European Focus Switzerland

Swissmedic – the Swiss Agency for Therapeutic Products
Registration activities relating to quality and GMP

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Summary
Swissmedic, Swiss Agency for Therapeutic Products – this is the full name of the new public agency of the Swiss Federation founded on January 1, 2002. The new Swiss Law on Therapeutic Products (Heilmittelgesetz – HMG) also came into force on this date, placing all activities concerning medical products under the control of the Swiss Federation. The new agency was formed from the amalgamation of the Intercantonal Office for the Control of Medicines (IOCM) and departments of the Swiss Federal Office of Public Health. Swissmedic is responsible for the control of all therapeutic products such as drugs, vaccines, blood, blood products, narcotics and medical devices.

Swiss legislation differs from EU regulations on various points. After a short introduction to Swissmedic's general activities, this article will focus on current activities in the fields of drug production, quality registration and GMP, together with differences between Swiss and EU regulations.

Introduction
As a controlling authority and active advisory body, Swissmedic, the Swiss Agency for Therapeutic Products, is the national Swiss authority for medical products and makes a major contribution to a high-quality health system. On January 1, 2002 Swissmedic, formed from the old IOCM (Intercantonal Office for the Control of Medicines) and departments for medical devices, blood products and vaccines of the Swiss Federal Office of Public Health, came into being as an independent public agency. It is affiliated to the Swiss Department of Home Affairs. As the supervisory authority for medical products, Swissmedic has around 280 full-time employees and is responsible for the availability of high-quality, safe and effective medical products in Switzerland. When registering new medicinal products, Swissmedic uses internationally valid registration criteria. This means that medicines may only be sold in Switzerland if their safety, efficacy and quality have been sufficiently proven and tested. If risks arise after the product has been registered, the agency takes the necessary safety measures. Through targeted postmarketing surveillance, information, and co-operation regulated by international treaties, Swissmedic makes sure that medical products are safe and are handled correctly.

Legal basis
The central legal basis is the Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products). Swissmedic came into being at the same time as the coming into force of the Law on Therapeutic Products on January 1, 2002. In enforcing this law particular care should be taken that the efficiency and independence of the Swiss control of medicines are preserved, that there are favourable basic conditions for research and development in the medical products sector, and that market competitors meet the same legal safety and quality requirements (HMG Art. 1, Section 3).

Together with the Law on Therapeutic Products, a number of ordinances were passed. Here only those of greatest importance to the manufacturing industry are given:

1. Ordinance on approvals in the medicinal products sector of 17.10.2001
2. Ordinance on medicinal products of 17.10.2001
3. Ordinance on the requirements for registration of medicinal products of 09.11.2001

All of these ordinances and accompanying instructions can be found on the Swissmedic homepage (www.swissmedic.ch) under Laws and standards/General legal basis.

ICH guidelines and EMEA guidelines, together with further guidelines from national authorities (eg, the FDA), are also consulted during assessment. It is important to know that, ultimately, scientific principles and arguments are the deciding factors when assessing registration documentation, rather than these guidelines.

Objectives and processes for achieving them
The objectives are established in the Swiss Federation charter. Swissmedic’s core activities essentially comprise the processes whereby those objectives are achieved.

The most important aim of the control of therapeutic products is to provide the population with effective, safe and top-quality medicines. This requires open dialogue with all bodies involved, particularly the pharmaceutical industry. The guiding principle of the Swissmedic vision is: “To protect the health of humans and animals we ensure that medical products are used effectively and safely. Our service to
customers is characterised by professionalism, high-quality information, and national and international integration." Particularly with questions of pharmaceutical quality, the provision of top-quality medical products must be a matter of concern to the Marketing Authorisation Holders and the authorities. The responsibility for this lies primarily with the firm’s technical management. Article 5, Section 1 of the Ordinance on Approvals in the Medicinal Products Sector therefore emphasizes: "the technical manager has direct technical control of activities and, in particular, ensures proper handling of medicines. He/she is responsible for the quality of the medicinal product and must ensure that it complies with the valid specification and is produced in accordance with the rules of Good Manufacturing Practice (GMP). He/she is authorised to issue rulings."

