The Impact of Implementation of ICH Guidelines in Non-ICH Countries

Report of a WHO Meeting
Geneva, 13-15 September 2001

World Health Organization
Geneva
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Regulatory Support Series, No. 9

World Health Organization
Geneva
2002
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Executive Summary

Efforts to harmonize various elements of drug regulatory activities have been initiated by various intergovernmental organizations at regional and interregional level in the past decade. The driving force behind these efforts has been the increase in global trade in pharmaceutical products, but also the growth in the complexity of technical regulations related to drug efficacy, safety, and quality.

The present report was prepared by a meeting of regulatory officials convened by the WHO Secretariat in September 2001. It considers issues arising from recent developments in activities for the global harmonization of regulatory requirements for pharmaceuticals in relation to the activities of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). The meeting gave special attention to the report on “International harmonization of regulatory activities: future options” produced in 1999-2000 by a WHO review team (see WHO Drug Information, vol. 14(3), pp. 145-159), as well as further developments related to ICH activities.

The ICH initiative, which started in 1990, is an interregional venture covering 17 high-income countries. It includes drug regulatory authorities of the European Union (European Agency for the Evaluation of Medicinal Products, EMEA), Japan (Ministry of Health, Labour and Welfare, JMHLW), and USA (Food and Drug Administration, US FDA), assisted by the research-based pharmaceutical industry associations of those countries (the European Federation of Pharmaceutical Industries’ Associations - EFPIA, the Japan Pharmaceutical Manufacturers Association - JPMA, and the Pharmaceutical Research and Manufacturers of America - PhRMA). The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) acts as the secretariat of ICH. WHO, Canada (represented by Health Canada) and the European Free Trade Area (EFTA) have observer status in ICH activities. ICH has produced over 45 guidelines describing technical requirements related to the process of drug registration. These guidelines are at present implemented by regulatory authorities of the ICH countries.

The ICH guidelines are produced by groups of eminent specialists drawn from the regulatory authorities and pharmaceutical companies of the ICH countries. Their scientific level is high and they represent an up-to-date approach to technical requirements. The costs related to full implementation of the guidelines are considerable, but it is argued that they are offset by more rapid registration of new drugs in the ICH countries.

The ICH initiative was originally intended to be limited to the evaluation and registration of products containing new chemical entities and new products obtained by biotechnology introduced on the market of the ICH countries. In the course of time the guidelines started to exert an influence in the ICH countries on requirements related to existing products, especially in respect of the quality of generic (multi-source) products and pharmaceutical substances (starting materials). If implemented,
the extension of ICH requirements in these areas may lead to a considerable increase in requirements imposed on local manufacturers in non-ICH countries where drug use is based on well established products, linked in many countries to the manufacture of generic versions of essential drugs. A new situation concerning ICH activities arose in March 1999 with the creation, within the ICH Steering Committee, of an ICH Global Cooperation Group with, inter alia, the aim of expanding the use of ICH recommendations to non-ICH countries. ICH’s mounting profile, the proposed active dissemination of the guidelines and their adoption by some non-ICH countries have led to a growing perception that they represent international standards.

This new development created a specific challenge for WHO as an intergovernmental organization with the constitutional task of setting international standards related to pharmaceuticals. The difficulties arising from such a position were recognized in a resolution of the Ninth International Conference of Drug Regulatory Authorities (ICDRA), held in Berlin in April 1999, which requested that WHO, when participating in the ICH process, take into account the implications for non-ICH countries.

The report of the meeting of regulatory officials considers the implications of the ICH process and globalization of its guidelines, describing the benefits of the ICH process but also setting out concerns about attempts to extend the influence of this process to non-ICH countries. It presents also more specific considerations on regulatory requirements in the areas of drug safety, efficacy and quality. Special emphasis is placed on the question of global harmonization of regulatory requirements for generic drugs. The report also describes the challenges for WHO in respect of the international harmonization of drug regulatory activities in the light of the ICH process.

