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Review

Role of ICH in Harmonizing Drug Regulations

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Abstract

The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration. Harmonisation of regulatory requirements was initiated by the European Community (EC), in the 1980s, the EC moved towards the development of a single market for pharmaceuticals. ICH regulatory authorities are among the first to evaluate new chemical entities and new products obtained from biotechnology. ICH provides various guidelines which are categorised into four category, Quality guidelines, safety guidelines, efficacy guidelines and multidisciplinary guidelines. These guideline give special concern for the patient population, large-scale human clinical trials lasting up to one year can begin in the absence of completed carcinogenicity studies in rodents.

Keywords: ICH, united states, pharmaceutical industry, EC

INTRODUCTION

The International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.[1]

ICH stands for "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use". ICH's logo has been designed with a view to representing the letters "I", "C", "H" in a manner which embodies the letters in an abstract human form. The principle colour of the logo is

blue, a colour often synonymous with healthcare, and which adds an air of vitality and wellbeing to the depicted abstract figure. Purple was chosen as being complementary to blue.

1. Mission

ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical Guidelines and requirements for pharmaceutical product registration. Harmonization is achieved through the development of ICH Guidelines.

2. History[2]

Since ICH's inception in 1990, the ICH process has gradually evolved.

ICH's first decade saw significant progress in the development of ICH Guidelines on Safety, Quality and Efficacy topics. Work was also undertaken on a number of important multidisciplinary topics, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).

During the second decade, the development of ICH Guidelines continued, but with more attention given to the need to: Maintain already existing Guidelines as science and technology continued to evolve;

- Expand communication and dissemination of information on ICH Guidelines with
- Other regions; Facilitate the implementation of ICH Guidelines in the ICH regions;
- Coordinate with other organizations, particularly for the development of electronic standards.

In its third decade of activity, ICH's attention is directed towards extending the benefits of harmonization beyond the ICH regions. Training, as well as active participation of other regions in Guideline development is seen as key in this effort.

3. Industry ICH Parties:[4]

- Europe: the European Federation of Pharmaceutical Industries and Associations (EFPIA);
- Japan: The Japan Pharmaceutical Manufacturers Association (JPMA);

USA: the Pharmaceutical Research and Manufacturers of America (Pharma).

- WHO, the ICH Observer, has been associated with the ICH process from the beginning to act as a link with countries and regions beyond ICH. WHO is a non-voting member who is part of the ICH SC.

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) which has been closely involved with ICH since its inception participates also as a non-voting member.

4. Work products

Guidelines: ICH has developed over 60 harmonized Guidelines aiming at eliminating duplication in the development and registration process, so that a single set of studies can be generated to demonstrate the quality, safety and efficacy of a new medicinal product.[5]

ICH has also developed Questions and Answers (Q&As) when additional guidance and advice were considered necessary to help the interpretation of some harmonised Guidelines.

CTD: The Common Technical Document (CTD) describes the common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities.

eCTD: The electronic Common Technical Document (eCTD) has been developed for the electronic submission of the Common Technical Document from applicant to regulator, in order to facilitate international electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI).[6]

MedDRA: The Medical Dictionary for Regulatory Activities (MedDRA) terminology has also been developed under the auspices of ICH.

Consideration documents: The Consideration documents have been developed by discussion groups i.e., Gene Therapy Discussion Group, and ICH & Women Discussion Group to report specific scientific considerations.

AIMS AND OBJECTIVES

The main aim is to determine the role of Ich to harmonise drug regulations.

Objectives

- ICH structure
- ICH Steering Commitee composition
- Process of harmonization
- ICH meetings

DISCUSSIONS

The Value and Benefits of ICH to Drug Regulatory Authorities- Advancing Harmonization for Better Health

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), launched 20 years ago, is an unparalleled undertaking. ICH brings together the drug regulatory authorities of Europe, Japan, and the United States, along with the pharmaceutical trade associations from these three regions, to discuss scientific and technical aspects of product registration. It is ICH's mission to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines.

