WHO Drug Information

Contents

International Harmonization

ICH Pharmaceutical Quality System Q10

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline *Pharmaceutical Quality System Q10* was adopted at the ICH meeting in Portland (Oregon, USA) in June 2008. Within Step 4 of the ICH Process, the guideline is recommended for adoption by regulatory bodies of the European Union, Japan and USA. The guideline describes a robust quality management system model that can be implemented throughout the different stages of the product lifecycle.

The ICH Q10 quality vision

In the 1930s, Walter Shewhart (1) developed Statistical Process Control methods and the PDSA spiral — plan what you want to do, do it, study the results, make corrections (total quality management), and start the cycle again (continuous improvement).

Shewhart's student, W. Edwards Deming (2) is credited with improving production in the United States during World War II. From 1950 onwards, he taught top management in Japan on how to improve design, product quality, testing and sales in global markets through various methods, including the application of statistics. Deming demonstrated that Shewhart's spiral is roughly analogous to the scientific method: one has a theory (or hypothesis), and puts it to the test; studies the results and takes action based on those results. This is the road to scientific learning. PDSA is the road to organizational learning.

In the 1950s, Dr Joseph M. Juran (3) started a production management system at Toyota which has continued to evolve over the decades. In the 1980s, Toyota cars became the model of global choice because they lasted longer than other cars in the same category and required much less service. About a decade later, it became clear that it was the way Toyota designed and manufactured the cars that led to high consistency in the process and product.

In 2003, the ICH Steering Committee agreed on a new quality vision to emphasise a risk- and science-based approach to pharmaceutical production in an adequately implemented quality system. As a consequence, the guidelines on Pharmaceutical Development (Q8), Quality Risk management (Q9) and Pharmaceutical Quality System (Q10) were drafted. As these concepts and principles are rather new in the pharmaceutical area, proper implementation is important to bring clarity, further explanation and remove ambiguities and uncertainties.

Table 1 overleaf lists some frequently used terms defined in the ICH Pharmaceutical Quality System Q10 guideline.

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Table 1. Pharmaceutical Quality System guideline definitions

Continual Improvement: Recurring activity to increase the ability to fulfil requirements

Enabler: A tool or process which provides the means to achieve an objective

Knowledge Management: Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components

Performance Indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process, or system, also known as "performance metrics" in some regions

Product Realisation: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers' requirements.

Quality Objectives: A means to translate the quality policy and strategies into measurable activities

Quality Policy: Overall intentions and direction of an organization related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality risk management: An active approach to identifying, scientifically evaluating and controlling potential risks to quality

Senior Management: Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site (ICH Q10 based in part on ISO 9000:2005 Quality management systems)

Pharmaceutical Quality System

The Q10 glossary defines the Pharmaceutical Quality System (PQS) as a "management system to direct and control a pharmaceutical company with regard to quality." The PQS describes a set of policies, processes and procedures required for designing (non-clinical and clinical research) and execution (development, manufacture, distribution and postmarketing activities) of changes in the pharmaceutical industries that employ science- and risk-based principles and approaches related to product quality (ICH Q8 and ICH Q9) at each life cycle stage. This also promotes continual improvement leading to the fulfilment of patient needs and improved business performance.

The guideline introduction states that "ICH Q10 is not intended to create new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional."

