1 Legal framework conditions in Switzerland

3.1.1 Therapeutic Products Act

Distribution according to Article 4 paragraph 1 letter e TPA, means the transfer or release, either free of charge or in return for payment, of a therapeutic product, including activities as Mäkler* and Agents*. It does not include the dispensing of therapeutic products. This means that for all the trade activities with medicinal products, including brokering*, procuring, selling, donating or offering for free as well as promoting, including through advertising, these products are covered by the TPA and require an establishment licence from Swissmedic, either a licence for import, export, wholesale, trade abroad or as Mäkler* and Agents*. Although these activities are not all defined in details, it is understood to cover all activities in their widest sense, not being limited to physical movements of the goods.

Like all activities in connection with medicinal products that require licences, the conditions and valid due diligence requirements within the framework of obtaining an establishment licence for Mäkler* and Agents* are based on the provisions of the TPA. In addition to general due diligence, the licence holder must in general take all measures that are required in accordance with the current status of science and technology in order to avoid endangering the health of humans and animals (Art. 3 TPA). This applies not only to the manufacturing and the distribution of ready-to-use medicinal products but also for the manufacturing of active pharmaceutical ingredients and semi-finished medicinal products. Since manufacturers of medicinal products must comply with the recognised rules for good manufacturing practice (GMP) (Art. 7 para. 1

[1] Definitions of Brokers* such as Mäkler* and Agents* according to the Swiss legislation see Annex 1

TPA) and guarantee the quality of goods purchased throughout the entire supply chain, this requires firms that distribute medicinal products to guarantee the compliance of the goods they acquire, deliver and/or broker. As for certain medicinal products, export is prohibited (Art. 21 TPA), activities as Mäkler* or Agent* related to these medicinal products are prohibited as well.

3.1.2 Medicinal products licensing ordinance

Articles 24 - 26 MPLO define the requirements to obtain an establishment licence as Mäkler* or Agent*. This includes a functional quality management system with active involvement of the senior management, a responsible person that has direct supervision, an appropriate organization, a documentation system and fulfillment of duty of diligence. Appropriate measures in place that ensure an appropriate procuring of the medicinal products, documented evidence on the activities and the sales deal. The responsible person has to ensure the direct supervision on the activities as Mäkler* and Agents*.

3.1.3 The Code of Obligations

With regard to the definition of Mäkler* and Agents*, the TPA refers to the Code of Obligations (SR 220) according to Appendix 1. In order to be accepted as Mäkler* and Agents* they have to operate strictly within the limits of these definitions. They must have a permanent address and contact details in Switzerland.

This means that Mäkler and Agents are not wholesalers themselves, but they normally act on behalf of wholesalers. Mäkler/Agents look for potential customers for products of the contract giver or for specific products in which the contract giver is interested, however, they work in their own name (own legal entity). The sale of the product then takes place directly between the contract giver of the Mäkler/Agent and the customer, whereas Mäkler/Agents are no longer involved in the sale.

This also means that Mäkler* and Agents* operate on the basis of corresponding contracts on behalf of one or more contract givers. Only contract givers that are themselves in possession of a valid establishment licence for activities with medicinal products are acceptable. A contract giver of Mäkler* and Agents* must be able to prove its status as an officially approved wholesaler or manufacturer of medicinal products in his origin country. Acting on behalf of a Mäkler* and Agent* unable to provide a wholesale or manufacturing licence from the competent medicinal product control authorities is only reliable if proof can be provided that the contract giver's place of business does not require an official permit to trade in medicinal products. In this case, the contract giver must be able to provide an equivalent form of compliance proof.

3.2 Falsified medicinal products

Falsified medicinal products constitute a particular threat to the health of consumers and are considered to be a scourge by the international community. Not only is their trading prohibited, of course, but licence holders have the particular duty to identify falsified medicines and to avoid or, using the appropriate measures, to prevent them from reaching the legal sales channels.

Basically, all types of medicinal products can be falsified. From experience, however, the following categories are particularly liable to be counterfeited:

- Expensive medicinal products such as oncological medicines and those against the HI virus (AIDS);
- Medicinal products that are also used as "lifestyle drugs" and have a wide user base: for example erectile stimulants, slimming products, anabolic steroids;

- Medicinal products that have already appeared in the form of counterfeits in other European countries.

If such medicinal products are offered on the market at particularly low prices or if their origin is unclear, particular care is necessary. This also applies with regard to products offered from countries or regions with less stringent official controls and thus known to lead to a greater risk of falsified medicinal products in circulation. This should also be taken into account by any licence holder when selecting and examining sources of supply or clients.

In the international environment, a strengthening of the requirements within the framework of fighting falsified medicinal products is taking place. In 2013 revised Guidelines for the Good Distribution Practice of medicinal products came into force in Europe and, these Guidelines have been integrated into the legal provisions in Switzerland. Chapter 7 defined the standards for outsourced activities to other firms and persons. For trade with active pharmaceutical ingredients, section 17 of the EU GMP Guide Part II includes specific provisions for brokers. Mäkler/Courtiers and Agents are a part quantity of brokers and therefore these requirements are applicable.