The meeting makes the following recommendations:

• WHO should maintain its position as an observer within the ICH Steering Committee, adopting a more proactive role;
• WHO should maintain its position as an observer in the ICH Global Cooperation Group, making clear that its participation is not to be considered as an automatic endorsement of ICH guidelines or procedures;
• WHO should establish a consultation procedure for assessing, as early as possible in the ICH process, the usefulness of new ICH guidelines for the pharmaceutical industry and the drug regulatory authorities in non-ICH countries;
• WHO should establish a mechanism to review and build on ICH guidelines in order to produce WHO guidelines. It should also assess the benefits and risks of implementing selected ICH drug quality guidelines and the possible impact of the pharmacopoeia harmonization activities in the ICH regions on standards for the manufacture of generic products in non-ICH countries;
• In order to improve access to essential drugs of assured quality, especially in developing countries, there is an urgent need for WHO to intensify its efforts to further develop international standards and guidelines for the approval of generic products in consultation with the generic drugs industry, related organizations and national authorities;
• ICH should be encouraged to benefit from the work already carried out by WHO in the area of pharmacovigilance, and all ICH countries should be encouraged to participate more actively in the WHO Programme for International Drug Monitoring:

The meeting requested WHO to bring the above recommendations to the attention of both the WHO Expert Committee on Specifications for Pharmaceutical Preparations and the Tenth International Conference of Drug Regulatory Authorities (ICDRA), Hong Kong, June 2002.
1. Introduction

A meeting of regulatory officials was convened by the Department of Essential Drugs and Medicines Policy to discuss the impact of implementation of ICH guidelines in non-ICH countries. The meeting discussed ICH guidelines and reviewed an article recently published by WHO (see WHO Drug Information, vol. 14(3), pp. 145-159).

The meeting took place in Geneva on 13-15 September 2001.
2. WHO's role in developing global standards for pharmaceutical products

WHO has a constitutional mandate:

- to act as the directing and coordinating authority on international health work,
- to develop, establish and promote international standards for food, biological, pharmaceutical and similar products.

WHO's work in the drug regulatory area is based on a number of principles, in particular:

- The primary goal of regulatory work is to protect public health by ensuring the regular availability of good quality, safe and efficacious pharmaceuticals and by contributing to their rational use.
- Global norms and guidelines are a frame of reference; for their effective implementation, they need to be adapted to meet the specific needs, priorities and conditions of individual countries.
- International harmonization of regulatory requirements is a gradual process that can contribute to meeting public health goals when it is undertaken in relatively homogeneous groups of countries and when it takes into account existing gaps among national regulatory capacity and aims at bridging them.

In its Thirty-first report (WHO Technical Report Series, No. 790, 1990), the WHO Expert Committee on Specifications for Pharmaceutical Preparations stated that the approach to drug regulation must be attuned to available resources. It noted that problems in establishing regulatory control have too often resulted from the introduction of provisions successful elsewhere but of a complexity that precludes their effective implementation in the country of adoption.

Finally, WHO is the leading organization in the area of pharmacovigilance through its Collaborating Centre for International Drug Monitoring in Uppsala, Sweden. The Centre’s principal tasks are:

- to coordinate the WHO Programme for International Drug Monitoring and its more than 60 participating countries,
- to collect, assess and communicate information to participating countries about the harms and risks of drugs and other substances used in medicine, in order to improve patient therapy and public health worldwide,
- to collaborate with Member States in the development and practice of the science of pharmacovigilance.

One of the major products of the Centre is the WHO drug dictionary. This international classification of drugs provides the proprietary names of medicinal
products used in different countries, together with all active ingredients. Many countries recognize and use it as the international standard reference text.

It is against this background that WHO has been engaged in international regulatory harmonization initiatives over the past decade, involving several national drug regulatory authorities at regional and interregional levels.

In most cases the driving force behind harmonization initiatives has been the need to hasten access to pharmaceutical products and respond to the forces of international trade with adequate standardized technical regulations on safety, quality and efficacy. In this sense, the international harmonization process has not been fully consistent with the WHO principles stated above, even if, by reducing unnecessary duplication of regulatory requirements, it has allowed therapeutic advances to be made more rapidly and at a lower developmental cost.

