Commentary

Providing Quality Therapeutics in Switzerland: Role of the Stakeholders and Recent Incentives for Further Improvements

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ABSTRACT

Quality therapeutics play an important role in Switzerland's health care and economy. Switzerland holds a key position in the world of research and development, as well as in drug production. Recently, new emphasis has been placed on promoting clinical research and maintaining Switzerland's position as a center of excellence in the field. Recent revisions to the law regarding medical trials in human research allow for better allocation of regulatory resources and simplified procedures for drugs already authorized in Switzerland. The country has its own regulatory agency, the Swiss Agency for Therapeutic Products (Swissmedic), which is a public institution of the Swiss government. Swissmedic is responsible for ensuring safety in medicines, particularly regarding authorizations and market surveillance in the sector of medicinal products and medical devices. Although the centralized authorization procedure of the European Union for medicines does not apply to Switzerland, there are mutual recognition mechanisms between the Swiss medicine regulatory authority and the European Medicines Agency. Swissmedic is also in charge of postmarketing safety and oversees the national pharmacovigilance center, which collaborates closely with the World Health Organization center in Uppsala. In addition, university hospital–based clinical pharmacologists, who are involved in basic science and clinical research, regulatory affairs, ethics committees, and pharmacovigilance, promote quality therapeutics. This article discusses the role of the various stakeholders and the recent efforts made to provide a better allocation of resources aimed at further improving quality therapeutics in Switzerland.

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INTRODUCTION

Switzerland is a leading force in the European pharmaceutical industry and was ranked third on the list of the top 5 investors in pharmaceutical research in Europe in 2012.[1] That same year, Switzerland was the leading European exporter of pharmaceutical products. This highlights the key position of the country in the world of research and development as well as in drug production. Switzerland is thus a strategic market in which to develop and launch new therapeutic products. In 2011, Switzerland hosted 468 manufacturers that were Good Manufacturing Practice certified.[2]

Switzerland produces various drugs (including new active compounds and generics), as well as biotech and gene tech products (including innovative biopharmaceuticals and biosimilars). In pharmaceutical research, >85 patents per 1 million employees were registered from Switzerland between 2000 and 2010. Moreover, between 2007 and 2010, of the 20 countries with the largest number of publications, Switzerland was the most productive, at 3.6

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publications per year for every 1000 inhabitants, according to the bibliometric evaluation of research in Switzerland made by the State Secretariat for Education. In term of citations, Switzerland occupied second place in the world rankings during the same period (behind only the United States).[3]

However, despite these positive findings,[3] it is noteworthy that Switzerland has experienced a decrease in clinical research over the last few years in all clinical trial phases, especially marked in Phase I research (–58%). Therefore, in 2013, the motivation to strengthen biomedical research, and clinical research in particular, led to the approval by the Federal Council of a master plan solidifying measures to maintain and boost Switzerland as a center of excellence for research, development, and production in the biomedical industry.

As part of this master plan, a working group of the Swiss Academy of Medical Sciences and the Federal Office of Public Health recently published recommendations on how to encourage clinical research.[4] The emphasis is mainly on increasing the teaching of clinical research early in the medical student curriculum and on early identification and orientation of potentially interested fellows. In addition, hospitals are strongly encouraged to create work conditions that allow time for clinical research and support research commitments.

The present article describes the actual rules for performing clinical research in Switzerland, how the drug regulatory system works, and the role of the different stakeholders in promoting quality therapeutics.

CLINICAL TRIALS NOTIFICATION AND APPROVAL

Clinical trials can only be conducted in Switzerland if they have been approved by 1 of the 9 national Ethics Committees (ECs). Since January 2014, the roles of these ECs and of the Swiss medicines regulatory authority have been redefined, the former being in charge of scientific and ethical assessments as well as the risk/benefit balance approval of the research project, whereas the latter is now in charge of the quality and the safety of the studied product.[5]

According to the 2014 revision of the Ordinance on Clinical Trials in Human Research from the Federal Act on Medicinal Products and Medical Devices, ECs must classify research products into 1 of 3 categories. Category A includes products that are already authorized in Switzerland, used in accordance with the prescribing information or used in a different dosage or indication, but within the same group of *International Classification of Diseases*. The disease for which they are prescribed must be self-limiting, and the studied dosage should be lower than that specified in the prescribing information or should be recognized as standard in internationally accepted quality criteria guidelines. Category B products are those already authorized in Switzerland, but which do not fall into category A. Category C encompasses those products that are not authorized in Switzerland.

Category A products are exempted from providing notification to the Swiss medicines regulatory authority. When required, submission to an EC and to the regulatory agency can be made simultaneously. This revised status of the Ordinance on Clinical Trials in Human Research allows a more targeted use of resources and competencies and the avoidance of redundant evaluations and procedures, and aims at reducing the required time for acceptance.

SWISSMEDIC

Switzerland has its own regulatory system, and the centralized authorization procedure of the European Union (EU) for medicines does not apply to Switzerland. However, there are mutual recognition mechanisms between the Swiss medicine regulatory authority and the European Medicines Agency (EMA), which we discuss later in more detail.