Scope of the Pharmaceutical Quality System

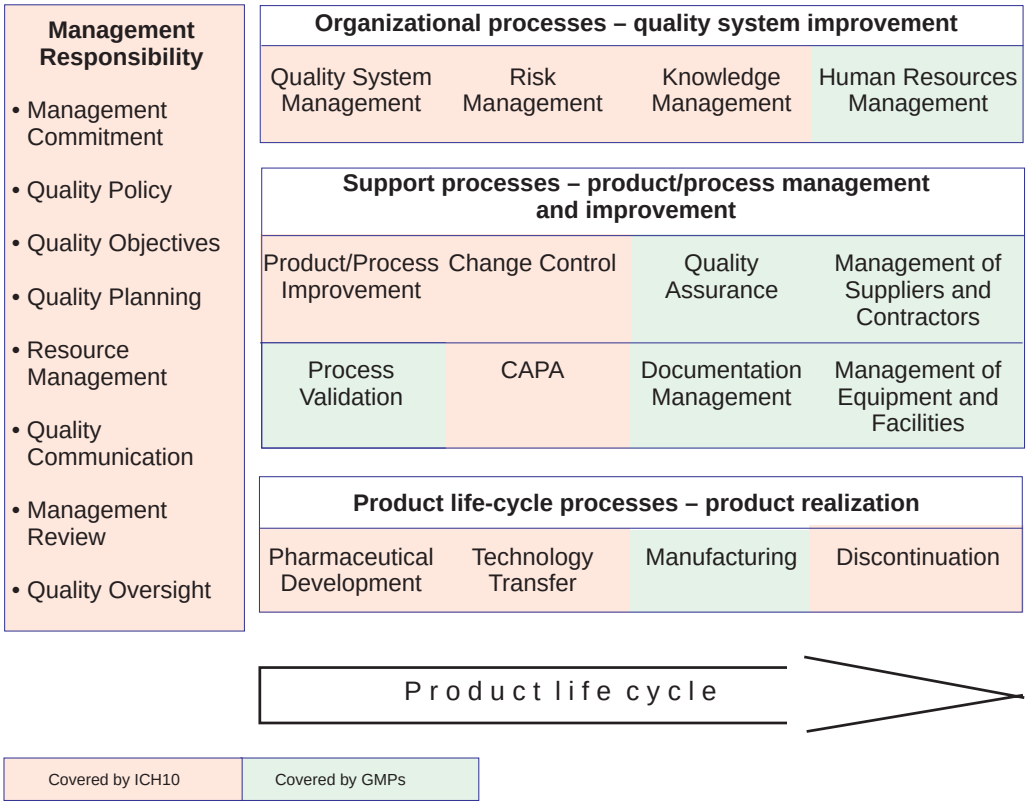
PQS applies to all systems supporting the development and manufacture of pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product life cycle.

Relationship of ICH Q10 to regional GMPs

Figure 1 overleaf —drawn from comments of the European Union during the development of the guideline and adapted to this review article — illustrates the principal differences between ICH Q10 and GMPs.

Activities overlap to some extent (e.g. clinical batches are manufactured accord-

Figure 1. Relationship of ICH Q10 to regional GMPs



ing to GMPs during Pharmaceutical Development, or Human Resource Management includes GMP training) but the diagram permits focusing presentation in this article to the pink rectangles.

Enablers: Knowledge Management and Quality Risk Management

Knowledge Management and Quality Risk Management will facilitate achievement of the following objectives of the PQS:

• Achieve product realization

• Establish and maintain a state of control

• Facilitate continual improvement

Management Responsibility

Management should establish a quality policy to include expectations of compliance with applicable regulatory requirements. The quality policy should be communicated to and understood by personnel at all levels in the company.

Management should provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the PQS and continually improve its effectiveness.

Management should assess the conclusions of periodic reviews of process performance and product quality and of the PQS.

Continual improvement of process performance and product quality

Data collection on performance indicators — quality attributes of the drug product and the parameters of the manufacturing process — starts with the design and development of pharmaceutical quality from the very beginning of the product life cycle. In an eternally successful organization, “People routinely do things right first time”, (Philip Crosby). Product and process variability is explored. Pharmaceutical development results in knowledge which establishes that the selected formulation is suitable for the intended use and the manufacturing process can be scaled up to production level. Process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.

The goal of technology transfer activities is to pass on product and process knowledge [analytical methods, active pharmaceutical ingredients (APIs) and pharmaceutical dosage forms] between pharmaceutical development and manufacturing, and within or between manufacturing sites to achieve product realization. (According to this description, transfer of technology takes place within the same quality system. The effective transfer of knowledge and experience between two quality systems may not follow the same methodology, for example, when the API and the pharmaceutical product are manufactured by different companies.) This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

In the third stage, the PQS should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

In the terminal stage of the product lifecycle, a pre-defined approach should be used to manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

Pharmaceutical Quality System elements

Process performance and product quality monitoring system

An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement.