A prerequisite for any harmonized approach to international drug regulation is the existence in each of the participating countries of a functioning, effective drug regulatory system. In the present context, this is understood to include a full drug registration process; the availability of unbiased drug information; oversight of promotional activities; post-approval drug safety monitoring; quality control testing; pharmaceutical inspection services; and certified compliance with good manufacturing practices.
3. The International Conference on Harmonisation (ICH)

The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 as a tripartite venture representing regulatory bodies and research-based industry. The major aim of ICH is to provide a forum for constructive discussion on the real and perceived differences in technical requirements for the registration of new chemical entities. Other objectives are: to achieve greater harmonization in the interpretation and application of technical guidelines for the registration of new active substances or products obtained by biotechnology by its members; to improve the efficiency of global drug development; to reduce redundant studies; and to improve pharmacovigilance activities and quality assurance.

The co-sponsors of ICH are: the European Commission and the European Federation of Pharmaceutical Industries’ Associations (EFPIA); the Japanese Ministry of Health, Labour and Welfare (JMHLW) and the Japan Pharmaceutical Manufacturers Association (JPMA); and the United States Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). These six co-sponsors are the voting members of the ICH Steering Committee.

ICH thus represents 17 countries comprising 15% of the world’s population and accounting for 90% of the US$ 320 billion global pharmaceutical sales of the year 2000. ICH regulatory authorities are among the first to evaluate new chemical entities and new products obtained from biotechnology.

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) provides the ICH Secretariat. WHO, Canada (represented by Health Canada), and the European Free Trade Association (EFTA) hold observer status in ICH and its Steering Committee.

To date, ICH has produced more than 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 current ICH terms of reference are as follows:

- 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 harmonized technical requirements leading to a greater mutual acceptance of research and development data;
- To avoid divergent future requirements through harmonization 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 harmonized guidelines and their use such as to encourage the implementation and integration of common standards.

A procedure has been adopted by ICH for the selection of major harmonization topics, participation of interested parties, and performance of practical work related to the production of a guideline related to the topic. The ICH party or observer proposing a new harmonization action must first present the issue in the form of a concept paper. This is then discussed by the ICH Steering Committee and a preliminary determination is made on whether the topic is of sufficient interest to all parties and can be accommodated within the ICH work schedule. When interested parties apart from the six ICH sponsors and three observers are identified, the Steering Committee invites, as appropriate, those additional parties to the discussions on the topic just prior to its acceptance by the Steering Committee. The Steering Committee then appoints an expert working group (EWG) to review the differences in requirements between the three ICH regions and to develop the scientific consensus needed in order to reconcile any such differences. EWGs do not have a fixed membership and each of the six ICH parties nominates a topic leader as the contact point for the topic. The observers to ICH, the pharmacopoeia authorities, and representatives from the self-medication and generics industries have been invited to participate in various EWGs.

The process of production of a harmonized ICH guideline consists of several steps. In step 1, an initial draft of the guideline is prepared by the EWG and circulated through successive revisions until a consensus is reached. The draft is then forwarded to the Steering Committee. Step 2 is reached when the Steering Committee agrees that there is sufficient scientific consensus on the technical issues for the draft guideline or recommendation to proceed to the next stage of regulatory consultation. In step 3 the draft guideline leaves the ICH bodies and becomes the subject of regulatory consultations in the three ICH regions. An opportunity is also offered to industry associations and regulatory authorities in non-ICH countries to comment on draft documents, which are distributed using IFPMA and WHO contact lists. In step 4 a final text of the guideline is prepared by the EWG and submitted to the Steering Committee for adoption, which takes the form of signature by the three regulatory parties to ICH affirming that the guideline is recommended for adoption.
throughout the three regions. After completion of step 4, the tripartite harmonized
text moves immediately into the final step (step 5) of the process, which is its regulatory implementation. This is carried out according to separate national/regional procedures identical to those that apply to the endorsement of other regulatory decisions in the EU, Japan and the USA. The importance of step 5 should be stressed, as only then do individual guidelines become effective in the countries concerned.
4. Expanded ICH initiatives

Following the completion of the majority of ICH’s initial objectives for harmonization in 1997, the ICH parties agreed that harmonization activities should enter another phase to take account of the need for updating existing guidelines and extending global harmonization.

The terms of reference of ICH were amended in that year (see section 3 above) to include provisions on:

- monitoring and updating existing guidelines;
- facilitating the adoption of new or improved technology;
- facilitating the dissemination and communication of information on harmonized guidelines and their use.

A provision on contributing to the protection of public health from an international perspective was added to the terms of reference in 2000.

