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Pharmaceutical Harmonisation in Europe and Beyond[1]

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Summary

The European pharmaceutical legislation ensures adequate protection of patients, efficient control of medicinal products and objective information for rational use. It provides incentives for the development of orphan drugs for rare diseases and of specific medicines for children.

Starting in 1995, the European Medicines Agency has produced an efficient marketing authorisation system for new human and veterinary medicines and a tradition of transparency with the publication of all its assessment reports. The monitoring of drug adverse effects (pharmacovigilance) has been gradually strengthened together with the fight against falsified medicines. Patients and professional organizations take part in EMA's governance.

Since 1995, the EMA evaluation has led to the granting of about 1300 EU wide marketing authorizations for human medicines and about 220 authorizations for veterinary medicines. About 4000 scientific advices were given during drug development. Since 2000, around 2200 orphan drug designations were granted, leading to some 170 marketing authorizations.

When the International Conference on Pharmaceutical Harmonisation was established in 1990 between Europe, the US and Japan, several ICH features were inspired by the European experiment. The ICH process involves the best regulatory and industry experts from the 3 regions, in the presence of observers from WHO and other interested regions. After 25 years of successful activities, ICH was formalized as an international association of 16 members and 33 observers from all over the world: the International Council for Harmonisation.

Looking to the future, regulators must try to avoid excessive complexity and bureaucracy at a time when personalized medicines are ripe for continuous and more flexible evaluations. Harmonising requirements and best practices between regions will allow patients to enjoy worldwide a better access to safe, affordable, effective and good quality medicines.

Key words: *International pharmaceutical harmonization; International Conference on Harmonisation of pharmaceutical requirements (ICH); European Medicines Agency (EMA); European pharmaceutical legislation; Brexit and pharmaceuticals*

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Introduction

It takes long and costly efforts of research and development and solid independent evaluations to bring a major new drug onto the world market. Nevertheless, an exciting new treatment can trigger serious adverse effects, even after a wide range of safety test in animals and well controlled clinical trials in thousands of patients have been conducted. In response to serious incidents, many countries have introduced pre-market approval systems and post-marketing surveillance schemes. These considerable advances for public health have also generated delays and costs in acquiring the required knowledge and expertise, hence the need to avoid unnecessary duplications.

Over half a century, Europe has progressively introduced binding rules, scientific guidelines and expert capacities to face these challenges. Starting in 1965, marketing authorisation procedures, testing and labelling requirements were progressively harmonised in Europe. Pharmaceutical legislation became an important component of the "1985/1992" EU Single European Market programme.

My personal experience is very much related to pharmaceutical harmonisation. During the 1970's, I became involved as a French representative to European Community, European Pharmacopeia and World Health (WHO) meetings. The European Commission recruited me in 1979 to organise the activities of the newly created scientific committees for human medicines and then for veterinary medicines. The veterinary aspects will not be further developed in this article.

I became responsible for the pharmaceutical harmonisation programme leading to the European Medicines Agency, which I then directed from 1995 to 2000. In parallel, I took a personal initiative to set up the International Conference on Harmonisation of pharmaceutical requirements (ICH) with the US Food and Drug Administration and Japan, starting in 1990. Later, I took part in the launch of a similar international harmonisation initiative for veterinary medicines (V-ICH).

In this article, I would like to put harmonisation efforts in perspective after 45 years of common testing requirements (Directive 75/318/EEC), 30 years of ICH activities and 25 years since the EU Medicines Agency was set up. Both at European and international level, I tried to rationalise drug testing in order to avoid repetition of tests in humans and animals and to accelerate access to innovative medicines. In doing so, I always gave priority to public health protection. The European experiment had a significant impact on international harmonisation of guidelines and application format, in particular on ICH.

First harmonisation steps: EU guidelines and notice to applicants

Given the growing fragmentation of medicines approvals in Europe, it was necessary to agree on a set of unified and sound regulations and guidelines and to encourage regulators to adopt adequate regulatory and procedural tools. It all started with Directive 75/318. EEC on norms and protocols for drug testing and the creation of the Committee on Proprietary Medicinal Products (CPMP) consisting of representatives from member states competent authorities.