In 2000, the 10th Anniversary of ICH, Dr. Caroline Nutley Loew of the Pharmaceutical Research and Manufacturers of America (PhRMA) wrote a report, The Value and Benefits of ICH to Industry, which detailed ICH's creation, procedures, and guideline development in the areas of safety, efficacy, and quality. Dr. Loew's report anticipated that the Common Technical Document (CTD) would revolutionize the submission procedures for industry's regulatory staff. Dr. Loew characterized the CTD as "offering potential benefits to industry far greater than any other single ICH topic," and predicted the CTD would afford significant savings in time and resources as complex multiple submissions were replaced by a single technical dossier submitted in the three ICH regions facilitating simultaneous submission, approval, and launch of new drugs. In calling the CTD "a topic whose value to industry cannot be underestimated," Dr. Loew noted that with full incorporation of the CTD and the electronic CTD (eCTD), ICH could turn its sights to disseminating guideline information to nonICH countries, yielding additional benefits to both regulators and industry.

Ten years later and in anticipation of ICH's 20th Anniversary, the value and benefits of ICH to regulators have been realized. Moreover, implementation of the CTD in 2003 promoted the involvement of drug regulatory authorities (DRAs) not initially part of ICH, thereby extending ICH's harmonized approach. The development of the Global Cooperation Group, which includes representatives from five regional harmonization initiatives and the newly established Regulators Forum, created to promote participation by non-ICH countries interested in implementing ICH's strategies, have also helped incorporate the CTD into regulatory processes, creating a common regulatory language that promotes faster access to life-saving treatments to patients beyond ICH regions. In recognition of the increasingly global face of drug development, ICH recently updated its logo to emphasize the benefits of harmonization for better global health.

Shift in Emphasis

Substantial benefits to DRAs resulted when ICH shifted emphasis from the input of information by industry to the output of information by regulators. This transition was made possible by the development of a common submission format the CTD which greatly influenced regulatory review processes, ultimately leading to a harmonized electronic submission and e-review initiatives, which, in turn, have enabled implementation of good review practices. These activities are having a global effect on information review and sharing among drug regulatory authorities.

Originally, ICH focused on input by industry the technical submission requirements for pharmaceuticals for human use. Harmonizing the differences in these requirements through ICH guidelines helped industry reduce development times and save resources. To extend the benefits of harmonization, industry proposed assembling the building blocks of information intended for inclusion in a submission into a consistent harmonized format, referred to as the CTD, which would relieve pharmaceutical companies of the time, workforce, and financial burdens of assembling a submission for one DRA and then having to reformat it for another. This new consistent format also greatly benefited the U.S. Food and Drug Administration (FDA), enabling the agency to establish templates for each of the review disciplines while promoting more consistent review practices and processes.

Prior to the advent of the CTD, regulatory reviewers received an application from one company and spent a year or more engaged in its review. When the review was completed, reviewers received the next application most likely in a different format and had to learn the structure of the new application. As a result, review staff were constantly on a learning curve when new assignments were received—time they could have better used reviewing the information as opposed to simply trying to find it.

When industry proposed the CTD in 1996, ICH regulators were hesitant to change their submission formats, believing it would be too disruptive to the review process. They needed convincing that harmonizing the submission format had value. Regulators asked industry to do a feasibility study. That study, conducted in May 1996, evaluated the time it took to convert an FDA new drug application into an European Medicines Agency (EMA) submission, and the reverse. It also evaluated the number and types of staff needed to carry out the conversion of the submission formats. Regulators quickly saw the potential value of harmonizing submission formats.

Regulatory Benefits

The CTD has also made the exchange of information among drug regulatory authorities easier. For a number of years, FDA and the EMA have had a confidentiality arrangement in place allowing the sharing of confidential information, greatly increasing interactions between the two agencies. Now that submissions are received in the same format and, generally, at the same time, these interactions have become more efficient, facilitating discussions of common concerns as submissions are evaluated

Last, and perhaps most important, the CTD has facilitated electronic submissions (the eCTD). In the past, drug applications were voluminous, delivered to FDA by the truckload due to the sheer amount of paper involved. When the agency first transitioned to electronic submissions, an application was on a compact disc or hard drive. Although this certainly helped with transportation and storage issues, it did not necessarily enhance the review process. FDA has now implemented the FDA Electronic Submission Gateway, which allows a new drug application (NDA) to be sent electronically, essentially very much like e-mail. After being assessed for completeness, a submission is immediately and fully accessible on the reviewer's desktop. This innovation has alleviated the need for industry to create and assemble the many pieces of paper that constituted a traditional paper-based product application, organize the application, box thousands of pages, load the boxes on a truck, and deliver them to FDA all before a reviewer could even begin the assessment process.