Swissmedic, the Swiss Agency for Therapeutic Products, is the medicines regulatory authority and is a public institution of the Swiss government. The responsibilities of Swissmedic are similar to those of other health authorities. It is the enforcement entity regarding legislation on therapeutic products and, as such, is responsible for ensuring that the products are effective and safe but also of high quality. Swissmedic therefore deals with authorizations and market surveillance in the sector of medicinal products and medical devices.[6] Swissmedic is run by an agency council appointed by the Swiss government and by an executive director, but it is also supported in its regulatory task by the Swiss Medicine Expert Committees (SMECs).

SMEC members provide independent advice and recommendations on scientific and technical matters related to the development and evaluation of products regulated by Swissmedic. SMEC members give advice on various aspects of clinical investigations and applications for marketing approval of drugs. SMECs are

divided into the Human Medicines Expert Committee and the Veterinary Medicines Expert Committee. Committee members are scientific experts (eg, physicians, researchers, statisticians), and they are elected by the agency council. The public and the patients are not represented in these committees. To promote transparency and ensure independency, SMEC members must declare their potential conflict of interests; these lists of conflicts of interest are made accessible to the public. Mutual recognition mechanisms exist between Swissmedic and EMA; however, there are principal differences (discussed later in more detail).[6–8]

Swissmedic requirements for marketing authorization application (MAA) are available on their Web site.[6] Because Switzerland has its own regulatory system and is not involved in the centralized authorization procedure of the EU, MAA applicants must hold a Swissmedic-delivered establishment license. This requires creating a quality management system, which must be inspected and accepted by Swissmedic.

Article 13 Procedure

Unlike EMA, which always performs a complete assessment regardless of whether the product has already been accepted in another market (eg, the US market), Swissmedic may consider previous foreign regulatory agency assessments and advice in its product evaluation. This procedure is discussed in Article 13 of the Therapeutic Products Act.[6,9] In these cases, Swissmedic will perform its own evaluation, but the Article 13 procedure allows the process to be accelerated by taking into account the advice of reference authorities of countries having a similar control system. These countries include EU members as well as the United States, Canada, Australia, New Zealand, Singapore, and Japan. The Article 13 procedure may be applicable for any drugs including orphan drugs but with several exceptions (eg, oncology products). The Article 13 procedure does not apply to these exceptions; they must follow the standard full evaluation, unless they satisfy the requirements for a fast-track procedure (discussed later).

Previous approval from a foreign reference country may include known active substances or generics, new active substances, or extended indications and parallel submissions to Swissmedic and EMA for marketing authorizations or modifications. This procedure allows medical products already authorized in foreign countries to be available as quickly as possible for Swiss patients and aims at ensuring targeted use of the agency's resources.[6] This regulatory pathway should not been mistaken for the EU mutual recognition procedure, whereby member states recognize marketing authorization of another member state. Swissmedic makes its own evaluations and conclusions in any case and can deny authorization to a drug that has previously been accepted in a reference country.

Fast-Track Procedure

A fast-track procedure is available to ensure that patients have early access to innovative medicines for life-threatening diseases.[6] This procedure decreases the maximum evaluation time limits from 330 to 140 days. To be eligible to enter the fast-track pathway, products must satisfy 3 conditions: they must be a promising therapy for severe, debilitating, or life-threatening illness; current treatments of these illnesses must be only partially effective or absent; and the unmet medical benefit expected from the use of these products must be considered high.

The accelerated assessment procedure is also available within the EU. However, the definition of eligibility is somewhat broader in the EU because the procedure applies to medicines "of major interest from the point of view of public health and from the view point of therapeutic innovation."[7] In the EU, the accelerated assessment procedure decreases the maximum evaluation time limits from 240 to 150 days.

Orphan Drugs and Simplified Procedures

Under various circumstances, products may qualify for a simplified review procedure. This is the case for known active substances or complementary medicine. Orphan drugs that are not approved in a reference country can also seek authorization under a simplified procedure. In line with the EU regulation, proof that the disease affects <5 people in 10,000 must be offered. Although the EMA does not recognize an orphan status granted in another region and the designation must be validated by the EMA's committee for orphan medicinal products,[7] Swissmedic will often recognize an orphan status bestowed by another country or region.

Pharmacovigilance

Pharmacovigilance activities are a part of the Swissmedic mandate, and Swissmedic oversees the national pharmacovigilance centers. Marketing authorization holders are required to continuously monitor the safety of their products and to report findings to Swissmedic.[6]

Since 2001, the adverse drug event reporting system in Switzerland has been an independent network of drug safety surveillance that relies on university hospital–based clinical pharmacologists to create a link between primary care physicians and other health care professionals and Swissmedic. There are 6 different regional pharmacovigilance centers located in the clinical pharmacology divisions of the university hospitals. Causality assessment, case investigation, and risk assessment are initially made by these regional centers, and the data are then forwarded to Swissmedic for final validation.