The vulnerability of international trade in medicinal products with regard to falsification is well known. Swissmedic therefore considers it to be essential for Mäkler* and Agents*, located in Switzerland, to strictly comply with the legal requirements, to carry out their due diligence and to take the necessary measures to minimise the risks inherent to trading in medicinal products. Below, we indicate specific measures that should be taken into account in the international trade with medicinal products to minimise the risk of falsified medicines, plus issues that are particularly worthy of note. These aspects are also examined within the framework of official inspections in accordance with Article 19 TPA and the relevant articles of the MPLO.

3.2.1 Trading partners

The entitlement for trading partners (suppliers and purchasers) to handle medicinal products must be proven and regularly checked. The procurement and offering of medicinal products must be designed in such a way that the products are protected against manipulation by unauthorised third parties and that falsified medicines are prevented from entering the legal distribution chain. Checking trading partners is particularly important if the goods are not obtained from the original manufacturers or from their official trading partners but from a broker or another trader of medicinal products. A supplier must be able to prove its status as an officially approved wholesaler or manufacturer of medicinal products in his origin country. Distributing goods from a supplier unable to provide a wholesale or manufacturing licence from the competent medicinal product control authorities is only reliable if proof can be provided that the supplier's place of business does not require an official permit to trade in medicinal products. In this case, the supplier must be able to provide an equivalent form of compliance proof.

Documentation related to checking the entitlement for trading partners should be available on site for each transaction. Depending on the language, consideration should be given to gather authentic translations of the documents or include other checks of the authenticity of the information.

Particular precautionary measures are also necessary if ready-to-use medicines are brought back from retail trade into international trade. Distribution of this kind of products is only allowed in exceptional cases for which full evidence can be provided, in accordance with international standards, that the goods were appropriately handled at all times and falsified medicines can be excluded.

3.2.2 Proof of the quality of the goods traded

Any licence holder must carry out appropriate checks on the quality of the goods distributed and be able to provide proof thereof in a suitable form. Such proof can be, for example, based on certificates from the original manufacturer containing details of the quality of the goods and confirming compliance with internationally recognised GMP requirements during manufacturing. These controls of the quality aspects of the active pharmaceutical ingredient or the formulated medicinal product should however also take into consideration the correctness of the primary container, its labelling, the packaging, the shelf life or the secondary packaging, as well as related documentation.

3.2.3 Storage

It should be known if storage premises are used for intermediate storage of the goods or during their transport. These storage premises must be qualified for storing medicinal products and appropriate evidence should be available.

3.2.4 Transport

The transport conditions for each incoming and outgoing delivery of medicinal products must be known and ensured throughout the entire transport chain. Relevant proof must be available. The transport chain must be protected from risks of falsification.

3.2.5 Recall

The rapid recall of goods delivered must be possible at all times. This also applies in the case of suspected falsified goods. The procedure must be specified in detail and must include providing information to the competent medicinal product control authority rapidly.

3.3 Duties of the contract giver: Pharmaceutical companies

Mäkler* and Agents* are not the owners of the medicines. They act on behalf of a licensed pharmaceutical company and receive for their trading work a commission. Therefore pharmaceutical companies have to make sure that all their Mäkler* or Agents* (contract acceptor) are holder of a Swissmedic establishment licence as Mäkler* and Agents*.

A Swiss pharmaceutical company that mandates Mäkler* or Agents* in foreign countries has to ensure that the Mäkler* or Agents* abroad are under their control as critical service providers according to GMP chapter 7 and/or relevant GDP requirements.

3.4 Duties of the contract acceptor: Mäkler* and Agents*

The MPLO specifies the legal requirements regarding due diligence and states that the holders of licences as Mäkler* or Agents* need to operate an effective system to guarantee the pharmaceutical quality of medicinal products (Art. 24 para. 1 let. a MPLO), to document the relevant processes clearly (Art. 24 para. 1 let. d MPLO) and to guarantee the safe trading with medicinal products and the traceability of the purchasing and sales of medicinal products. The obligations of holders of licences as Mäkler* or Agents* are the following:

3.4.1 Effective system to guarantee the pharmaceutical quality of medicinal products

The Mäkler* or Agents* must operate an effective system to guarantee the pharmaceutical quality of medicinal products and it should involve active participation by the senior management

and the personnel. The quality system of a Mäkler* or Agent* should be defined in writing, approved and kept up-to-date. It should set out responsibilities in relation to the activities and include a quality agreement between the contract giving pharmaceutical companies and the Mäkler* and Agent*. The quality agreement should clearly define the responsibilities due to the legal requirements.

The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities (including outsourced activities with critical service providers) necessary to ensure confidence that the activities ensure maintenance of the quality and integrity of the products and supply chain at any stage.