Corrective Action and Preventive Action (CAPA) System

The pharmaceutical company should have a system for implementing corrective action (to prevent recurrence) and preventive action (to prevent occurrence) resulting from the investigation of complaints, product rejections, non-conformance, recalls, deviations, audits, regulatory inspections and findings, and trend analysis from process performance and product quality monitoring. Preventive action also includes, e.g., benchmarking, reviews (contracts, purchasing, processes), process capability studies, Statistical Process Control (SPC) analysis, Failure Mode Efffects Analysis (FMEA) and employee training programmes.

This methodology is useful where corrective action and preventive action is incorporated into the iterative pharmaceutical design and development process. CAPA is mainly used as an effective system for the modification or control of a manufacturing process by its results or effects (feed-back) or using its anticipated

results or effects (feed-forward) and continual improvement.

Change Management System
Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements.

Management Review of Process Performance and Product Quality
Management review should provide assurance that process performance and product quality are managed over the life cycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

Continual improvement of the pharmaceutical quality system
Management should have a formal process for reviewing the PQS on a periodic basis. The review should include, among others, the measurement of achievement of PQS objectives and the assessment of performance indicators. Management should follow up emerging regulations, guidance and quality issues that can impact the PQS. ICH Q10 encourages innovations that might enhance the PQS and product and process understanding — such as new approaches to process validation and monitoring in-process control strategies that may lead to real-time release mechanisms — as well as the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).

Conclusion

The concepts and principles of quality management have been widely used in the car industry since the 1950s but they are rather new in the pharmaceutical industry. Although ICH Q10 is not intended to create any new expectations beyond current regulatory requirements, pharmaceutical industries — also outside the ICH regions — are expected to implement the PQS because it is an indispensible condition for those companies that wish to become and/or remain competitive in product quality and productivity within global and regional markets.

PQS is equally applicable to innovator and generic pharmaceutical companies as well as to drug substances and drug products. Implementation of PQS continuously increases product and process understanding and provides opportunities for science-based dossier assessment and the increased use of risk-based approaches for regulatory inspections.

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African Medicines Regulatory Harmonization Initiative (AMRHI): a WHO concept paper

Essential medicines save lives and improve health when they are available, affordable, of assured quality and properly used. However, lack of access to essential medicines remains one of the most serious global public health problems (1). Millennium Development Goal number 8 declares that providing access to affordable essential drugs in developing countries is a fundamental human right (2).

The objective of the WHO project on Harmonization of Medicines Regulation in Africa (AMRHI) is to improve health in the African Region by increasing access to safe and effective medicines of good quality. This can be accomplished by strengthening the technical and administrative capacity of participating national medicines regulatory authorities. Collaborative mechanisms can provide a more transparent, streamlined process for the marketing authorization of pharmaceutical products and follow-up of products already marketed.

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Effective medicines regulation

Assuring the quality, efficacy and safety of medicines is an important task for medicines regulatory authorities (MRA) and is performed through subjecting all pharmaceutical products to pre-marketing evaluation, marketing authorization and post-marketing review. Countries may differ regarding registration systems since not all can implement a comprehensive medicine evaluation and registration system.

Currently, approximately 20% of countries have fully operational medicines regulation. Of the remainder, half have regulation of varying capacity, and 30% have either no or very limited medicines regulation. The reality is that many low-income countries cannot ensure the safety, efficacy and quality of medicines circulating on their markets because they are resource constrained in terms of staffing, standards, systems, and training. A number of additional factors explain observed weaknesses of drug regulation with regard to health systems or socio-economic development. Problems of ineffective regulation transcend national borders and have global implications (3).

Over two-thirds of the world's population live in countries with marginal or inadequate regimes for assuring drug quality, safety and efficacy. A recent WHO survey on the quality of antimalarials in seven African countries revealed that between 20 and 90% of products failed quality testing (4). Use of poor quality starting materials from unreliable sources is an ongoing problem in many countries (5). The prevalence of poor quality or even harmful medicines is a waste of resources that undermines already overburdened health-care systems, puts public safety at risk and increases the likelihood of drug resistance.

