Chapter 2
EU Perspective on ICH

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Abstract This chapter is considering ICH I in the context of the EU regulatory perspective, starting with a history of ICH in 1989, a time when the EU was pioneering a single pharmaceutical market in the EU. One major achievement of ICH, the agreed Common Technical Document for regulatory submission, is described in detail. Furthermore, the chapter explains how the ICH guidelines are implemented by the European Medicines Agency in the EU regulatory system. Given the fact that ICH has already a 20-year history, this chapter also elaborates on how important it is to maintain the guidelines, once adopted, by revising them or complementing them with addendums and/or questions and answers document updates based on new science or to ensure harmonised implementation. Finally, the chapter describes the efforts of ICH to provide training to developing countries, newly instituting their own pharmaceutical regulations and guidance, and to reach out beyond the EU, Japan and the USA and encompass new regions which have become important in drug development since the formation of ICH.

2.1 Introduction

The International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), launched 20 years ago, brings together the drug regulatory authorities of Europe, Japan and the USA, along with the pharmaceutical trade associations from these three regions, to discuss scientific and technical requirements for the development of medicinal products.

ICH's goal is to achieve greater harmonization in the requirements for product registration, thereby reducing duplication of testing and reporting during the research and development of new medicines.

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2.2 Brief History

Harmonization of regulatory requirements for medicinal products was pioneered by the European Community in the 1980s as the EU moved towards a single market for pharmaceuticals. Since the initiation of this effort, EU regulators have achieved what appeared almost impossible a few decades ago, a harmonised market across the 27 EU member states (Fig. 2.1).

In the WHO Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989, plans for harmonization among the leading regions for new pharmaceuticals EU, USA and Japan began to materialise. In April 1990, in a meeting hosted by EFPIA in Brussels, the ICH Steering Committee (SC) was established, and the first meeting of the ICH Steering Committee took place in October 1990 in Tokyo. In addition to the Steering Committee, the ICH structure encompasses the ICH coordinators, the ICH secretariat and last but not least the ICH Expert Working Groups, which develop and maintain the guidelines which are then adopted by the SC. All participants meet face-to-face at least twice per year and work collaboratively in the periods in between remotely.

Fig. 2.1 EU member states have a harmonised market for pharmaceuticals

The guideline development encompasses several steps. The process is kicked off by one or more ICH members proposing a new topic with a concept paper and business case to justify why this new topic will contribute to harmonization of requirements for registration and the expected benefits. Once the topic is accepted by the Steering Committee, the experts develop a draft guideline. After adoption of the draft by the SC, this "Step 2" document is published in each region for broad stakeholder consultation locally. At the end of the consultation, the Expert Working Group reconvenes to discuss the comments and prepare the final guideline, "Step 4", which comes into force in general 6 months later (Step 5 once implemented).

ICH has published and continues to maintain more than 50 guidelines on:

Q: quality, e.g. stability, analytical validation, impurities, pharmacopoeia harmonization, quality of biotechnological products, specifications, good manufacturing practice, pharmaceutical development, quality risk management, quality systems and chemical/biotechnology common guideline on the active substance
S: non-clinical safety testing, e.g. toxicity, carcinogenicity and genotoxicity studies, toxicokinetics and pharmacokinetics, reproductive toxicology, special aspects in toxicity testing of biotechnological products, pharmacology studies, immunotoxicology studies, safety of oncology products and photosafety
E: clinical efficacy and safety, e.g. clinical study reports, dose–response studies, ethnic factors, good clinical practice, general guidance on clinical trials, statistics, paediatrics, clinical safety, electronic submission of case safety reports, geriatrics, QT prolongation, pharmacogenomics definitions and data submission and development safety update report
M: multidisciplinary topics, e.g. medical dictionary for regulatory activities terminology/MedDRA, data elements and standards for drug dictionaries, and preclinical trials in relation to clinical trials

Last but not least, ICH is credited with the development of the Common Technical Document (CTD) and its electronic form (eCTD), a critical communication tool supporting the registration of new pharmaceuticals across the ICH regions.