Léon Robert, first chairman of the CPMP from Luxembourg, created 3 experts groups to issue European guidelines on quality, safety and efficacy testing. My first task was to implement these principles with the help of the successive chairmen of the expert groups for quality (Tony Cartwright, Jean Louis Robert), safety (John Griffin, Rolf Bass) and efficacy (Graham Dukes, Jean Michel Alexandre). I later set up the biotech working party (Geoffrey Schild, Giuseppe Vicari). And the pharmaceutical inspectors group to deal with the harmonisation of good manufacturing practices.

Based on his previous experience with the BENELUX countries, Léon Robert also recommended a tentative common dossier for the coordination of mutual recognition applications. In 1986, I suggested to formally agree a common format for all EU applications under the biotech/high tech coordination procedure and soon after, for all applications in Europe (notice to applicants).

I promoted the concept of "guidelines" to provide a publically agreed scientific interpretation of regulatory requirements. This approach, validated between regulators and the regulated, left a possibility for researchers to persuade regulators of the merit of better alternatives. It also became a tool for training new experts from governments, industry and academia. I persuaded the CPMP to set up transparent consultation mechanisms with industry researchers via their European trade association (EFPIA, directed by Nelly Baudrihaye), but also with health professionals and consumer, representatives in order to favour trust and integrity from all parties concerned.

I set up the pharmaceutical inspectors group to deal with the harmonisation of good manufacturing practices (GMP) and encouraged much closer cooperation with the European Pharmacopeia working under the umbrella of the Council of Europe in Strasbourg.

The main milestones of EU harmonisation during that period can be summarized as follows:

- 1975 - First Quality/Safety/Efficacy testing requirements,
- 1978 - Start of CPMP & expert activities and guidelines,
- 1981- Start of CVMP & veterinary expert activities and guidelines,
- 1986 - "Biotech/high-tech package" ; first notice to applicants,
- 1988 - Transparency of pharmaceutical pricing and reimbursement,
- 1989 - Harmonisation extended to plasma, vaccines and radiopharmaceuticals,
- 1990 - Future market authorisation system proposals,
- 1992 - 5 years patent term extension; advertising control; legal status of prescription; pack leaflets; wholesale distribution; homeopathic drugs,
- 1993 -Adoption of the EU authorisation system and medicines agency,
- 1994 - EU accession to the European Pharmacopoeia; pharmaceutical harmonisation within the European Economic Area (European Union plus Norway, Island and Lichtenstein).

In 1991, the EU testing requirements were revised and consolidated in Commission Directive 9I/507/EEC. The harmonised legislation and all the other requirements agreed at that time by the national competent authorities were published by the European Official Journal in several volumes of the "Rules governing medicinal products in the European Community" containing some 50 regulatory guidelines, together with the common application format (notice to applicants) and GMP provisions. The availability of pharmaceutical legislation in all EU official languages had a deep impact on many continents. Scientists from all parts of the world had an easy access to a consistent body of scientific guidelines and procedural advice to applicant (in English).

In parallel, the European Pharmacopeia in Strasbourg, published in English and French, became for us a pillar for harmonising conventional drugs components and attracted a growing number of observers from all over the world. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is the directorate of the Council of Europe in charge of the European Pharmacopoeia, but also for other activities of interest for the EU, such as the- coordination of a network of Official Medicines Control Laboratories and the combat against falsification of medical products and similar crimes (https://www.edqm.eu/en).

International harmonisation, starting in 1990: ICH guidelines and CTD

I would like to focus here on key aspects of the ICH. The proliferation of national testing and trial norms and the growing complexity of pharmaceutical research and development became obvious during the 1980s. The worldwide reference agency, the FDA, was criticized for the "drug lag" in the US, whilst Europe and Japan were in search for a better drug evaluation model. Having been involved in several diplomatic missions to the USA and Japan, I was persuaded of the increasing need to agree on transparent scientific requirements shared by a global scientific community.