Medicines regulation is a complex issue. It is the totality of all measures — legal, administrative and technical — which governments take to ensure the safety, efficacy and quality of drugs. This also involves assessment of the relevance and accuracy of product information.

The ability to regulate medicines effectively is determined by a number of

factors, including: the state of economic development, infrastructure and prevailing health-care system. A root problem is the lack of human and financial resources devoted to regulation and the effectiveness of collaboration with regulators abroad. Not all medicines regulatory authorities (MRAs) in developing countries have sufficient capacity to perform risk-benefit assessments. Among other things, this is often the result of inadequate political commitment exacerbated by interest groups that benefit from loose regulation and retaining of the *status quo* in the pharmaceutical sector. Hence, although the policy options to rectify this situation are relatively straightforward in principle, implementation may well be much more complicated.

Countries need resources, both human and financial. Lack of resources may be compensated to some extent by effective collaboration among countries and information sharing. Therefore, political leadership and commitment is critical. Meanwhile, it is important to mention that even if more financial resources are allocated to ensuring appropriate regulatory development within a region, the availability and expertise of human resources could remain a challenge over the medium term.

The need for harmonization

The circulation of substandard medicines in the developing world is a serious concern (6). The problem of substandard medicines include inadequate or overconcentration of ingredients, contamination, poor quality ingredients, poor stability and inadequate packaging. Reasons for the existence of substandard medicines are multiple: medicines manufactured for export are not regulated to the same standards as those for domestic use, while regulatory agencies in the less-developed world are poorly equipped to assess and address this problem.

A number of recent initiatives have been successful, most notably the establishment of the WHO Medicines Prequalification Programme (7). However, much more action is required in order to improve the operation of medicines regulatory authorities in resource-constrained countries to detect and contain substandard medicines. The formation of effective networks between regulatory authorities nationally and internationally facilitates sharing of scarce resources and eliminates duplication of effort. Networking of institutions in developing and developed countries, both formal and informal, is an important element in building regulatory capacity and trust, especially with regard to innovative products (8). Harmonization of medicines regulation is a desirable goal for many reasons (9).

- Companies have to generate only one data set for all regions and, consequently, the amount of human and animal experimentation is reduced.
- The cost of development of new drugs and their regulatory documentation is reduced, which would logically lead to lower prices.
- Common regulatory standards for evaluation and inspection facilitate regulatory communication and information sharing.
- Local products are more likely to be acceptable for export to other countries.
- Faster access to medicines of high public health value (paediatric medicines, medicines for major diseases or for emergencies in national settings etc.).
- Increased competitiveness resulting from newly developed common markets.

Existing harmonization initiatives

Harmonization in a broad sense means *harmonization of technical requirements*

for medicines regulation, i.e., legislation, guidelines, procedures, etc. These requirements relate to the quality, safety and efficacy of medicinal products and can differ in complexity from one type of marketing authorization application to another (i.e., innovator drugs vs. generics). In implementing medicines regulation, it should be noted that this will only be effective if all aspects of regulation are addressed. The results of a WHO multicountry study showed that several areas in drug regulation receive relatively little attention in the implementation process. The informal sector, post-marketing surveillance (quality and safety) and control of drug information were the most important of these (10).

Various international and regional initiatives exist in which regulators from developing countries participate. WHO convenes the biennial International Conferences of Drug Regulatory Authorities (ICDRA) where many important policy options, technical issues and actions related to harmonization have been debated, recommended and implemented as a result.

The International Conference on Harmonization (ICH) has core members from the research-based industry and regulatory authorities from the European Union, Japan and USA, with observers from Canada, EFTA and WHO. The ICH has made significant progress in harmonizing technical requirements used in the developed world, thus mitigating some of the problems associated with differing requirements of the three regulatory blocks.