As part of this expanded phase of ICH activities, the Steering Committee has established a Global Cooperation Group. The principles and terms of reference of the Group were finalized in 1999 and, following a formal approach from ICH, WHO joined it as an observer. The terms of reference of the Group include the provision of information on ICH and its activities and on ICH guidelines to any country, regulatory authority or company that requests such information. Thus, the Group’s aim is to disseminate finalized ICH guidelines in order to encourage their acceptance and adoption in non-ICH countries.

The implications of the creation of the Global Cooperation Group are discussed below.
5. Implications of the ICH process and globalization of ICH guidelines

The establishment of ICH in 1990 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 the many 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. For the regulatory authorities, new guidelines simplify the process of assessment and facilitate communication with the pharmaceutical industry.

5.1 Benefits of the ICH process

As already mentioned, ICH has produced more than 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 in the ICH countries. The scientific level of each guideline is high and reflects state-of-the-art technology.

The production of ICH guidelines has enabled the ICH countries, the originators of the process, to harmonize technical requirements for the registration of new pharmaceutical products to a substantial extent. Thus, the results of the ICH process have contributed to streamlining the research process in the pharmaceutical industry, assisting drug development by facilitating the assessment of candidate drugs. Because the time needed for regulatory assessment has been shortened the process has resulted in more rapid access to new medicines.

The pooling of resources mobilized by the ICH process has resulted in a number of state-of-the-art guidelines that could not have been achieved in so short a time in the individual regions. The ICH initiative has produced benefits for the regulators by creating a simplified drug regulatory review process.

ICH guidelines are also used by countries apart from the ICH members. They serve as educational and reference material, especially in fields where WHO has not issued documents or guidelines, and so provide an additional source of information. Their use as tools for seminars in the regional harmonization activities of the countries of the Association of South-East Asian Nations (ASEAN) is one example of their usefulness.
5.2 Concerns about ICH

While it is widely recognized that the ICH guidelines are of high quality and scientifically sound, there are areas of concern related to their implementation, particularly in countries that have not participated in the ICH process. These concerns, which are primarily the consequence of the ICH decision-making process, can be outlined as follows:

- The ICH process has involved 17 industrialized countries in the decision-making process. The views, priorities, and needs of the majority of WHO Member States have only sporadically been taken into consideration.

- There is a perceived lack of sufficient consultation with academic scientists, health professionals, and societal forces such as consumer and patient groups. While it is recognized that such consultation can only be carried out at the national level, the perception of powerlessness to influence the decision-making process remains. Experience indicates that national authorities tend to curtail explanations and discussions at the national level by referring to negotiations carried out at the international level.

- Proponents of ICH argue that the intention of involving WHO as an observer in ICH was to ensure that international concerns on the protection of public health interests are met. However, no realistic operational mechanisms have been created to ensure that due consultation enables national authorities not involved in the ICH process to understand the context and rationale underlying technical documents circulated for comment.

- While it is fair to assume that the partners within ICH are satisfied with the infrastructure and process, outside commentators have questioned the appropriateness of designating IFPMA to coordinate the process and provide the secretariat. Some critics consider that this structure and the substantial resources made available by research-based industry have led to an industry-driven agenda, while the regulatory authorities have difficulty in maintaining a public health-oriented approach to international harmonization. Whether or not this criticism is founded, the perception remains.

- The public health implications of the application of guidelines of greater technical complexity in developing countries may be far-reaching. In many countries, essential drugs required for the prevention and treatment of locally endemic conditions are not supplied by the major multinationals, but by local industry or by generic manufacturers. If these suppliers are unable to meet what may be unsubstantiated quality standards, the adverse impact of the withdrawal of these drugs on the health of the population might well be far more dramatic than that of any hypothetical risk posed by failing to achieve the ICH standards.