I took the opportunity of successive meetings of worldwide drug regulatory authorities (ICDRA) sponsored by WHO in Tokyo 1986, and Paris 1989, to advocate in favour of international harmonisation. In the margins of such meetings, I approached the USA and Japan delegates. As a result, and in order to reduce unnecessary repetition of tests in humans and animals and duplication of costly stability and quality controls, the European Union, together with the US and Japan, launched in 1990 the "International Conference for the Harmonisation of pharmaceutical requirements" (ICH).

Faced with the globalization of pharmaceutical markets, the competent authorities of the EU, US and Japan and the representatives of research based companies responsible for more than 90% of pharmaceutical R&D in the world accepted to combine their efforts and expertise to rationalise drug testing programmes without compromising public health.

Over the years, the ICH process has involved the best regulatory experts from the EU, Japan and the US, together with the best experts from industry and observers from WHO, Canada and Switzerland. During the nineties, ICH produced some 50 quality, safety, efficacy, and multi- disciplinary guidelines as well as a common electronic format for applications (e-CTD) and a common terminology (MEDDRA). The European, US and Japanese pharmacopoeias engaged in a specific harmonisation process in the framework of ICH.

Most of these achievements benefited from the EU harmonisation experience gained with scientific guidelines, common application formatting, and open consultation procedures. This also meant a heavy investment from European experts. I actively participated in major ICH conferences which endorsed most ICH guidelines and the Common Technical (CTD): ICH1: Brussels, 1991; ICH2: Orlando, 1993; ICH3: Yokohama, 1995; ICH4: Brussels, 1997; ICH5: San Diego, 2000.

Since then, the emphasis has been on maintenance and dissemination with an opening to other parts of the world through the Global Cooperation Group and International Pharmaceutical Regulators' Forum. During many years, ICH remained an informal setting, a platform for scientific consensus, involving the best experts worldwide and open to the rest of the world, with ongoing consultations and debates. ICH6, Osaka, 2003, closed the circle of major ICH conferences, which were taken over by regional events organised for example by the Drug Information Association.

I witnessed a genuine and continuous interest in ICH activities when I chaired the 3rd African Regulatory Conference in Accra, May 2012, when I introduced the 10th DIA Japan meeting in Tokyo, November 2013 and when I exchanged views with ASEAN pharmaceutical experts in 2015. Whilst acknowledging the huge successes, I reminded the audience that ICH remains a fragile construction, based on constant goodwill and consensus between experts whose main reward is peer recognition. The regulators must stay in control of every step of the process as all ICH outcomes have to undergo the normal EU, US or Japanese consultation and approval mechanisms. The ICH parties have in 2012 confirmed and reinforced the role of regulators. After 25 years of successful activities, ICH was formalized in 2015 as an international association, "The International Council for Harmonisation", comprising 16 members and 33 observers from all over the world, including WHO and regional harmonisation initiatives (www.ICH.org).

Harmonisation of authorisations through the European Medicines Agency

From the start, everybody agreed on giving patient access to safe, affordable, and effective, quality medicines, but how? The first phase of EU regulatory harmonisation was a pre-requisite, but could not automatically produce any harmonisation of national marketing authorisations. The mutual recognition between national authorities needed a much stronger coordination hub, whereas innovation called for a single evaluation of undisputed quality.

As a consequence, the European Medicines Agency was established in 1995 to pool the available expertise to assess biotech and other high tech products destined for the world market through a "centralized procedure". Other products, candidate for European markets, could have their national authorisation recognized, with the EMA acting as an arbitrator in case of dispute. The agency became a joint venture for the protection and promotion of public health, based in London, owned by national agencies as well as European Institutions and fully supported by patients, health professionals and innovative companies.

The EMA succeeded in setting up the new evaluation procedures and starting a solid tradition of transparency and openness with the full publication on the Web (www.ema.europa.eu) of all its assessment reports. It was also able to deliver in record time labelling and pack leaflets in all the official languages of the European Union. Right from the start the main stakeholders (patient and users groups, health professionals and industry) were invited to meet committees and staff on a regular basis and to take part in annual public evaluation meetings. Patients' representatives were later invited to take part in the governance and in a number of scientific committees.