In addition to a standard paper format, an electronic form for reporting adverse drug reactions (ADRs) is now available to be completed by primary reporters or small drug companies. Bigger pharmaceutical companies have direct access to the Swissmedic electronic reporting system. The reporting of ADRs is mandatory for all health care professionals and is optional for patients.[9]

The national pharmacovigilance center regularly publishes ADR bulletins, vigilance news, and updates on already known safety concerns in Switzerland. Information pertaining to ADRs is stored in a national ADR database. These reports are also forwarded to the World Health Organization collaborating center in Uppsala, and Swissmedic has access to all reports available in their database.

Routine and crisis communications are the responsibility of Swissmedic. A clear communication strategy for these communications is in place.[6]

DRUG PRICING, SOCIAL INSURANCE, AND REIMBURSEMENT

Drug pricing of the basic insurance for all residents in Switzerland is negotiated between providers (eg, pharmaceutical companies) and the Federal Office of Public Health, with the assistance of the Federal Medicines Commission. This commission incorporates representation from stakeholders, including physicians, pharmacists, insurers, and industry members.[2] The so-called "specialty list," which is a list of pharmaceutical products with the ex-factory prices and public prices (including distribution margins) to be reimbursed by the basic insurance plans, is available.[10] Swissmedic is not involved in drug pricing.

In Switzerland, 100% of the resident population is covered by a public health service, public health insurance or social insurance, or other sickness funds, and 29.5% are covered by private health insurance.[2] There are many insurance companies, rather than a single national insurance program. However, tariffs and drug prices in the basic insurance system are regulated.

These various services provide at least partial coverage for essential medicines for inpatients as well as outpatients. The so-called specialty list is the relevant reference and offers coverage for almost all diseases, including orphan drugs. In 2011, a total of 7500 pharmaceutical products were registered in Switzerland, of which >2500 were reimbursed by the basic public insurance.[2] There is a general 10% copayment, up to a maximum of 700 CHF annually (approximately US $700) for adults and 350 CHF annually (approximately US $350) for children. There is a franchise amount below which medical care is not reimbursed; this amount varies according to the premium per month the patient selects.

ROLE OF UNIVERSITY HOSPITAL–BASED CLINICAL PHARMACOLOGISTS IN CLINICAL THERAPEUTICS

In addition to being largely involved in basic science, translational, and clinical research and clinical trial units, the role of university hospital–based clinical pharmacologists in Switzerland is to promote quality drug therapeutics by integrating drug efficacy, safety, and costs.

Clinical pharmacologists are involved in drug regulatory affairs; there are 3 clinical pharmacologists among the permanent members of the Human Medicines Expert Committee, 1 of whom is the president of the board. Clinical pharmacologists are also represented in research ECs and hospital drug committees wherein they actively promote an evidence-based approach to decisional processes. The aim is to promote the use of drugs according to their MAA (and hence to limit off-label use) and also to take into account their reimbursement status (favoring the products that are in the specialty list or generics substitution).

Drug safety is among the primary targets of the hospital-based clinical pharmacologist because this topic is a major public health concern and because of the human toll and financial implications of ADRs. In Switzerland, 7% of hospital admissions are considered to be due to ADRs.[11]

As described earlier, hospital-based clinical pharmacologists have a crucial role in the independent ADR-reporting system network. They create the most efficient link between primary care physicians and Swissmedic and promote active reporting among health care professionals. Furthermore, Swiss clinical pharmacologists actively seek opportunities to enhance drug safety by education. At the

pregraduate level, clinical pharmacology has a substantial place in medical training in times of curriculum changes that emphasize small-group, problem-based learning formats in many areas of medicine such as internal medicine and psychiatry. Involvement in postgraduate medical training has also been centered on drug safety, and hospital-based Swiss clinical pharmacologists have developed consultation teams with expertise in therapeutic individualization to meet the challenge of increasing drug regimen complexity in either acute or chronic care settings. Thus, clinical pharmacologists provide other physicians with instruments for integrating comorbid diseases and pharmacogenomics or environmental factors into daily prescriptions. They also provide consultations on anticipation and detection of drug–drug interactions, drug dosage adaptation, therapeutic drug monitoring, drug exposure during pregnancy, toxicology, and poison management.

CONCLUSIONS

Various stakeholders collaborate to ensure quality therapeutics in Switzerland, including retaining high standards regarding quality of research and development and drug production, encouraging a fast and efficient ethical evaluation and marketing authorization process, and promoting postmarketing safety monitoring. To continue in this manner, as well as to respond to the noted decrease in clinical research in Switzerland over the last few years, many reflexions and efforts have recently been made. The 2013 master plan is devoted to strengthening clinical research, including the early identification of interested fellows and their early training; the 2014 simplification of the ethic approval procedure, with the classification of clinical trials into 3 categories (A–C); and intensifying existing collaborations between Swissmedic and EU or non-EU country agencies to allow for better allocation of resources and faster processes. The added value of hospital-based clinical pharmacologists in this process is another promising example of the changes being made.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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