Pharmaceutical regulatory change is driven by a number of factors, one of the most influential being the harmonization process lead by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (Detailed information and guidelines are available on the ICH homepage.) The ICH is essentially composed of six parties: the three major regulatory authorities of the USA, Europe, and Japan, and the three corresponding associations of pharmaceutical manufacturers. It would seem natural that the guidelines produced by the ICH are international in scope and purpose. The ICH produces “soft law” regulations that are by definition not legally binding. An ICH guideline has no more binding power than a resolution of the General Assembly of the United Nations. Once adopted by a country, they may become as binding as law (for example, the new Japanese good clinical practice [GCP] guidelines). As with resolutions, guidelines are adopted in a consensual way and reflect the minimum status of agreement on any topic. Considering this, the ICH has been successful in harmonizing regulations from all regions into one set of rules acceptable to all. Japan has accepted the changes necessary to reach agreement.

The regulatory authority

The Japanese regulatory authority is not well known to the rest of the world, as is the Food and Drug Administration (FDA). Japanese information is hard to access because of differences in language and culture. It is true that the Japanese Ministry of Health, Labor, and Welfare (MHLW) is a complex organization, although any regulatory authority is by definition complex. Its ancestor, the Ministry of Health and Welfare (MHW), implemented many current regulations and decisions. Information on both organizations is available on the Internet.
The pharmaceutical regulatory authority of Japan is the Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW. This is where the decision for application approval is formally made. Two other bodies deal with the pharmaceutical industry on a day-to-day basis. The Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), usually known as “The Center,” is the actual decision-maker for approval of new drug applications (NDAs). The Organization for Pharmaceutical Safety and Research (OPSR), also known as “Kiko” or “the DO” (Drug Organization), is an independent body, related to the MHLW, that is in charge of discussing drug development programs with industry. A merger of these two organizations has been announced in the past few years, and would result in the creation of an equivalent to the American FDA. The three aforementioned organizations are involved in approval reviews, and the regulatory body and ultimate decision-maker is the MHLW. Although it is not a requirement, companies are strongly advised to negotiate their development programs with the DO. More detailed information can be found in Pharmaceutical Administration and Regulations in Japan 2002, published by Japanese Pharmaceutical Manufacturers Association (JPMA) on their homepage.

The structure of Japanese regulations regarding development of pharmaceuticals is as follows: the Pharmaceutical Affairs Law (PAL), and especially its Article 14, is the organizing principle. This law is currently being revised. The MHLW implements legally binding regulations by way of ordinances. This is the way the MHLW has chosen to publish the PAL enforcement guidelines and, in 1997, to implement the guideline ICH E6, regarding GCP. Lesser regulations can be easily implemented through publication of a “Notification of the Pharmaceutical and Medical Safety Bureau (PMSB),” which makes them not legally binding. These regulations must be followed in order to obtain regulatory approval. This is how the guideline ICH E5 or the “ethnicity guideline” was introduced in Japan. Many other guidelines exist and, like in many other countries, older regulations sometimes coexist with newer ones. Old guidelines may remain applicable and it is important to consider following them, or else providing the MHLW with a reasonable argument regarding their obsolescence.

A revolution in Japan

The implementation in Japan in 1997 of the GCP guideline ICH E6, known in Japan as “the new GCP,” has had a considerable and almost revolutionary effect on the Japanese regulatory environment. Although ICH guidelines are usually simply translated into Japanese, ICH E6 was published in three separate documents, the most important of which is the Ministry Ordinance #28. An English translation of the Japanese GCP is available.

Traditionally, the pharmaceutical industry does not receive a lot of trust from the public in Japan, following a number of scandals in past and recent years. Western medicines are seen as potentially dangerous, and the Japanese authorities have always put the emphasis on safety and quality issues, rather than efficacy. Incentives for patients taking part in clinical trials were already low, because of the comprehensive coverage of medical costs that Japan offers, and the very strict rules for compensation. Doctors have no financial incentive, and academic incentive is limited in a pharmaceutical world in which Japan is usually the last place where companies develop their drugs. When a drug is first developed in the US and Europe, nothing of interest is left for the Japanese investigators to publish. The guideline worsened a situation that was already bad. Many organizations involved in clinical research found in 1997 and 1998 that they were unable to cope with the new regulations. The new written informed consent was a major difficulty, having been designed for a culture where doctors pay heavy malpractice insurance fees, and patients can sue if something goes wrong. Although the degree of
trust in their doctors has also decreased in Japan, it remains very high, and doctors would usually only have to “advise” their patients that a certain trial would be beneficial to obtain oral consent. Therefore, the practice of written consent became an issue, given that doctors lacked the time and training to obtain it, and that staff such as trial nurses or clinical research coordinators (CRCs) were not available. Contract research organizations (CROs) or site management organizations (SMOs) did not have the workforce necessary to help the industry and hospitals adapt to the new regulations.

In the years that followed, the number of patients involved in clinical trials was cut by half, as was the number of trials, number of submissions, and number of regulatory approval for new drugs. It is only now, more than 5 years after the new GCP went into effect, that the numbers have started to increase. This is mainly the result of a tremendous involvement in clinical research of CROs and SMOs.