Although in recent years the ICH Global Cooperation Group has intensified its work and has opened up to non-ICH countries, the ICH has been less successful in involving and having an impact on developing countries. This is because, in particular, harmonization implies a reasonable parity in existing regulatory capacity and a certain level of socioeconomic development. It should also be noted that ICH was created for new innovative medicines and the ICH parties are highly industrialized nations controlling the majority of the innovative industry, whereas most developing countries have generic markets with generic manufacture, or with no local manufacture at all.

Regional harmonization

Cooperative action at the regional level has proved more effective in many cases in strengthening regulatory capacity at the national level. Regional initiatives involved in harmonization include the Association of South-East Asian Nations (ASEAN), the Andean Community, the Gulf Cooperation Council, Mercosur and the Southern African Development Community (SADC). These offer different working models, ways of exchanging regulatory information and creating common technical requirements, pooling information on drugs in actual circulation (since markets have substantial regional and country differences in terms of origin and nature of products). In certain cases they share facilities (e.g. testing laboratories), and compare experience of side-effects of particular drugs in the post-marketing phase, identify substandard and counterfeit drugs, and so on. Practical and pragmatic steps to share regulatory resources, information and even facilities offer the most effective means to protect public health from substandard products in developing countries.

New regulatory pathways

Considering the reality of inadequate regulatory capacity in many developing countries, and also in smaller well resourced/developed countries, harmonization initiatives often rely on the approval or opinions emitted by regulatory authorities in well-resourced countries. This could carry some concerns because the risk/benefit balance in developing countries may be different from those in developed countries. As there is little

available evidence of differences in the risk/benefit profile of the majority of essential medicines in various environments, consideration of the assessments carried out in well resourced and fully operational MRAs in developed countries is a better option than no guidance at all or limited assessment with no added value.

There exist several examples of how regulators in developing countries may benefit from assessments carried out by well resourced regulatory authorities. These initiatives include, but are not limited to, US FDA tentative approval process for antiretroviral medicines, European Union Article 58 process for priority medicines in developing countries, Canadian Access to Medicines Scheme (known as the Jean Chrétien Pledge) and others. These initiatives could provide the support needed for capacity building of national regulatory authorities of developing countries through partnerships, or scientific and technical assistance.

WHO Medicines Prequalification Programme

The WHO Medicines Programme for medicines was set up in 2001 to provide United Nations procurement agencies, such as UNICEF, with a range of good quality products that meet international standards of quality, safety and efficacy. It does not intend to replace national regulatory authorities or national authorization systems for importing medicines but draws on the best national regulatory expertise available while pro-actively including and involving regulators from developing countries. Since its beginning, capacity building has been a major objective of the Prequalification Programme.

Over time, the growing list of products found to meet international standards has proved useful for anyone purchasing bulk medicines, including countries themselves and other organizations. For instance, the Global Fund to Fight AIDS, Tuberculosis and Malaria gives preference to medicines that have been prequalified by the WHO process, as well as by stringent regulatory authorities. This has proved useful to developing countries without the necessary resources to conduct similar level assessments and inspections, with the added potential of being actively involved in the prequalification process through their national regulatory experts.

Active involvement in the WHO Medicines Prequalification Programme has contributed to building national regulatory capacity and improving regulations and regulatory processes. Several African countries can serve as good examples. However, the responsibility for decision-making, and the processes required for that decision-making, as well as post-marketing surveillance, must remain a matter of national sovereignty.

African Medicines Regulatory Harmonization Initiative (AMRHI)

The overall objective of AMRHI is to improve health in the African Region by increasing access to safe and effective medicines of good quality for the treatment of priority diseases. This can be accomplished by strengthening the technical and administrative capacity of participating national medicines regulatory authorities. Collaborative mechanisms can be established to create a more transparent, streamlined process for the marketing authorization of pharmaceutical products and follow-up of products already marketed.