Regulation (EC) No 726/2004 imposed the use of the central procedure for all categories of innovative drugs. Since 1995, the EMA evaluation has led to the granting of about 1300 EU wide marketing authorizations for human medicines (and about 220 authorizations for veterinary medicines), without much controversy. About 4000 scientific advices were given during drug development (2/3 in the clinical field). Since 2000, around 2200 orphan drug designations were granted, leading to some 170 marketing authorizations. The EU Register of Medicinal Products can be consulted at http://ec.europa.eu/health/documents/community-register/html/index_en.htm .

EU good manufacturing practices are applicable to all exports. The WHO quality certification scheme applies to EU central and national authorizations. Each year, the EMA issues several thousands of WHO certificates for the benefit of other countries, including GMP, product summary and labelling and EU assessment reports. On request from the WHO, the EMA can also evaluate medicines which are not available in the EU (article 58 of EMA Regulation).

With the help of national inspectors (GMP, GCP and GLP) the EMA coordinates foreign inspections and implements the EU Mutual Recognition Agreements with Switzerland, Australia, Canada, New Zealand, Israel, Japan and the USA.

Regulatory harmonisation supported by the European Medicines Agency

From the beginning, the EMA became a major player for European and international harmonisation. The EU pharmaceutical harmonisation and EMA membership has been progressively extended to cover 28 EU countries plus Norway, Iceland and Lichtenstein. The EMA deployed significant resources for the preparation of the accession of so many new member states, given the considerable body of "acquis communautaire" to be transposed. Their experts were invited to participate in all scientific meetings at a very early stage under the EMA Pan European Regulatory Forum (PERF1 and PERF2), followed by the "Instrument for Pre-accession Assistance".

In 2001, all previous EU pharmaceutical provisions were merged into two Community codes combining all legal provisions concerning marketing authorisation and the manufacture, labelling, classification, distribution and advertising of medicinal products for human use (Directive 2001/83/EC) and veterinary products (Directive 2001/82/EC). After the successful introduction of incentives for the development of orphan medicines for the treatment of rare diseases in 2000, the regulation on paediatric medicines was adopted in 2006 and on advanced therapy products in 2007. The EU pharmacovigilance system was reinforced in 2005, 2010 and again in 2011. Certification of active ingredients and protection measures against falsified medicines were introduced in 2011. The revision of the EU clinical trials legislation was adopted in 2014.

The Commission provides an updated compilation of all relevant regulatory provisions, in 10 volumes, which can be downloaded at the following Website: http://ec.europa.eu/health/documents/eudralex/. For all these important Commission legislative initiatives, the EMA provided the required technical input.

Furthermore, the EMA has been put in charge with the implementing measures linked to the fast evolving EU legislation, including the creation of massive data bases partially open to the public such as: EudraVigilance (post-authorisation safety reports); EudraCT (registration of clinical trials); EudraPharm (authorised medicinal products); EudraGMDP (defects, manufacturing and distribution). The EMA has also developed several harmonised IT tools to improve the internal communications between all competent authorities through: a regulatory network's secure file-transfer system, the Eudra Data Warehouse, the European Review System (EURS), and a private network linking all European medicines regulators (EudraNet).

With the support of its numerous working groups, the EMA has intensely participated in the ICH activities alongside with the EU Commission. The EMA website compiles all final scientific guidelines published by the Commission "Eudralex" website, but also concept papers, drafts and an overview of comments received. To ensure consistency during the consultation period and to avoid discrepancies between publications, the EMA publishes since 2014 a summary of the scope and history of the relevant ICH topic, with a link to the full documentation on the ICH website.

Finally, the EMA has provided critical support to the Commission for application format (ICH CTD and e-CTD), and procedural and dossier requirements for variations, summary of product, package information and classification for the supply (Volume 2 of Eudralex).