A Harmonized Marketing Application

It was nearly 20 years ago when an initial discussion of a new concept called "harmonization" took place among drug product regulators at an International Conference of Drug Regulatory Authorities. Not long afterwards, in April 1990, I attended a meeting at the European Federation of Pharmaceutical Industries and Associations (EFPIA), where the concept was explored again in greater detail— for the first time with representatives from four pharmaceutical industry associations: EFPIA, the Japan Pharmaceutical Manufacturers Association (JPMA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA). Representatives from the regulatory agencies from Japan, the European Union, and the United States were also present. Not long after that meeting, the International Conference on Harmonisation (ICH) took its place as a pivotal organization in global pharmaceutical development and regulation. ICH's exceptional efforts in producing harmonized guidelines proved invaluable in helping both industry and regulators assess new medicines, thereby bringing those medicines to the patients who need them with new levels of efficiency and speed.

ICH Guideline Implementation

Under the regulatory framework in the EU, the Committee for Medicinal Products for Human Use (CHMP), within the European Medicines Agency (EMA), is responsible for preparing scientific guidelines to help applicants prepare marketing authorization applications for medicinal products. When implementing ICH guidelines in the European Union, the CHMP adopts the harmonized text of a guideline.

The CHMP has already been involved in the ICH process at an earlier stage in that ICH topics are included in the work program of the relevant CHMP working parties or ad-hoc groups. Once adopted by the CHMP, ICH guidelines have the same status as other European scientific guidelines and replace existing guidelines on the subjects covered.

Guidelines generally take effect six months after adoption. Although applicants may, with the agreement of the competent authority concerned, choose to apply a guideline in advance of this period, competent authorities should wait until this period has expired before requiring the guideline to be taken into account. In the EU, there are different types of pharmaceutical guidelines, which can be grouped broadly as regulatory or scientific. A regulatory guideline is a European Community document with explicit legal basis referred to in the legislative framework as intended to provide advice to applicants or marketing authorization holders, competent authorities and/or other interested parties on the best or most appropriate way to fulfill a legal obligation laid down in the pharmaceutical legislation of the EU. The basic EU legislation is thus supported by a series of guidelines published by the Commission. Scientific guidelines are intended to provide a basis for practical harmonization of the manner in which the EU Member States and the EMA interpret and apply the detailed requirements for the demonstration of quality, safety, and efficacy. Scientific guidelines also help facilitate the preparation of applications for marketing authorizations by the pharmaceutical industry. The scientific guidelines may relate to specific issues reflecting a harmonized EU approach, based on the most up-to-date scientific knowledge. New or updated guidelines are published by the EMA on its website. Additionally, the EMA publishes technical, procedural, and administrative guidance.

Ethnic Factors in the 21st Century

As the past decade saw pharmaceutical development trend toward multi-regional mega-trials (simultaneous subject recruitment from many populations in many parts of the world), new and complex questions emerged regarding across the board extrapolations of data. The E5 EWG was reconvened to address the issue in

2003 and in 2006 to create a series of 11 questions and answers (Q&As) that further clarified the guideline's implications in today's global clinical development landscape.

In April 2007 the health ministers of China, Korea, and Japan issued a Joint Statement and Memorandum of Cooperation, with clinical research cited as a specific area of cooperation. MHLW, in cooperation with China's State Food and Drug Administration and Korea's Food and Drug Administration, is now exploring ethnic factors in East Asia based on ICH's E5 Guideline.

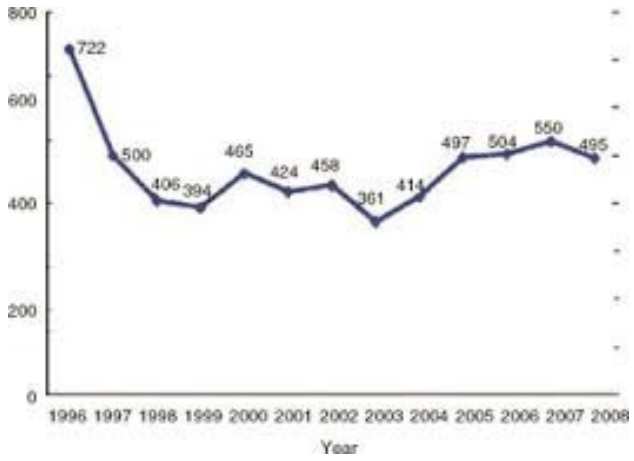

Fig 1: Clinical trials conducted in japan

MHLW instead took (and continues to take) constructive measures to galvanize Japanese clinical development, such as improving the infrastructures of the trial sites and encouraging training for clinical research coordinators. As a result, the number of multi-national trials conducted in Japan has steadily increased, demonstrating the country's emergence as an international center of pharmaceutical innovation (Fig. 1).