- Recent developments involving the ICH Global Cooperation Group suggest that ICH activities are being positioned with the aim of gaining wider international acceptance. ICH guidelines are being promoted and are increasingly perceived as the "best" possible standard for international harmonization. ICH has never claimed, and does not have international authority or capacity, to produce global standards. Nevertheless, although
ICH countries import large quantities of pharmaceuticals from non-ICH countries with weak regulatory systems, many countries are led to think that adoption of the guidelines is a necessary move to gain access to the pharmaceutical markets of ICH countries. This “spontaneous” dissemination of ICH products is not necessarily consistent with national priorities and represents a pressure that may lead to diverting limited national resources to unnecessary expenses entailed by the adoption of more costly regulatory requirements. In this connection, it is worth noting that the Ninth International Conference of Drug Regulatory Authorities (ICDRA) held in Berlin in April 1999 recommended that WHO, when participating in the ICH process, should take into account the implications for non-ICH countries.
6. Implication of the use of ICH guidelines by non-ICH drug regulatory authorities

6.1 Efficacy and safety

In the field of drug efficacy and safety ICH has produced 26 guidelines describing technical requirements related to the process of registration of new chemical entities and products obtained by biotechnology. As already mentioned, the scientific level of each guideline is high and reflects state-of-the-art technology.

Although intended primarily for ICH countries, guidelines related to drug safety and efficacy may also be of use to non-ICH countries to create awareness of the subject, and for reference and guidance purposes for national drug regulatory authorities when producing national legislation. They may also be used for education and training purposes. This applies particularly to ICH guidelines in the safety area (guidelines S1A to ICH S7, especially those on carcinogenicity and genotoxicity). It should be stressed that the majority of ICH guidelines in the areas of safety and efficacy deal with topics for which no documents of a regulatory nature previously existed, which considerably to their usefulness.

It should be recognized that WHO has produced only a limited number of materials on topics concerned with safety and efficacy. They relate to good clinical practice (GCP), for which WHO has produced guidelines, and to reporting of adverse drug reactions, for which WHO maintains its Centre for International Drug Monitoring in Uppsala, Sweden. As the WHO GCP guidelines are now in the process of revision, it is intended that the revised version should indicate the material contained in ICH’s guideline.

Attempts to apply some ICH guidelines related to drug safety and efficacy in practice in non-ICH countries can give rise to considerable difficulties, especially when full implementation is attempted in countries that lack adequate resources. Specific examples of such difficulties are presented below.

ICH guideline E5, “Ethnic factors in the acceptability of foreign clinical data”, recommends a framework for evaluating the impact of ethnic factors on the effect of the medical product. Some commentators claim that the guideline may limit the scope of decision of national regulatory authorities as to the need for clinical studies to be conducted in the country. This may create problems with the verification of the actual efficacy of drugs in local situations, and may also create obstacles for local pharmaceutical development. At the same time, the need for local clinical trials must be scientifically justified.

ICH guideline E2C “Clinical safety data management: periodic safety update reports (PSUR) for marketed drugs”, which lays down a format and content for comprehensive periodic safety updates and recommends a six-monthly periodicity
for such update reports, is highly resource-intensive. The resources required to
maintain the system are beyond the means of most non-ICH countries. It may be
considered that non-ICH countries would benefit more from a digest of work done
by the ICH drug regulatory authorities on each individual product, provided such
digests are produced and suitably disseminated.

The ICH GCP guideline (E6, “Good Clinical Practice: consolidated guideline”) deals
with the planning, conduct, monitoring and reporting of clinical trials. Its object is to
facilitate the mutual acceptance of clinical trial data in ICH countries. However,
WHO’s constituency includes all the world’s cultures. The purpose of the WHO GCP
guidelines is to provide globally applicable guidance for the conduct of clinical trials,
thereby assuring the ethical and scientific integrity of research.

The ICH GCP guidelines are used by non-ICH countries to develop their own GCP
guidelines. They are more detailed and user-friendly than current WHO GCP
guidelines, but they do not address country-specific issues. The conduct of clinical
trials should be linked to scientific justification. There is a need for WHO to revise its
current guidelines taking these factors into account. The WHO GCP guidelines are
currently being revised to adopt a modular approach that will enhance their
educational value.

ICH guideline M3, “The timing of non-clinical safety studies for the conduct of
human clinical trials for pharmaceuticals”, is important for regulatory authorities
that control and assess product development prior to drug product approval. It also
provides the pharmaceutical industry with guidance on the approach that should be
taken to perform various tests prior to submission of evidence to regulatory
authorities. It would be useful to non-ICH countries for better awareness and
understanding of requirements so that they could establish national approval
requirements appropriate to their situation.