2.3 Common Technical Document

One major achievement of ICH is the development of the Common Technical Document (CTD) which revolutionised the submission procedures for industry. The creation of this single technical dossier and later its electronic form, the eCTD, accepted by all the three ICH regions, resulted in significant savings in time and resources, facilitating simultaneous submission, review and approval of new drugs. Prior to the CTD, industry spent irrational amounts of time trying to adjust technical data formats to the specified formats of the different regions. The format in the EU reflected at that time the format as required by the EU Directive 75/318, while other regions had other formats. The CTD not only greatly accelerated the preparation of marketing authorisation applications for industry but also made the exchange of

information among drug regulatory authorities easier, facilitating discussions of important topics during the evaluation of applications.

The CTD was a major step forwards because it also enabled the creation of the electronic format of submission, the eCTD, which transformed the marketing authorisation application from many thousands of pages in numerous boxes to be delivered to the Agencies to paperless delivery in electronic format. But it is not only the delivery which was made easier with the introduction of the eCTD; also the review was greatly facilitated by the new, easily navigatable format which enabled the exchange of inquiry and response of the pharmaceutical review and evaluation process.

2.4 ICH and the EU Regulatory System

In the EU, pharmaceutical guidelines can be grouped either as regulatory or scientific.

The basic EU legislation is supported by a series of regulatory guidelines published by the European Commission. A regulatory guideline is a document with explicit legal basis referred to in the legislation and intended to provide guidance to industry, regulators and/or other interested parties on the best way to fulfil a legal obligation.

Scientific guidelines are intended to provide a basis for practical harmonization of the requirements of the European Medicines Agency (EMA) for the demonstration of quality, non-clinical pharmacology and toxicology (safety) and efficacy (investigation of clinical efficacy and side effects) for new medicinal products. Scientific guidelines which cover a range of topics across quality, safety and efficacy are called multidisciplinary (see above).

Scientific guidelines also help facilitate the preparation of applications for marketing authorisation by the pharmaceutical industry.

ICH guidelines are normally part of the scientific guidelines adopted by the Committee for Medicinal Products for Human Use (CHMP). In terms of clinical development, ICH covers the general requirements, while the requirements for specific therapeutic fields are covered by regional guidelines of the ICH regulators. In the EU, the CHMP develops the guidelines relating to investigation of medicinal product in specific therapeutic fields, e.g. cancer, diabetes, schizophrenia, etc.

In addition, some ICH guidelines have been integrated into EU legislation. For example, following the adoption of the ICH guideline Q7 (good manufacturing practice (GMP) for active pharmaceutical ingredients) and the E6 guideline on good clinical practice (GCP), EU legislation was amended to require GMP for starting materials and GCP for clinical trials.

In all cases, the CHMP is involved in the ICH process early, and ICH topics under development are included in the work programme of the relevant CHMP working parties or ad hoc groups for input into the process. Once adopted by the CHMP, ICH guidelines have the same status as other EMA guidelines and replace (supersede) older existing EMA guidelines that were already available on the subjects covered.

Guidelines are generally implemented 6 months after adoption, but applicants are of course free to apply them earlier.

In addition, the EMA experts are providing proposals, as do other ICH members, for new guidelines/update (revision) of existing ones in the form of concept papers outlining the scientific rationale of the proposals and business plans outlining the expected impact of the proposal on harmonization of requirements (also in terms of savings in refining, replacing, reducing animal testing) and expected resources required for the development/ revision of the guideline. This latter aspect has become particularly important in recent years as resources in all ICH members have become more limited. A new topic or a revision of an existing topic means in practical terms the formation of an Expert Working Group, which usually has between 15 and 30 members depending on the complexity of the topic. These experts need to meet at least twice per year face-to-face for a number of years until the finalisation of the guideline, which has important financial implications. The Steering Committee will, therefore, take this into account and prioritise proposals accordingly. When choosing non-clinical topics, the impact of the new guideline/revised guideline on refining, reducing and replacing animal studies is of paramount importance for the EU.

2.5 The Importance and Tools of Maintenance of Existing Guidelines: Geriatrics and Non-clinical Guidelines

ICH guidelines aim to represent the gold standard of scientific knowledge at the time they are issued. However, in many areas, science and other changes mandate an updating of the guidelines. In general, there are three tools to update the guidelines: revision of the main body of the guideline, development of an Annex to the guideline and the development of a questions and answers document, the latter of which is usually used as an implementation guide.

This book contains a comprehensive discussion of the non-clinical guidelines which have been implemented and the history of the implementation process by various members of the subject EWGs; therefore, experience with a Clinical Efficacy Guideline, which has recently been updated at the request of EU experts, has been selected for detailed discussion here.