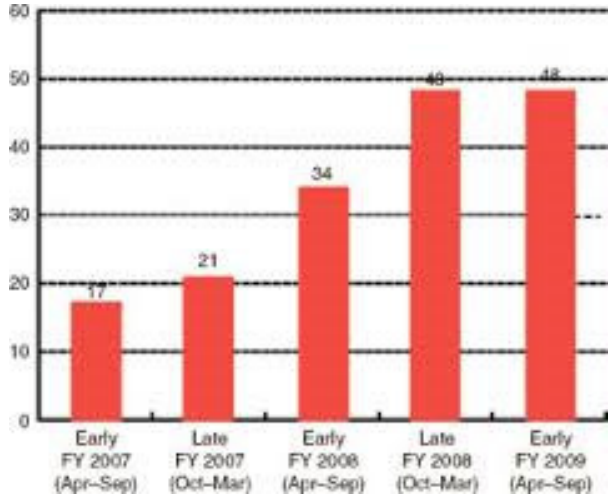

Fig 2: Multi national clinical trials conducted in japan

Revised ICH Terms of Reference

- To maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients;
- To contribute to the protection of public health from an international perspective;
- To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data;
- To avoid divergent future requirements through harmonisation of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products;

- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal and material resources, without compromising safety;
- To facilitate the dissemination and communication of information on harmonised guidelines and their use such as to encourage the implementation and integration of common standards

The Global Cooperation Group – A Bridge from ICH to the World Beyond

For the first decade of its existence, ICH focused on the development of guidelines and standards for use in the ICH member regions (European Union, Japan, and the United States). By the late 1990s, however, ICH recognized the growing interest in ICH guidelines beyond the ICH regions. Reasons for this interest were rooted in several interrelated factors. There was a growing recognition of the utility of ICH guidelines as reference documents that define sciencebased principles and approaches and many of the ICH guidelines were not limited to new drugs giving them broader relevance. The globalization of industry, both innovative and generic, drove (and continues to drive) a need for common standards, and the overall trend towards global drug development strategies spurred the interest of non-ICH countries in stimulating innovation, building local capacity, and promoting earlier access to important new therapies

In response to this growing interest, ICH created the Global Cooperation Group (GCG) in March 1999. The GCG serves to promote a better understanding of ICH guidelines and ICH itself, facilitated through open communication and fluid dissemination of information. The choice of name for the group was reflective of the desire to establish global linkages that extend beyond the three ICH regions.

From the outset, the GCG established a number of important operating principles that have guided its work to this day, notably that ICH will never impose its views on any country or region and that the GCG will work closely with WHO and other international organizations to achieve its goals.

The Regulators Forum

The first Regulators Forum, hosted by the U.S. Food and Drug Administration, was held in Portland, Oregon, in June 2008. Regulators were invited from countries with a history of ICH guideline implementation (Australia, Chinese Taipei, Singapore, and South Korea) as were regulators from countries where major production and clinical research is done, such as Brazil, China, India, and Russia. Also in attendance were representatives from the Regional Harmonization Initiatives (RHI) also participating in the Global Cooperation Group (GCG).

The first Regulators Forum saw the formulation of a vision statement:

- To discuss and share best practices on issues related to the implementation of ICH guidelines and their impact on regulatory systems in non-ICH countries
- To assist in identifying training and capacity needs for action by the GCG. The Forum will support GCG activities and objectives and promote a more comprehensive understanding of ICH guidelines
- Create a regulator-only environment for open discussion of important issues regarding the implementation of ICH guidelines for regulators around the world
- To supplement not replace the GCG A discussion also took place on the purpose, focus, and benefit of the group. There was consensus that the Forum would provide an excellent opportunity for non-ICH regulators and RHIs to learn about implementation of ICH guidelines and that participation in the ICH process would confer trust and confidence in those guidelines while developing links to other regulatory efforts and challenges.

The fourth Regulators Forum was held in St. Louis, Missouri, in October 2009. Discussions suggested that the scope of topics to be considered in the future may extend beyond the original concerns of the Forum—ICH guidelines to include numerous other topics of common interest. But the more immediate benefits of the Forum are clear and substantive:

- Ease of communication and personal contact with increased interactivity between meetings
- Receiving updates from other regulators on current issues
- Learning from each others' experiences Analyzing differences in the interpretation of ICH guidelines

Guideline Information Dissemination/Uptake in Non-ICH Countries

As other authors have noted, it was clear from the early days of ICH that drug regulatory harmonization efforts, guidelines, and processes would affect countries and regions beyond the European Union, Japan, and the United States. At the inception of ICH, the World Health Organization (WHO), Health Canada, and European Free Trade Association (EFTA) had ICH observer status, with WHO seeking to represent the interests of non-ICH member countries.