ICH guideline M1, “Medical terminology” (including Medical Dictionary for
Regulatory Activities Terminology, MedDRA Terminology), was developed as a
medical terminology covering all aspects of drug regulation ranging from
authorization to post-marketing surveillance. It contains terms for adverse drug
reactions (ADRs) and also for diseases, investigations and patient history. It includes
terms from the WHO Adverse Reaction Terminology (WHO-ART) and ICD-9, but
uses a different structure and many more terms. The advantages of using MedDRA
have been stated as specificity for data entry, flexibility for data retrieval, and
standardization for international communication. However, there are significant
problems in the use of MedDRA by non-ICH countries, particularly difficulties in
installing and using the terminology and its cost. Recommendations by WHO to ICH
to retain WHO-ART as a pharmacovigilance subset of MedDRA and to involve WHO
in the review of MedDRA were not considered by ICH to be workable. ICH’s
position has forced WHO to continue with the further development of WHOART.
The relationship of WHO-ART with ICD-9 and 10 also has important public health
and epidemiology aspects. There is no satisfactory proposal from ICH to address
these points.

A new ICH initiative to develop activities in the area of post-marketing surveillance
was proposed at the Fifth International Conference on Harmonization (November
2000). Three topics were suggested in the first instance:
(1) periodic safety update information;
(2) safe roll-out of new drug products;
(3) case reporting.

The proposal might have implications for the WHO Programme for International Drug Monitoring.

6.2 Quality

In the field of drug quality ICH has produced 15 guidelines describing technical requirements related to the process of registration of new chemical entities and products obtained by biotechnology. Again, the scientific level of each guideline is high and reflects state-of-the-art technology.

Guidelines related to drug quality may also be of use to non-ICH countries to create awareness of the subject and for reference purposes for national drug regulatory authorities when producing national legislation. They may also be used for training purposes, especially to trigger discussion on approaches to setting quality standards.

However, ICH has relied increasingly on advanced pharmaceutical technology in its standard setting, on the assumption that this technology will lead to greater safety of new drugs, while the ICH guidelines relating to drug quality have introduced a general tightening of specifications for pharmaceutical starting materials. For example, ICH guideline Q3A (“Impurities in new drug substances”) includes the requirement that each organic impurity (whether identified or unidentified) present in a substance in the amount of 0.1% or more (in some cases 0.05% or more) should be considered as a qualified impurity (i.e. its safety should be established). This raises the question of the basis for the selection of the borderline figure, as the additional safety benefits from these rigorous standards have not been demonstrated but the costs incurred by manufacturers in meeting the requirements are significant.

Setting such norms may have considerable repercussions on current manufacturing practices, as only pharmaceutical companies with substantial resources can achieve the necessary standards. This is a concern if the guidelines are intended for global application. Smaller pharmaceutical companies, generic companies and many larger companies responsible for essential drug production in developing countries may be effectively squeezed out of drug manufacturing if ICH guidelines start to be interpreted as the only global standard. For example, the ICH guidelines Q3A (“Impurities in new drug substances”) and Q3C (“Impurities: guideline for the residual solvents”) were developed for new products but their application has been extended by the European authorities to cover all products registered in the European Union.

Another type of difficulty has arisen with ICH guideline Q7A, on “Good Manufacturing Practice guide for active pharmaceutical ingredients”. The guideline introduces and expands the requirements for manufacturers of pharmaceutical active starting materials, and so creates increased rigidity in the starting material supply
system, with consequent effects on starting material prices and availability. The applicability of this guideline for non-ICH countries has been questioned.

Although formally the Pharmacopoeial Discussion Group (which consists of representatives of the three pharmacopoeias of the ICH countries) acts outside the ICH system, in practice its activities are closely linked to ICH’s activities. Of special importance is the acceptance of the requirements included in ICH guidelines Q3A and Q3C (see above), which are gradually being introduced into Pharmacopoeia monographs published in the ICH countries.
7. WHO guidelines for generic drugs

Regardless of discrepancies in their precise legal definition, generic drugs are widely available worldwide, represent the majority of drug regulatory work in most countries, and are the most common approach to moderating pharmaceutical expenditure.