2.5.1 Geriatrics

The initial guideline on requirements for geriatric patients “Studies in Support for Special Populations: Geriatrics” was finalised in 1993. In this guideline, it stated among others that “Geriatric patients should be included in the Phase 3 database (and in Phase 2, at the sponsor’s option) in meaningful numbers. The geriatric subpopulation should be represented sufficiently to permit the comparison of drug response in them to that of younger patients. For drugs used in diseases not unique

to, but present in, the elderly a minimum of 100 patients would usually allow detection of clinically important differences. For drugs to treat relatively uncommon diseases, smaller numbers of the elderly would be expected. Where the disease to be treated is characteristically associated with ageing (e.g., Alzheimer's disease) it is expected that geriatric patients will constitute the major portion of the clinical database".

The minimum number of 100 patients was dictated at that time, mainly by minimum requirements in terms of detecting side effects specific to the geriatric population. The demographics of the society have changed rapidly in the years since this guideline was finalised, and new drugs are used extensively in elderly patients including those aged over 65 (the conventional definition) but also above 75 and above 85 (the real elderly population of our times) without proper knowledge of their safety and efficacy in this population.

Around 2006, the European Union Geriatric Medicines Society (EUGMS) raised the possible need for an EU "geriatrics" legislation to address the need for clinical trials in the elderly based on the rationale that there are complex changes of pharmacokinetics/pharmacodynamics (PK/PD), due to ageing, co-morbidity and polypharmacy and that the efficacy and safety of drugs in older people cannot be deduced from randomised clinical trials performed in young and adult subjects or from meta-analysis including a small number of subjects. There was intense discussion in the EU and internationally on this issue, and as an alternative more flexible and more global proposal, a revision of the ICH guideline on geriatrics was tabled. ICH regulators reviewed the geriatric data in marketing application submissions, and the conclusion was that the vast majority of applications had 100 geriatric patients, not less but also not more, which was no longer considered acceptable.

In the Steering Committee meeting in Yokohama in November 2007, the EU presented a CHMP concept paper proposing a revision of the geriatrics guideline to reconsider age cut-offs, the very elderly, frail elderly; co-morbidities; PK/PD interactions; specific PK studies; and specific formulations. The Steering Committee adopted the EU proposal to convene an informal expert group to work via teleconference with a view of preparing a proposal for the next meeting. The EU was appointed rapporteur, and the proposal was adopted in June 2008 in Portland. The expert group was mandated with drafting a questions and answers document to better reflect the current requirements in this age group.

The Q&A document adopted in September 2010 changed the previous approach. While maintaining the flexibility of the initial document, the new document emphasised the need too have sufficient data in the populations reflected in the demographics of the disease to assess the benefit/risk in these populations:

> Geriatric patients can respond differently from younger patients to drug therapy in a number of ways and such differences can be greater in patients 75 years and older:
>
> (a) The geriatric population has age-related physiological changes that can affect the pharmacokinetics of the drug, and the pharmacodynamic response to the drug, both of

> which can influence the drug-response and the dose response relationship. (b) Geriatric patients are more prone to adverse effects since they often have co-morbidities and are taking concomitant therapies that could interact with the investigational drug. The adverse effects can be more severe, or less tolerated, and have more serious consequences than in the non-geriatric population. With the increasing size of the geriatric population (including patients 75 and older) and in view of the recent advances in pharmacokinetics and pharmacodynamics since the ICH E7 guideline was established in 1993, the importance of geriatric data (from the entire spectrum of the geriatric patient population) in a drug evaluation program has increased." … "In the marketing application, depending on the numbers of patients, data should be presented for various age groups (for example <65, 65–74, 75–84 and >85) to assess the consistency of the treatment effect and safety profile in these patients with the non-geriatric patient population. As single trials may not have sufficient numbers of geriatric patients to allow such analyses, these will often need to be carried out on pooled data. Any such analyses will need to consider consistency across studies.

This new approach to geriatrics was the goal of the EU regulators when they proposed to revisit this guideline.