In the early 1990s, some countries, such as Australia, sought to minimize their own unique requirements by adopting what were then seen as international best practice standards. A factor in those decisions, however,

was the emerging reality: the pharmaceutical industry was increasingly globalized and the major market regulatory requirements for new and innovative medicines were best reflected in the developing ICH guidelines.

QUALITY OF BIOTECHNOLOGICAL PRODUCTS

Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products Q5D Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

SPECIFICATIONS

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Global harmonization and the ICH

HARMONIZATION of various elements of drug regulatory activities has taken place in the last decade and has involved intergovernmental initiatives at regional and interregional levels. The driving force behind the harmonization effort is the need to improve availability of pharmaceutical products and to respond to the forces of international trade with adequate standardised technical regulations on safety, quality and efficacy. By reducing unnecessary duplication of regulatory requirements, it is proposed that therapeutic advances will be made more rapidly and at a lower developmental cost.

A prerequisite to any harmonized approach to international drug regulation is the existence in each of the participating countries of a functional drug regulatory system. This is understood as full drug registration processes, pharmaceutical inspection services and certified compliance with good manufacturing practice.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 by the drug regulatory authorities and research-based pharmaceutical industries of the European Union, Japan and the USA to focus on new drug development requirements. ICH is a tripartite venture of 17 high-income countries. To date, it has produced over 45 guidelines describing technical requirements related to specific components of the drug registration process drawn up by groups of specialists from drug regulatory authorities and the pharmaceutical industry of the ICH countries. The scientific level of each guideline is high and reflects state-of-the-art technology. The cost related to full implementation of the guidelines may in some cases be considerable but, it is argued, this is offset by more rapid registration of new drugs in the ICH countries.

The ICH initiative was established to harmonize the documentation needed for drug development and subsequent regulatory evaluation of products containing new chemical entities or products obtained by biotechnology. WHO is accorded observer status within the ICH Steering Committee, but is not directly involved in the process of drafting or developing ICH guidelines and has no control over their approval.

Benefits of the ICH process

The establishment of ICH 10 years ago reflected a need felt by the research-based industry and certain governments to streamline the approval process for the registration of new drugs. The tendency of many countries to regard ICH guidelines as international standards further supports the argument that there was a need for such a process. The widespread reference to ICH guidelines by countries attests to the quality of their technical content. Indeed, many of the scientists involved in the ICH working groups responsible for developing the different guidelines have contributed to the high calibre of technical and scientific content in the recommendations. They argue that while recognising serious omissions in some of the guidelines, this should not detract from the quality of the content of those already approved.

While the structure of the ICH was clearly exclusive from the outset, this position continues to be defended by its supporters as an appropriate partnership to achieve ICH aims and objectives. The omission of other participants, such as the generics industry, was not seen as a barrier to ICH work, as the original aim was not to harmonize the approval of generic drugs. Similarly, the ICH partners would argue that before countries implement the guidelines, regulatory authorities are able to involve consumer groups, who can give comments. Additionally, in all the countries represented within ICH, there are appropriate mechanisms which allow public comment on the guidelines before they are finally adopted.

One of the most important criticisms of the ICH process is that its guidelines have been increasingly perceived as the ‘gold standard’ for international harmonization. The ICH has never claimed to have formal international authority to produce global standards and it further indicates that it is in no position to compel national drug regulatory authorities to adopt these standards. Nevertheless many countries consider adoption of

the guidelines as a necessary move. ICH proponents argue further that the intention of involving WHO as an observer in ICH was to ensure that international concerns about the protection of public health interests are met.

INTERNATIONAL HARMONIZATION: A REGULATOR'S PERSPECTIVE

Different countries take different approaches to medical products regulation, depending on a number of factors, said Hubert Leufkens, Chair, Dutch Medicines Evaluation Board, and Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University for Pharmaceutical Sciences. This is true even when they are geographically proximate, operate under the same legal framework, and rely on the same scientific processes and the same data to make their decisions. Some regulatory regimes may be more risk-averse, while others may prioritize potential benefits. Whether they emphasize risks or benefits may vary from one instance to another. As a result of these discordant outcomes from regulatory decision making, said Leufkens, patients in one country may have access to medications that others do not have, which regulators may be hard pressed by patients, providers, politicians, and the media to explain.