Swissmedic is responsible neither for the pricing of medicines nor for issues relating to monopolies legislation. Similarly, regulation of the market does not fall within its remit.

Organisation
The three organs of Swissmedic are the Agency Council (comprising seven members), the director and the review body. The responsibilities of the Agency Council are similar those of a board of directors of a limited company.

Management at Swissmedic controls the following departments: "Non-prescription Medicines, Medical Devices and Businesses", "Biological Medicines and Laboratories", "Prescription Medicines, Veterinary Medicines and Pharmacovigilance", "Inspectorates" and "Finance and Infrastructure". These departments are supported by the staff departments "International Affairs", "Planning and Quality Management", "Communication", "Personnel and Organisation" and "Legal Affairs". The process network defined as part of total quality management regulates the integration of the individual business processes.

International co-operation
The Swiss office for medicines control exchanges knowledge and experience with foreign institutions and is actively involved in the international harmonisation of medicines control. Co-operation with foreign authorities is regulated by Article 64 of the Law on Therapeutic Products. Under certain conditions confidential data can be exchanged with other authorities, particularly to avert serious health risks. Swissmedic implements bilateral agreements with the European Community on Mutual Recognition regarding medicines control. For this reason the test procedures need to be described in such a way that they can be repeated. They can be performed Experimental analyses at the Swissmedic laboratories support quality assurance. The fast-track process enables innovative, lifesaving medicines to be made available to patients as rapidly as possible.

Memorandum of Understanding with the FDA
The Memorandum of Understanding signed by ministers regulates the exchange of information between Swissmedic and the American Food and Drug Administration (FDA). In view of the global nature of the pharmaceutical market, the control authorities need to be more integrated.

The increased co-operation between the FDA and Swissmedic covers human and veterinary medicines and medical devices. Easier exchange of information enables early identification of risks and thus efficient intervention by the authorities. The aim is to implement safety measures as rapidly as possible in order to protect patients. The increased co-operation with the USA includes data on adverse drug reactions, quality defects and recalls of medicines and medical devices, and also details from registration applications and inspection reports on drug manufacturers.

Registration
Meditines that require registration include synthetic prescription or non-prescription human medicines, complementary and herbal medicines, biological medicines, vaccines and blood products, and veterinary medicines. During the registration procedure Swissmedic assesses the quality, efficacy and safety of the medicine using documentation submitted by the firm responsible (Marketing Authorisation Holder).

Since July 1, 2003 the common technical document (CTD) format has been obligatory for medicines with new active substances. The regulation will apply to generic medicines from January 1, 2005. Documentation should take into account the applicable guidelines of the International Conference of Harmonisation (ICH). In addition, as mentioned above, EMEA and FDA guidelines on assessment of the adequacy of documentation are taken into account. However, the state of the art always serves as the basis for assessment of documentation validity, and any controversial assessments are decided on these grounds. The fast-track process enables innovative, lifesaving medicines to be made available to patients as rapidly as possible.

Experimental analyses at the Swissmedic laboratories support quality assessment. For this reason the test procedures need to be described in such a way that they can be repeated. They can be performed before registration or, if necessary, during postmarketing surveillance.

If the three key criteria of quality, efficacy and safety are satisfied, Swissmedic establishes the supply category (prescription status/points of supply), approves the product information, and issues the registration certificate.

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Rules governing the notification of changes

Similarly to the EU, the Swiss Law on Therapeutic Products or rather the Medicines Ordinance (Arzneimittelverordnung) recognises three types of notification:

1. Changes that must be notified: Swissmedic is notified of these minor changes and if no objections are raised by the agency in the 30 days after receipt, the change goes ahead. Changes that must be notified are listed in Annex I of the ordinance on the registration of therapeutic products, and the accompanying instructions lay down the precise conditions and the documents to be submitted.

2. Changes that must be approved: all changes that do not require notification or registration must be approved. Medicines thus changed may only be sold after approval of the change.