2.5.2 Non-clinical Guidelines

In the spring of 2006, EU regulators proposal on the review of ICH Safety (non-clinical) Guidelines was circulated to the ICH Steering Committee. The proposal was justified on the basis of better regulation and the need to keep guidelines up-to-date and focused on implementation of guidelines, as well as the high political importance of ensuring that the use of animals in drug development is kept under review in the context of the 3R Agenda: refinement, reduction and replacement of animal experiments. The EU team reported on the work carried out by the CHMP Safety Working Party to review all ICH guidelines. The EU non-clinical experts recommended a review of the S2 genotoxicity guidelines, the S6 guideline on preclinical safety for biotechnology products and the M3 guideline on timing of non-clinical studies. The Steering Committee accepted the EU proposal for the organisation of an informal meeting of experts in Yokohama in June 2006 to discuss the need for a review of ICH non-clinical safety guidelines and make recommendations to the SC based on these discussions.

This EU proposal resulted in major revisions to the harmonised requirements in all three areas to reflect the current state of the art. The process also showed that revising a guideline is at least as difficult and time consuming as drafting a new guideline also due to the fact that adoption of changes in established approaches by all six ICH parties is a very difficult task. The addendum to the S6 guideline was finalised in June 2011, the revision of the M3 guideline was finalised in June 2009 and the related questions and answers document in June 2011 and finally the revision of the S2 guideline was finalised in November 2011.

2.6 ICH Reaching Out to the World Beyond: The Global Cooperation Group

For the first 10 years or so, ICH focused on the development of guidelines and standards for use in the ICH regions, i.e. European Union, Japan and the United States. By the late 1990s, however, ICH recognised the growing interest in ICH guidelines beyond the ICH regions. On the one hand, there was a growing recognition of the broader utility of ICH guidelines. On the other, the globalisation of industry drove a need for common standards both in ICH and non-ICH regions with significant role in the development and utilisation of new drugs.

This was the basis for the creation of the Global Cooperation Group (GCG) in 1999. The goal was better understanding of ICH guidelines through open communication and dissemination of information facilitated by trainings.

From the beginning, it was made clear that that GCG does not aim to impose ICH guidelines on any country or region and that the GCG will work closely with WHO and other international organisations to achieve harmonization and greater utilisation of ICH guidelines.

Partnerships were created with Regional Harmonization Initiatives (RHI), networking national authorities in all parts of the world such as the Asia-Pacific Economic Cooperation (APEC), the Association of the Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network for Drug Regulatory Harmonization (PANDRH) and the Southern African Development Community (SADC).

Training in the broad sense is a key GCG focus and the EU experts have been very active in delivering training in many non-ICH regions in the last years. But as recent workshops on clinical trial assessment and inspection showed, training has moved beyond simply an understanding of ICH guidelines to the active consideration of application of ICH guidelines in the assessment of studies and data.

2.7 The Globalisation of the Pharmaceutical Market and the Regulators' Forum

More recently, ICH recognised the need for further change to mirror the global face of drug development. This led to the creation of the Regulators' Forum in 2007 to enable the representation of individual drug regulatory authorities (DRAs) from regions that were either a major source of active pharmaceutical ingredients (APIs), clinical trial data, or had adopted ICH guidelines. The participation of DRAs is distinct but also complementary to that of Regional Harmonization Initiatives representatives in the GCG.

The first forum took place in 2008 in Portland. Regulators were invited from countries with a history of ICH guideline implementation (Australia, Chinese Taipei, Singapore and South Korea) and also from countries which are currently

important in manufacturing of medicinal products and contacting clinical trials, such as China, India, Brazil and Russia.

Compared to GCG, the focus of the Regulators' Forum is to create a regulator-only environment for open discussion of issues related to the *implementation* of ICH guidelines for regulators around the world. In the meanwhile, the Regulators' Forum has established itself as a very useful satellite meeting of every ICH meeting and has succeeded in facilitating communication and interactive contact among ICH and non-ICH regulators with topics often around similarities and differences in the interpretation of ICH guidelines across regions. Some non-ICH countries, such as Australia, opted to harmonise their own requirements by adopting what were then seen as international best practice standards, and they chose the ICH guidelines as benchmark. A factor in those decisions was the emerging reality: the pharmaceutical industry was increasingly globalised, and the regulatory requirements for new and innovative medicines were best reflected in the developing ICH guidelines which at that time represented all major regions in terms of drug manufacturing and non-clinical and clinical research.

2.8 Outlook

ICH recognises that the world has changed since its creation, and new regions have become important in drug development in addition to the original members EU, USA and Japan. This is, however, not a reason to discontinue ICH. ICH should be used as a very successful international platform with a measurable significant output to link all players together for the benefit of drug development.