Leufkens presented an example in FDA's revocation of approval of Avastin for metastatic breast cancer. Although FDA originally approved the drug for this indication, evidence that it did not extend life or improve the quality of life, while increasing the risk of serious side effects, prompted FDA's subsequent decision. Yet, Avastin remains approved for metastatic breast cancer in other countries. Such contradictory situations, some of them widely publicized, can erode public trust in the system. However, Leufkens considers FDA's public report on the reasoning behind its decision a model of balance and perspective. Generally, the way agencies communicate about variance is extremely important and needs greater clarity, he said.

Schellekens and colleagues (2011, p. 175) stated that regulatory systems should be assessed "in terms of their ability to ensure patient safety, enhance public health, and stimulate innovation." Their effectiveness at achieving this latter aim are much in doubt, as the introduction of new and innovative drugs has decreased sharply, despite rapid advances in biomedical research, said Leufkens. Schellekens and colleagues (2011, p. 175) further stated, "Although the reasons for this innovation deficit are not fully understood, many observers see the increasing demands of the regulatory systems as one of the main drivers."

Leufkens asserted that regulators need to answer four important questions in assessing a new pharmacologic product:

1. What is the precise diagnosis it is intended to affect?
2. What endpoints were measured in the research, and are they clinically relevant to the disease or condition at issue?
3. What target population will benefit?
4. What kind of comparison is useful, needed, and feasible?

Although these questions appear straightforward, addressing each of them presents challenges. Leufkens gave examples for each, keyed to the numbers above, including the following:

1. Diagnosis of psychiatric conditions varies from one country to another
2. In oncology, use of overall survival rates versus progression-free survival as endpoints; or in diabetes, the use of blood glucose levels versus or in addition to other measures, with an increasing preference for clinical outcome measures, rather than simple biomarkers
3. Use of biomarkers to identify populations, inasmuch as different nations have different capabilities to conduct a robust biomarker identification effort
4. Divergent views on whether placebo recipients constitute an appropriate comparison group versus active controls (e.g., patients receiving standard treatment), with the trend being for greater emphasis on the latter

Regulators use dossiers prepared by manufacturers in determining whether to approve a new drug. Problems associated with these dossiers are not infrequent. Leufkens said typical problems that can contribute to different regulatory decisions include the following:

- Poor presentation: For example, the dossier presents data in a confusing way or presents too much data, in which case the drug itself often receives a poor assessment.
- Conversely, some dossiers may mask data shortcomings by the strength of their presentations.
- Coping with innovation: It may be difficult for regulators to assess a new concept, so the default is to request more information, but whether such requests actually produce an improved product is debatable.
- Some advanced therapies, including gene therapies, may appear to regulators as too risky.

In the end, some of the variance in approval decisions across nations arises through the dynamics of their individual review committees and their decision-making styles and processes. Some nations base their processes on precise rules, whereas others base them on principles. The latter approach gives greater flexibility to regulators, said Leufkens, but also reduces the system's predictability.

The labeling of a drug, which includes the indications for which its use is approved, can vary among countries and change over time as new information is compiled. Sometimes the number of indications is expanded and sometimes reduced, particularly if complications arise that suggest use needs to be more tightly controlled. A study of approaches used by FDA and EMA in the evaluation and approval of new anticancer indications found real difference in the regulatory agencies' wording for nearly half (47 percent) of the indications. However, the differences were clinically meaningful in only 10 of these instances (Trotta et al., 2011).

Similarly, a study of differences in regulatory actions by FDA and the European Union related to biologicals appeared at first to suggest these differences were quite large, but further analysis indicated that clinically relevant differences were much smaller (Giezen et al., 2008). The more important feature was the timing in the two entities' actions. FDA was more likely to advise clinicians about potential problems sooner than was the EU, and in some cases even to require a "black box warning" sooner.

Leufkens concluded that there may always be differences in the ways people look at the data, how they weigh the potential benefit or harm of specific products, and how they try to respond to their populations' unmet medical needs.[6]

Similarities and Differences Among GCC States

The GCC is a political and economic union involving seven Arab States of the Arabian Gulf with shared economic and social objectives. It was created 25 May 1981 comprising Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen. These countries are often referred to as the GCC States. It should be noted that Yemen hopes to gain full GCC membership by 2016.