WHO provides a comprehensive set of guidelines in the area of quality assurance of pharmaceutical products. These guidelines are established and maintained through a consultative procedure and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are submitted to WHO’s governing bodies for endorsement and subsequent implementation by Member States. The guidance texts include recommendations in the area of good manufacturing practices (GMP) and inspection, product assessment and registration, distribution, quality control, laboratory services, and international trade in pharmaceuticals. More specifically, guidance is provided for the production of pharmaceutical products and starting materials, as well as particular types of pharmaceutical products, e.g. sterile and biological products, and herbal medicines. In the area of product assessment and registration, specific advice is available for stability testing, interchangeability and selection of comparator pharmaceutical products for equivalence testing, assessment of herbal medicines, packaging, etc. Various schemes are recommended, including model certificates for pharmaceutical products moving in international commerce and certificate of analysis and compliance with GMP requirement in connection with manufacturing site inspections.

For more than 50 years, the International Nonproprietary Names programme has provided names that allow the identification of pharmaceutical substances worldwide.

WHO prepares specifications that enable basic tests, screening tests and full pharmacopoeial analysis to be performed. The work is centred on the drugs included in the Model List of Essential Drugs and the drug substances and finished dosage forms recommended by the WHO programmes responsible for priority diseases such as malaria, tuberculosis and HIV/AIDS. In connection with the International Pharmacopoeia, WHO also establishes International Chemical Reference Substances.

A consultative meeting of experts working on the preparation and maintenance of the International Pharmacopoeia recently (September 2001) confirmed the importance of maintaining the concept and current form of the monographs published in the third edition. In the light of the increasing shift to more sophisticated methods and the more stringent test limits being proposed internationally, it was considered important to emphasize the robustness of the tests published to date, since there are no scientific data available suggesting that the approach currently used needs to be tightened. A statement in this sense has been
prepared for endorsement by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its 37th meeting in October 2001.

All these standards, guidelines and guidance materials cover numerous aspects of pharmaceutical quality and regulatory requirements that are of particular relevance for generic drugs. In comparison with ICH quality guidelines, the major differences are that WHO documents:

- cover a much wider subject area;
- also include guidance materials of a practical or educational nature;
- indicate requirements and specifications of much wider applicability.

Although originally intended only for new active substances (NAS), ICH guidelines on quality have an impact on established active substances (EAS) for these reasons:

- Many NAS will eventually become EAS;
- Some guidelines have been already extended to all existing drugs,
- It is easy to argue that many quality requirements should be the same for NAS and EAS.

As stated earlier, this is cause for concern, particularly in the light of the cost implications of the work of ICH and its associated pharmacopoeias, which appear to be technology-driven and not based on documented public health needs.

In contrast, the following principles guide WHO’s work in the development of guidelines and standards:

- a public health-oriented approach, which requires that:
  - specifications and guidelines should be tailored to meet public health needs;
  - any increase in the technical complexity of specifications should be based on documented public-health needs;
  - maximum advantage should be taken of technical progress and strategies leading to improved access to efficacious and safe drugs of the appropriate quality;

- careful consideration of issues related to effective implementation, which implies:
  - appropriate mechanisms to enable organizations from the generic drugs industry - taking into account broad geographical representation - to participate in the consultation process for the development and maintenance of quality guidelines,
  - appropriate dissemination, promotion and training strategies,
  - strategies to improve confidence in generic drugs on the part of health professionals and the public.
8. Challenges for WHO

The existence of international harmonization initiatives in different parts of the world demonstrates the importance that governments attach to drug regulation; at the same time, it offers opportunities for countries to review and improve their regulatory systems. It is evident from the discussion above that WHO faces a number of challenges if it is to fulfil its constitutional mandate and meet the expectations of its Member States in greatest need.

These challenges can be outlined as follows:

- Countries’ priorities, needs, resources, and requirements differ substantially. These differences have enormous implications for WHO’s work, both when developing global guidelines and when advising Member States on their adaptation and adoption.

- To achieve effective implementation, WHO’s activities, (e.g. WHO Programme for International Drug Monitoring, International Pharmacopoeia) require improved dissemination, promotion and communication strategies.

- There is a need to analyse in greater depth whether the more stringent product specifications resulting from the introduction of certain ICH quality guidelines will produce additional public health benefits.