Collaborative mechanisms for drug regulatory systems and processes at the regional/sub-regional levels should translate into improved regulatory approval processes and operational efficiencies at the national level. In this

regard, the project aims to increase the capacity of national medicines regulatory authorities and specifically strengthen the administrative, structural and technical elements of medicines regulation. In doing so, the project will help countries to enhance and facilitate their decision-making processes regarding the registration of medicines, as well as exercise more control over medicines circulating on the market. Regulatory capacity building and facilitation of information exchange are thus indispensable components of the project.

Specifically, the project objectives include:

1. To create a collaborative network through partnership between regulatory authorities of participating countries and/or selected sub-regional economic blocks.

2. To harmonize technical requirements for the regulation of medical products and build confidence so that agreed harmonized standards are respected by participating authorities.

3. To establish a framework for joint evaluations of application dossiers and inspections of medicine manufacturing sites.

4. To strengthen the capacity for regulatory oversight.

5. To develop information management systems and promote the exchange of regulatory information.

Political commitment

A fundamental issue is the political commitment of Member States to participate in the harmonization process. The experience of existing harmonization initiatives has shown that all such processes have led to upgrading of public services. In less resourced counties, unfortunately, consumers still continue to pay out-of-pocket for most medicines. Improved regulation, with more sophisticated requirements, usually eliminates substandard cheap medicines from the market but could lead to an increase in prices. In this regard, it is suggested that action should focus initially on mutually agreed standards, technical assistance and capacity building issues and aim for gradual and carefully balanced harmonization of actual markets.

The willingness of sub-regional secretariats and potential member countries to participate in the harmonization process should be assessed beforehand. It is also very important that participating countries demonstrate their commitment to continue the harmonization process and to carry the financial burden of maintaining the secretariat, investing in developing and maintaining technical capacity of their staff, paying for travel to joint assessment meetings, inspections, etc. The Initiative should also operate as a catalyst for sustainable processes.

Leadership and maintenance

One important question is whether a permanent secretariat of the harmonization process needs to be established. If yes, how should it be managed and operated and whether it should be based in one of the countries or should rotate at specified intervals of time. Experience has shown that well qualified, effective and stable secretariats are crucial for the continuity and success of regulatory networks.

Rotating secretariats may have disadvantages as opposed to stable, permanent secretariats. However, rotating national staff in terms of time-limited secondment may be an option to consider. The secretariat could also be reinforced by inviting, on a secondment basis, competent and experienced regulators from well-established authorities from outside the region. Additionally, the secretariat must have access to highly qualified legal advice

from potential participating countries. The organization of meetings of legal advisers would be highly appropriate as a mechanism to discuss and share commonalities and differences in the respective legislative areas.

Of particular value would be the establishment of a steering committee of representatives of participating member countries to give oversight and act as a coordinating body. Representatives of donor organizations could have observer status. Governing bodies and procedures of the project should, as far as possible, represent a sustainable model for long term management of a collaborating network.

The issue of availability of sufficient resources in MRAs is of importance for the project. Most resource-constrained countries currently base their regulatory decisions for NCE applications on the opinion taken by other well-resourced countries. Evaluation of new innovative medicines specific for country needs — such as medicines for neglected diseases and certain paediatric medicines — may necessitate creating special collaborative mechanisms for assessment and approval.

The African medicine market is basically a “generic” market and local manufacturing, where it exists, is also limited to generic medicines (with perhaps some exceptions in countries such as South Africa). Limiting the scope of the project to generic applications in the first instance may help to fast track the initiative because this will restrict the number of guidelines that need to be harmonized.

Such action could be considered a first phase, followed by harmonization of regulatory guidelines specific to new medicines whose safety, efficacy and quality requirements, at least in the long term, should be the same. It also should be decided to what extent harmonization maintenance of already authorized products will be covered, including variations and renewals. A number of WHO guidelines that are directly relevant to these questions exist and are updated regularly. These guidelines are adopted by many countries both for local use and for reasons of international harmonization (10).

Differences in regulatory capacity and national legislation

The issue of differences in capacity between national regulatory authorities of different countries is also very important. The results of a recent WHO pilot project on a registration technical package have demonstrated that even in a relatively homogenous group of participating countries, from a socioeconomic development perspective, there are serious differences in regulatory capacity.