The quality system should include an emergency plan which ensures effective recall of medicinal products by interacting with the suppliers, contract givers and customers. A change control system should be in place. This system should incorporate quality risk management principles and be proportionate and effective.

Deviations from established procedures should be documented and investigated. Appropriate corrective and preventive actions (commonly known as CAPA) should be taken to correct deviations and prevent them in line with the principles of quality risk management.

3.4.2 Organisation

A responsible person of the Mäkler* or Agent* should be appointed by the management, who should have clearly specified authority and responsibility for ensuring that a quality system is implemented and maintained and the legal obligations fulfilled. The responsible person must ensure a direct supervision on the establishment licence holder and ensure in particular compliance with the duties of diligence. If the responsible person of the Mäkler* or Agent* has only a part time mandate, a log book on his presence on site and his work as responsible person should be available.

The responsibilities of personnel should be defined in writing. The quality system should ensure that any member of personnel involved in the activities of a Mäkler* or Agent* is be trained in the issues concerning falsification of medicinal products as well as in the applicable national legislation and in the legislation of the countries where the Mäkler* or Agent* is active on behalf of the contract giver.

Suitable and sufficient premises, equipment and facilities should be available to ensure confidentiality and controlled access to the trading information and the complete documentation. Key equipment should be qualified if necessary to ensure correct installation and operation. It is the duty of the responsible person to ensure that there is close, expert supervision within the firm and that safety and product integrity is maintained at any time.

3.4.3 Documentation

Relevant standard operating procedures must be available to describe the activities. Records should be made contemporaneously and ensure traceability of the activities. Agents must record the transactions. Holders of an establishment licence as Mäkler* or Agents* should collect and preserve documents that are appropriate for proving the pharmaceutical quality of the medicinal products procured. The records should include at least the delivery date, quantity, batch number and precise description of the medicinal product plus the name and address of the supplier and recipient.

In addition, at least the following procedures and instructions, along with the corresponding records of execution, should be in place:

(i) procedure for complaints handling;
(ii) procedure for assessing potential risks regarding falsified medicinal products and for informing competent authorities and marketing authorisation holders of suspected falsified medicinal products;
(iii) procedure for supporting recalls;
(iv) procedure for ensuring that medicinal products distributed have a marketing authorisation;
(iv) procedure for verifying that their supplying wholesale distributors hold a distribution authorisation, their supplying manufacturers hold a manufacturing authorisation and their customers are authorised to supply medicinal products;
(v) records should be kept either in the form of purchase/sales invoices or on computer, or in any other form for any transaction in medicinal products distributed and should contain at least the following information: date; name of the medicinal product; quantity distributed; name and address of the supplier and the customer; and batch number.

Records should be made available to the competent authorities, for inspection purposes and archived for the period stated in national legislation but at least for five years.

Mäkler* or Agents* must maintain complete traceability and retain documents relating to the identity of the goods and of the original manufacturer, purchase orders, bills of lading, receipt documents, plus authentic analysis certificates, manufacturer's batch number and information regarding retest and expiry dates. The controls should be documented and the documents should be available on site for each transaction.

3.4.4 Qualification of suppliers and customers

The licence holder must make sure, that the suppliers and the customers are entitled to be involved in buying or selling medicinal products. The licence holder must be in a position to demonstrate appropriate documentation for each transaction.

3.4.5 Source of medicinal products

The licence holder as Mäkler* or Agent* should establish a distribution pedigree of the whole supply chain from manufacturer to the Mäkler* and Agents* and its customers, indicating flow of goods and financial flow. The Mäkler* or Agent* must ensure that medicinal products are not sourced from unknown or illegal sources and are not intended for an illegal purpose. The licence holder as Mäkler* or Agent* must be in a position to demonstrate appropriate documentation as a proof.

3.4.6 Information duty

The establishment licence holder as Mäkler* or Agent* must collect any information that may be relevant for the quality and/or safety of the medicinal product that is obtained from suppliers, customers or any other information source of his trading partners, especially also information that might be related to a recall. He must forward all information relevant to quality of the products to the recipient and/or the supplier and to the contract giving pharmaceutical company. In all cases, informing the recipient regarding the original manufacturer and the original batch number of the goods delivered and confirming that the information on the package has been verified and is correct.

3.4.7 Notifying competent authorities

The competent authorities, the contract-giving pharmaceutical company and the MAH (if licensed) must be immediately informed by the licence holders as Mäkler* or Agents* of any suspected falsified medicines offered in the supply chain and the actions taken.

4 Changes to the previous version

- Chapter 3.1.3: Precision
- Annex 1: Article 418a wrong title in English; Article 418c missing subtitle in Italian translation

5 Annexes

- Annex 1: Table – Abstract Swiss legislation due to Mäkler and Agents
- Annex 2: Checklist – Mäkler and Agents