The demographics of the GCC states (see Table 1) show the Gulf Region as an area of 3,100,922 km², with a total population of 61.5million, a median age of 26.4 years and an average life expectancy of 73.8 years.

The biggest country with the largest population and a dominant economy in the region is Saudi Arabia.9 Kuwaitis have the longest life expectancy and Qatar's population has the highest median age. Yemen has the lowest GDP, which may impact life expectancy there; it is the shortest in the region (63.4 years). The high-level demographic trends of the GCC States may influence demand for pharmaceutical products in the region. The percentage of the population aged over 65 years is expected to grow from 2.7% in 2010 to 4% in 2020. This population sector averaged 3% growth annually during 2004–09, while the world population rose only 1%.

Older people generally need more medical care and have more expensive health profiles than younger people. Improvements in life expectancy over the past quarter of a century have left the GCC with an increasing number of elderly people requiring care.

Furthermore, increased urbanization and higher per capita income in the GCC states have led people to consume unbalanced diets and have increased the incidence of lifestyle-related diseases such as diabetes and cardiovascular ailments. This has increased the market for drugs such as insulin.

Although patents for many drugs are expiring, an increase in lifestyle diseases would help maintain revenues of prescription drug manufacturers in the long term and encourage prospects for generics manufacturers in the near future.12 It is therefore of paramount importance to take into account the local cultural issues as well as the demographic variations in the funding framework of the GCC regulatory agencies.

To this end, the structure, responsibilities and scope of the individual GCC regulatory authorities were explored through personal communication with key regulators in the region . Five authorities fall under the Ministry of Health and are fully funded by their respective governments. Saudi Arabia and Yemen, however, have independent, standalone authorities relying on registration fees as the major source of their funding.

All seven GCC authorities regulate pharmaceutical products for human use with their main scope of activities revolving around marketing authorization, postmarket surveillance and quality control analysis. They also have a variety of other responsibilities depending upon their size and resources.

Regulatory Approval Times Determine Patients' Access to Medicines The speed of marketing approval for new drugs affects healthcare professionals and patients, as well as manufacturers. An unnecessarily long approval process delays access to new medicines that could potentially enable clinicians to improve patients' health. Variation in the speed with which new medicines become available in different countries has been studied since the early 1970s and some marked differences have been found.

The type of model and extent of scientific review used to assess the application dossier in each GCC state need to be addressed. The approval time is not the only reason, of course, for delays in patients' access to medicines. Other parameters impact the speed and efficiency of the approval process in new markets including the company strategy and the national registration requirements such as the need for the submission of the Certificate of Pharmaceutical Product (CPP). The extent of the authorities' reliance on the CPP depends on the review model employed by the importing country.

The length of the review process depends on the type of product being registered and the requirements of the approval process. Different countries impose different registration requirements on manufacturers.

However, it is possible to exploit these differences for the benefit of both the pharmaceutical industry and the regulatory authorities. For manufacturers, registering new products in countries with less-rigorous

requirements can help them produce evidence to support registration in other countries. This would benefit the regulators if it leads to a richer and better quality dossier for subsequent submissions.

Furthermore, the time taken to register a pharmaceutical product differs from country to country and from product to product. The longest review usually occurs when the benefits of the product are not evident because of the lack of expertise among the reviewers and external expert committees. There is a strong argument for carrying out the assessment at a regional level, rather than at a country level. In the GCC-DR system, the assessment process is shared among the GCC states and the decision is made by agreement.

The challenge facing the GCC states is not to implement a new centralized system, but to establish an effective method for sharing workload, which requires harmonizing the standard of the regulatory practices of each individual authority with the ultimate goal of shortening the review time.

The GCC-DR committee, with 14 members (two senior managers from each of the seven countries) manages the GCC review process but is not able to function as a single authority, such as the US Food and Drug Administration (FDA) with approximately 3,000 staff. Each country has its own authority with its respective identity, which also plays a prominent role in the overall functioning of the GCC-DR committee.

The efficiency of a review process is judged by the length of time from submission of the application to the date of patients' access to the new medicine. A previous attempt to evaluate the length of the milestones and stages involved in the regulatory review processes for different authorities19 and a particular study on the GCC regulatory authorities carried out by Hashan highlighted important aspects of the drug approval procedures in each of the seven member states

However, the study provided limited information about the approval timelines and the lengths of the milestones and stages involved in the review process simply because the authorities did not have an electronic tracking system to monitor such activities. For example, Kuwait's pricing department is independent from the registration department, so the pricing process is not part of the review process, in contrast to the other GCC authorities, whose pricing step is part of the review process.