Most participating countries have expertise and experience in evaluating the quality aspects of an application dossier but only one or two had expertise in evaluating the clinical (efficacy and safety) parts. In recent years, WHO has conducted an assessment of the medicines regulatory systems in some African Member States using the WHO assessment tool. However, for many countries, information is either absent or out of date.

WHO role in implementing AMRHI

There may be many ways of introducing medicines harmonization to Africa. However, WHO proposes focusing on two scenarios that seem the most feasible.

In the first scenario, WHO’s involvement could be limited to assisting foundations, funding agencies, or any other partner in developing and finalizing the proposal and then hand over the project to an appropriate party such as a professional international organization, or regional or subregional agency for implementation.

The implementing agency, in this case, would take full responsibility for selection

of the partners, for performance of the planned activities and for reporting outcomes of the project to the donors. WHO would provide technical expertise in the preparatory phase of the project but involvement would not go beyond this point.

In the second scenario, WHO would take the lead in the project, from both a managerial and organizational point of view, would develop and finalize the project proposal and select partners for the implementation phase in collaboration with Member States. WHO's competitive advantage in running such an initiative is expressed by its constitutional mandate and role in medicines regulation standard setting. In the framework of this mandate, and during decades of work in the field, WHO has gained valuable experience and, with its regional and country offices, has established a global network of research institutions, collaborating centres and individual experts upon which it can draw.

Historically, WHO has actively supported several harmonization initiatives such as ASEAN and SADC. In the case of the Pan American Network for Drug Regulatory Harmonization (PANDRH), the secretariat is provided by the WHO Regional Office for the Americas.

Providing technical support to countries to strengthen national drug regulatory capacities is one of WHO's key activities. To ensure that good quality pharmaceuticals are available, WHO sets norms and standards, develops guidelines and advises Member States on issues related to quality assurance of medicines in national and international markets. WHO assists countries in building national regulatory capacity through networking, training and information sharing. Further, no other organization is involved in a comparable amount of capacity building worldwide.

WHO has well-established working relations with medicines regulatory authorities, nongovernmental organizations and many other partners and major players. WHO can also build on the competence and know-how of other UN organizations such as UNICEF, UNIDO, or UNDP and the International Atomic Energy Agency (IAEA) for issues related to radiopharmaceuticals. Such partners constitute valuable resources in the successful implementation of the harmonization initiative together with the WHO Regional Office for Africa and WHO country offices in African Member States.

Implementation of AMRHI

1. Mapping exercise
A logical start to the initiative is assessment of the situation in potential participating countries with regard to:

- regulatory capacity and experience of the MRA;
- volume and structure of the pharmaceutical market; and
- existing respective regulations and legislation (including international treaties and agreements).

With better understanding of the situation, appropriate future activities can be planned. This mapping exercise should also look beyond the regulatory framework to all environments and legal requirements impacting medicines regulation, regulatory harmonization and international cooperation. Countries with legislation not enabling participation in the project will also be identified. This mapping exercise could be followed by two consecutive meetings.

2. Brainstorming kick-off meeting
This meeting with responsible representatives of potential participating MRAs would assess commitment to participate in the project. Representatives of the

harmonization initiatives that are already operational (EU, ICH, ASEAN, Gulf Cooperation, SADC and others) could attend this meeting to share experience on expected buy-in for the participating countries.

3. Regional stakeholders meeting
This meeting would involve other interested parties including, but not limited to:

- Local industry associations;
- Importers/wholesalers of medicines;
- Representatives of medical community;
- Representatives of pharmacist communities;
- Consumer groups;
- Other interested ministries (finance, trade);
- Representatives of customs authorities;
- Representatives of regional and sub-regional economic blocks;
- Other interested parties identified during the kick-off meeting.

4. Roadmap
As a result of these meetings, a roadmap should be proposed describing the scope and speed of implementation of the project and the sequence of proposed activities, as well as expected outcomes, country buy-in, and support and effort required to achieve successful functioning of the initiative. Decisions on secretariat, management structure and principle procedures should be adopted. Mechanisms for legally acceptable handling and sharing of commercially-sensitive information should be proposed. A draft consensus document setting out a basis for further development of the project should be drafted and agreed.