The impact of Brexit on pharmaceuticals

After more than 50 years of European pharmaceutical constant harmonisation, the exit of the UK from the European Union (Brexit) marks a clear regression. In summer 2019, when this article was written, the question of Brexit still raised major uncertainties for health services in the UK (see Lancet 25/02/2019 "How will Brexit affect health services in the UK?" Nick Fahy and al.).

Pharmaceutical supplies are likely to be affected by Brexit, both in the UK and the rest he European Union. The UK produces 9% of € 250 billion EU pharmaceutical production. The UK imports € 20 billion and exports € 12 billion to the rest of the EU. A « no deal or hard Brexit", could result in an acute deficit for insulin, anti-cancer drugs, diagnostic agents and medical devices in the UK. There could be an increase if falsified medicines in case of rupture of normal pharmaceutical exchange channels. The EMA has published a questions-and-answers document for patients, healthcare professionals on the work of EU authorities to prevent Brexit shortages.

In this highly regulated sector, the exclusion of the UK from the EU regulatory system implies major transfers of several hundred legal entities such as marketing authorizations holders, pharmacovigilance centers, quality control sites, clinical trials sponsors. Pharmaceutical companies were regularly informed by the EMA of the

changes to be made in preparation of Brexit and to prevent shortages. https://www.ema.europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit . Heads of national agencies in Europe also provided advice for decentralized procedures (http://www.hma.eu/535.html).

A hard Brexit would mean a significant loss of expertise for pharmaceutical research and development and for regulatory activities. Between 2007 and 2017, UK research received € 1.5 billion (20%) from EU health research funding and 25% of the EU Innovative Medicines Initiative.

The European Medicines Agency had to face a costly move from London to Amsterdam in March 2019. It might lose 20% of its past 900 work force and also 20% of its external expertise provided by the UK, at a cost of € 15 million per year. The EMA published a continuity business plan to reduce lesser priority activities in 2018 and 2019. The UK Medicines and Healthcare products Regulatory Agency will no more be able to participate directly in EMA evaluations, inspections, alert and data exchanges, although a lot of it is publically accessible.

In Europe, regulators and regulations must avoid excessive complexity and bureaucracy at a time when personalized medicines are ripe for a continuous but more flexible evaluation. I sincerely hope that in case of Brexit, close relations could be maintained between the EU and UK in pharmaceuticals, as expected by all parties concerned in the sector. In any case, joint activities will continue to take place within the European Pharmacopeia and ICH, and in some form or another, with the EMA.

Conclusion

Given the principles of product liability prevailing in all industrialised countries, and the legitimate questions raised by the public about the quality, safety and efficacy of drugs, sound and universal pharmaceutical regulations and smart and competent regulators are in the general interest of citizens.

Over the last 50 years, the European pharmaceutical harmonisation process had a significant impact in the rest of the world, especially after the first decade of ICH achievements. Over the last 20 years, pharmaceutical harmonisation has made further progress in several parts of the world. Regional harmonisation initiatives expressed the wish to be associated with ICH, such as the Asia Pacific Economic Cooperation (APEC), South East Asia (ASEAN), the East African Community (EAC), Southern African Development Community (SADC), the Gulf Health Council (GHC), the Pan American Network for Drug Regulatory Harmonization (PANDRH).

When the ICH became institutionalised in 2015, I suggested that patients' representatives should become directly involved in the process, like they already are at EU level. The World Health Organization should play a more pro- active role in ICH discussions, dissemination and feedback on existing or new guidelines in order to avoid divergent norms with other regional initiatives.

Back in 2000, at ICH5 in San Diego, I argued that ICH achievements should encourage companies to submit simultaneous submissions to FDA, EMA and Japan. The 3 regions would of course keep a final say. I noticed with interest that attempts have been made between the EMA and FDA to conduct, in a limited number of cases, parallel evaluations relevant to quality by design, and parallel scientific advice.

Major regulatory agencies should attempt to publish their respective evaluations of new medicinal products in a similar format. Patient organisations and independent observers could then compare final outcomes and measure the real degree of international harmonisation achieved so far, for the benefit of WHO and the rest of the world.