Increasing the Effectiveness of the GCC Regulatory Review Process

New medicines take years to develop and at every stage of the approval process, Competent Authorities review and assess research results. The scientific evidence developed by the pharmaceutical company is evaluated to ensure that the product can be made available for use or prescribed to patients. Regulators must balance the speed of availability of a medicine to patients with the time required to fully evaluate its risks.

A strong, well-funded, consistent and transparent regulatory review system is essential to protect the public health and build confidence in the safety and efficacy of marketed drugs. Therefore, strengthening the regulatory authorities in the GCC region is vital so they all have the expertise and tools to effectively evaluate new medicines.

In general, the GCC authorities are structured differently and the scientific guidelines are not fully standardized across them. To solve this problem, they are consistently improving the effectiveness of their communication with each other and with industry.

To submit a new drug application in the GCC states, it is important to assess the regulatory review systems (regulations, directives and guidelines) and the regulatory requirements in each country in advance. Differences in pharmaceutical legislation and registration requirements can be determined from the administrative data (e.g., type of documents and certificates requested), pharmaceutical data (e.g., requirements for stability data) and clinical data (e.g., placebo-controlled studies or comparative studies). It is critical to identify key milestones and stages within each country's review process that could be adopted as best practice across the GCC region.

Building Quality into Regulatory Harmonization

Confidence in the regulatory system depends on the availability of resources and skills required to perform a high-quality review. These resources include adequate staff, budget, information technology and work facilities.

There are four key determinants of a high-quality review process:

An effective capacity development strategy that involves retaining experienced staff through salary benefits as well as collaborations with other authorities for skill developmentan efficient IT system for tracking application assessment and decision makingeffective networking with other regulatory authorities to exchange best practices and to have appropriate insight into the capacity and performance of the authorityaccountability and transparency of decisions A range of interest groups try to influence drug regulatory authority decisions, ranging from politicians to patients and clinicians. Strong and defensible decision making is an authority's best protection against any influence.

Despite the considerable number of analytical and comparative studies on regulatory performance and submission in terms of metrics, there is limited research in the field of quality management, particularly the quality of the regulatory review process, the quality of decision making and the quality of the dossier submissions.

A study conducted by Hashan explored measures the six GCC authorities (Yemen was not in the GCC group at the time) used to improve the quality of the review and decisionmaking process, including standard operating procedures (SOPs), good review practices, peer review, assessment templates, transparency, resources and training and continuing professional development programs.

The study revealed the majority of quality management tools were not used by most GCC authorities, and the ones in place were being used differently by each authority, which made it difficult to perform comparisons. In addition, the impact of the quality measures on the efficiency of the review process was not determined. This was due to the lack of electronic tracking and monitoring systems, which made it difficult, if not impossible, to determine the impact of quality measures on performance outcomes.

This study was the first to examine the quality management tools and to highlight areas where the quality of the GCC review processes was being monitored. It provided the opportunity to familiarize the GCC authorities with the quality measures that could be of benefit for their regulatory review outcomes. It is essential and reasonable to follow-on the progress made with regard to the measures used to build quality into the review and decision-making processes in the GCC States.[7]

CONCLUSION

Finally, ICH looks to the future. It has established a structure to maintain the guidelines, and at the same time is looking to make available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. As well as making information available, the group will act as a resource in the understanding, and even acceptance, of many of the guidelines. From an industry perspective globalization is arguably the most important issue it faces, and the ability of these guidelines to effect intra-company globalization is a facet of ICH that cannot be ignored. This is already happening within companies. Its value has not been quantified; however, the companies able to embrace these principles today will be the world leaders tomorrow. Companies who fail to see the value of harmonization the value that is already being felt by the scientists carrying out the development, and the value that is yet to be realized in the full drug development cycle will be left at the starting line of the industry's globalization race.

Drug regulation is interplay between law and science, as well as among regulators and pharmaceutical companies, with input and influence from patients and healthcare professionals. These stakeholders help to determine the regulatory environment in each of the seven GCC authorities and cannot be neglected in the course of the assessment of each country's regulatory practices.

A focused view of the regulatory review process and the quality measures currently used to improve the standard of the assessment procedure is critical to underscore the similarities and differences among the GCC regulatory authorities. However, these similarities and differences cannot be exploited unless they are placed in the context of the GCC harmonized strategic plan.

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