3. New registration owing to a fundamental change, eg, change in pharmaceutical form or active substance.

In view of the new EU variations regulations valid from October 1, 2003, Swissmedic decided to test, during 2004, the currently valid rules governing notifiable changes and, where appropriate, to harmonise the regulatory provisions.

Manufacturing control

GMP inspections are generally conducted by regional inspectorates every two years. Approvals are issued by Swissmedic. The technical manager (EU: qualified person) has overall responsibility for the quality and registration conformity of the medicines produced and for adherence to GMP rules. EU GMP guidelines and, for active substances, ICH (PIC/S) guideline Q7A are applicable. In Switzerland the production of active substances is also inspected and corresponding GMP certificates are issued.

Medicines requiring new registration

With the coming into force of the new Law on Therapeutic Products on January 1, 2002, according to Article 95 many products which previously had cantonal approval require new registration. Even with these medicines, which are often produced only in small quantities, it is important to guarantee their efficacy, safety and quality. These are often medicines that are rarely used (orphan drugs) or which are antidotes. However, the same registration requirements as for other medicines must always be applied and exceptions must be carefully justified. An interim period applies and a special working group is dealing with applications which had to be submitted by 31.12.2002.

Activities of the official medicines control laboratory (OMCL)

Tests on samples of new types of drugs or high-risk drugs before registration and during postmarketing surveillance ensure that commercially available products are safe and comply with the registered specifications. The agency can request samples of a medicine or obtain them from retailers for this purpose. The ordinance on the registration of therapeutic products therefore expressly requires that test procedures be described in such a way that they can be repeated during a control. Test procedures which are not properly described may be rejected as early as registration. The samples requested from the company should come from a normal production batch.

Bioequivalence and bioanalysis

Various events have caused Swissmedic to check submitted bioavailability studies in close detail and, in particular, to closely examine the analytical part. In this case, the state of the art is considered to be the FDA guideline “Bioanalytical methods validation” of June 2001. Other procedures are possible, but they must be justified. It is often observed that anomalous results are not satisfactorily justified.

Quality defects and batch recalls

In accordance with Article 59, Section 2 of the Law on Therapeutic Products, anyone producing or selling medicines must report to the Agency any quality defects and any further findings or evaluations which could affect the basis of the assessment.

Swissmedic assesses reports and establishes measures. If batch recalls are necessary, the Marketing Authorisation Holder must inform the relevant people and the batch recall is published in specialist publications and in the Swissmedic journal. Swissmedic belongs to the PIC Rapid Alert system and, if necessary, exchanges the information with the other authorities. This procedure is also in line with the EU reporting procedure.

It is important that Swissmedic is correctly informed of any quality defects which arise. For example, Swissmedic must immediately be notified if stability tests show any deviations casting doubt on the quality of the medicine. In accordance with Article 59, Section 4, producers and patient organisations, as well as interested third parties, can report adverse effects and events. In all cases Swissmedic will consult the Marketing Authorisation Holder to reach a decision which both guarantees patient safety and is commensurate with the situation.

Outlook

Swissmedic came into being at the start of 2002. The Director of Swissmedic recently stated: "We can be pleased with the results of the intensive structuring and reorganising phase. Swissmedic is currently operational in all areas. Among other things, during the past year a comprehensive risk analysis and risk assessment was performed, the allocation of responsibilities was resolved with the cantons, a criminal law service was founded, long-overdue ordinances were drawn up and measures against the import of counterfeit medicines and internet trade were introduced. Swissmedic will continue to use all its powers to ensure that medicines are effective and safe.

Dr Hans Ulrich Gally is a qualified chemist with a doctorate in Biochemistry, and has been Quality Reviewer at Swissmedic, the Swiss Agency for Therapeutic Products, since Spring 2002. Previously he worked for 22 years as Head of Quality Control, Head of Production, and Head of Quality Management at various manufacturing firms, his last position being as Technical Manager at Knoll AG, Liestal (Switzerland). He is head of the SAQ’s (Swiss Association for Quality) expert group on pharmaceutics and chemistry.

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