- Present developments in the international harmonization of drug regulation should be seen as a challenge to WHO to review the standards and guidelines that it has already established.

- Currently, WHO attends meetings of the ICH Steering Committee and the Global Cooperation Group as an observer. These roles are important and should be maintained, However, appropriate strategies for consultation and communication with Member States need to be developed to ensure that WHO is not seen as de facto automatically endorsing ICH products, but as providing advice on the potential impact of those products on non-ICH Member States.

- WHO needs to develop a more effective strategy to achieve global acceptance of standards for generic products, to ensure that the regular supply of quality essential drugs is not jeopardized by standards that are unnecessary and unrealistic.

- Technical requirements have an ethical dimension reaching from research and development for new drugs to the establishment of specifications that are meaningful for public health.

As clearly indicated above, ICH does not appear to be the best forum for the discussion of technical requirements for generic drugs. In order to ensure the supply of essential drugs for the majority of the world’s population, particularly in the
developing countries, there is an urgent need for WHO to further strengthen the
development of international standards and guidelines on the assessment of generic
products. This should be done with the priority focus on demonstrated public health
need and in closer consultation with the generic drugs industry, related
organizations, and national authorities of both ICH and non-ICH countries.

Finally, WHO is the leading organization in the area of pharmacovigilance. In the
light of the proposed expansion of ICH into pharmacovigilance, it is a challenge for
WHO:

- to establish links with ICH to avoid unnecessary duplication;
- to become more active in developing guidelines on pharmacovigilance;
- to disseminate its reports and data more widely;
- to raise awareness of its work by encouraging all Member States to participate
  in the WHO Programme for International Drug Monitoring.
ICH has made it clear that it is committed to maintaining the status quo to achieve full effectiveness of the ICH process. However, other groups have influenced ICH to change some of its procedures. Although it is considered unlikely that ICH would accept a significant change in either the membership of its Steering Committee or current procedures for the modification or development of guidelines, WHO should be encouraged to find ways to work more closely with ICH to involve and seek input from other countries.

The following recommendations are proposed for implementation by WHO. They are dependent on resources being made available for their implementation.

- WHO should continue to be an observer in the ICH Steering Committee, adopting a more proactive role by proposing topics for guideline development and expressing opinions on the potential public health implications of guidelines proposed.

- WHO should continue to be an observer within the ICH Global Cooperation Group, taking measures to ensure that its participation is not considered as an automatic endorsement of ICH guidelines or procedures.

- WHO should continue to produce briefing notes on ICH meetings for regulatory officials of non-ICH countries and consider ways of making them widely available, including use of the Internet.

- WHO should set up a consultation procedure to start assessing, as early as possible in the ICH process, the usefulness of new ICH guidelines for the drug regulatory authorities and the pharmaceutical industry in non-ICH countries. WHO should establish a mechanism to review and build on ICH guidelines in order to produce WHO guidelines, where relevant for public health.

- WHO should assess the benefits and risks of implementing selected ICH drug quality guidelines and the possible impact of pharmacopoeia harmonization activities in the ICH regions on standards for the manufacture of generic products in non-ICH countries.

- Recommendations from such reviews should be disseminated to Member States on a continual basis. Within the context of the consultation process, on request, WHO should be prepared to offer specific advice to national authorities in non-ICH countries.

- In the light of the wide range of regulatory environments, WHO should support non-ICH Member States and regional harmonization initiatives in evaluating the usefulness, feasibility and impact of implementing ICH guidelines.

- In order to improve access to essential drugs of good quality, especially in developing countries, there is an urgent need for WHO to intensify its efforts.
to develop international standards and guidelines for the regulatory assessment of generic products. This should be done with the focus on demonstrated public health need and in consultation with the generic drugs industry, related organizations and national authorities.

- There is a need for expanded cooperation between WHO and ICH in the area of pharmacovigilance in order to ensure that ICH countries can benefit from the work already carried out by WHO in this area. All ICH countries should be encouraged to participate more actively in the WHO Programme for International Drug Monitoring.

The meeting requested WHO to bring the above recommendations to the attention of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and the Tenth International Conference of Drug Regulatory Authorities (ICDRA), Hong Kong, June 2002.
ANNEX I – List of Participants

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The Impact of Implementation of ICH Guidelines in Non-ICH Countries

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