In 1997 the new GCP regulations allowed the CROs to take over responsibility of phase 2 and 3 clinical trials. The availability of skilled personnel has been the limiting factor for these companies and they struggle to recruit new staff in the population of pharmacy graduates. As a result, CROs in Japan are still extremely busy, and availability is minimal. SMOs traditionally staffed phase 1 units, and had to be legally separate from CROs for fear of collusion (industry and hospitals must stay apart: CROs help industry; SMOs help hospitals). In hospitals involved in phase 2 and 3 clinical trials, SMOs now assume the training of physicians and nurses, setup of clinical trial centers, staffing with the CRCs, writing of standard operating procedures (SOPs), and interaction with monitors or auditors from the regulatory authority. Even more than CROs, SMOs suffer from a lack of qualified staff. Most CRCs in Japan are currently involved in the training of other CRCs.

The concept of ethnic bridging

The guideline ICH E5, the ethnicity guideline, can also be qualified as one of the most influential guidelines of the past few years in Japan. The aim of this guideline was to reduce duplication of clinical studies by setting up a process for evaluating the possibility of extrapolating clinical data from one regulatory area to another. Overall, this guideline has been successful in reducing the necessity to reproduce clinical research programs in Japan for drugs that have already been approved in the West. The guideline describes in detail which drugs may be more easily “bridged” from one area to the other. Experience has proven that it is by closely negotiating with the DO that companies have the best chances of obtaining approval.

In all cases, additional information regarding the pharmacokinetics of the drug in the new population is needed. This can be done by comparing data obtained in Caucasian volunteers with new data obtained in Japanese subjects in Japan or in the West. The best way is to design a comparative trial involving both Japanese and Western subjects in one protocol. The guideline is carefully worded to allow these studies to be performed in Japan, in the West, in one site, or in two sites. All possible combinations have been tried, and none is completely satisfactory.

Single-site studies conducted in the West have been faced with the difficulty of recruiting Japanese volunteers outside of Japan. The subjects’ visa situation as well as tax issues have limited the availability. In addition, the authorities regularly question the quality of the Japanese subjects recruited abroad.

Two-site studies simplify the question of recruiting, each arm of the study being conducted locally. The difficulty here lies in harmonization of the protocol to fit two facilities, and in cross-training of the staff to perform the same study in two different locations.

The number of foreigners present in Japan limits single-site studies conducted in Japan with Caucasian volunteers. We have succeeded in creating a panel of approximately 450 volunteers, most of them located in the Kanto area. This method is of the greatest interest to Japanese authorities as well as pharmaceutical companies. Ultimately, ethnicity is a political concept, and there is no absolute way to determine it scientifically. Here again, the quality of foreign subjects in Japan may be questioned, and several ways to assess ethnicity have been designed, to the satisfaction of Japan’s regulatory authority. The data generated this way have been judged acceptable by the MHLW.

ICH E5 defines two types of ethnic factors that may have an influence on drug development. Intrinsic factors are genetic and related to the actual human population of the regulatory area. Extrinsic factors are related to the culture of the area. Early after the publication of the guideline in
Japan, attention was focused on intrinsic ethnic factors, especially genetic differences in drug metabolism. It is true that the frequencies of various types of metabolizers for mephenytoin or cytochromes is notably different according to the country considered. However, this is no longer considered a major problem in bridging strategies.

**The future of drug development**

The regulatory authorities of Japan have consistently expressed the view that major bridging issues lie rather on the side of extrinsic factors, such as differences in disease definitions, modalities of treatment, application of GCP regulations, and the design of clinical trials, especially for the selection of end points. It has also been clear that the bridging process is a temporary one. It actually constituted a threat to Japanese clinical and medical research, with fewer and fewer clinical trials being conducted in Japan. With the help of CROs and SMOs, this trend is already changing, and the numbers of consultations with the DO are rapidly increasing, for bridging strategies as well as traditional and global drug development. For companies, it is easier to market a new drug in a country where it has been tested and where opinion leaders are familiar with it. The incentives for physicians in clinical research are increased by the possibility of publishing interesting data. The future of drug development lies therefore in its globalization. Large pharmaceutical corporations have started to conduct multinational phase 3 trials involving Western and Japanese sites, leading to global simultaneous submission to the main regulatory authorities of the World. This will be facilitated by the adoption of a common technical document (CTD) framework for electronic submissions. Global submission and approval will bring the products to the main pharmaceutical markets quicker, to the benefit of the industry and patients. These strategies must be taken into account as early as possible in the drug development process. The participation of international CROs is needed to help pharmaceutical companies implement these strategies. In the particular case of Japan, knowledge of international and national regulations is not enough. Companies need to have a good understanding of cultural differences to negotiate their drug development programs with the authorities.

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**Revisión del entorno farmacéutico y de la regulación en Japón**

Los drásticos cambios en las medidas regulatorias en Japón desde 1997 han tenido un impacto considerable en la forma cómo se han desarrollado nuevas medicinas. La misma autoridad regulatoria se ha transformado. Los ensayos clínicos ahora se realizan de acuerdo con guías internacionales. Los datos clínicos generados en un área son aceptados en el resto del mundo en algunos casos a través de un proceso de puente, lo que parece ser sólo temporalmente. El futuro del desarrollo de fármacos depende de los ensayos clínicos multinacionales y de la presentación simultánea a las principales autoridades regulatorias.

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**Environnement pharmaceutique et réglementaire japonais**

Les changements réglementaires draconiens au Japon depuis 1997 ont eu un impact considérable sur le développement des nouveaux médicaments. L’autorité réglementaire elle-même a été transformée. Les essais cliniques sont maintenant réalisés selon les directives internationales. Dans certains cas, les données cliniques collectées dans une partie du monde sont acceptables pour le reste du monde par l’intermédiaire d’une procédure relais considérée comme temporaire seulement. L’avenir du développement du médicament repose sur des essais cliniques multinationaux et la soumission simultanée aux autorités réglementaires principales.
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