5. Establishment of the AMRHI secretariat and Steering Committee
As an outcome of the regional stakeholders meeting, an AMRHI secretariat, Steering Committee and expert bodies should be established. The secretariat will carry out routine implementation work, while the Steering Committee will be acting as a coordinating body for the harmonization initiative.

6. Common technical requirements (guidelines) for regulation of medicinal products and starting joint activities
According to an agreed scope and speed of harmonization, technical documents identified for harmonization and a working plan would be agreed. As a principle, preference should be given to the adoption or amendment of existing regulatory guidelines rather than development of a completely new set.

The working plan should be regularly updated to reflect newly arising needs and developments. Step-by-step cooperation should be based on progress made in the harmonization of technical requirements for individual regulatory activities, e.g. following the harmonization of GMP requirements, the exchange of inspection reports, confidence building exercises for inspectors, and recognition of inspection findings may start.

7. Development of a training and confidence building plan for regulators
A Training plan should be developed in line with harmonized standards and procedures. Training should, as far as possible, respect the following principles.

Trainers external to the participating MRA will support the developmental capacity of local trainers recruited from the expert staff of participating MRAs. Training at national level — both of regulators and other stakeholders — will be led by staff of participating authorities. Training will be oriented to acquiring practical knowledge and confidence building. Learning by

doing will be promoted. In order to strengthen confidence between participating MRAs, rotation of staff should be promoted and organized. An option to be considered is the establishment of a regional centre to provide sustainable training in regulatory affairs and related matters. Some preparatory work in this direction has already been undertaken by WHO in Africa.

8. Joint evaluation of application dossiers and inspection of manufacturing sites

A framework for assessment of application dossiers should be developed which respects the agreed scope of harmonized procedures and experience from existing regulatory networks. Each participating authority will be given the opportunity to participate in the assessment process and inspections according to available capacity. Harnessing available outcomes of regulatory assessments and a risk-based approach to the assessment will be promoted. Procedures will be proposed for communication of assessment outcomes at different stages of drug evaluation between participating authorities and applicants. Publicly available evaluation outcomes will be identified and procedures will be proposed for dealing with objections from applicants against evaluation outcomes.

9. Information management and exchange systems

Focal communication points and information exchange mechanisms will be proposed to support regular regulatory activities and processes and to manage emergencies. This will include communication among participating MRAs, communication with the secretariat and with applicants/authorization holders. Internet communication could be used as the principle communication platform. Attention should be paid to the security of commercially confidential data.

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Safety and Efficacy Issues

Moxifloxacin: adverse hepatic reactions

European Union — Finalizing a review of the safety of moxifloxacin-containing medicines for oral use, the European Medicines Agency (EMEA) has concluded that these medicines should only be prescribed in the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia when other antibiotics cannot be used or have failed. The Agency also recommended strengthening the warnings for oral moxifloxacin medicines.

Moxifloxacin is a fluoroquinolone antibiotic for the treatment of acute exacerbation of chronic bronchitis, community-acquired pneumonia, acute bacterial sinusitis and, in some Member States, for mild to moderate pelvic inflammatory disease.

At its July 2008 meeting, the Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of oral moxifloxacin medicines continue to outweigh its risks. However, due to safety concerns, mainly related to an increased risk of adverse hepatic reactions, the CHMP recommended restricting their use in these indications. For acute bacterial sinusitis and acute exacerbations of chronic bronchitis, they should only be prescribed when other antibiotics cannot be used or have failed. For community acquired pneumonia, they should only be given when treatment with other antibiotics cannot be used.

The CHMP also recommended that the warnings of oral moxifloxacin-containing medicines should be strengthened concerning the risk of diarrhoea, heart failure in women and older patients, severe skin reactions and fatal liver injury. Doctors are advised to prescribe oral moxifloxacin-containing medicines according to the updated product information and to consider the official guidance on the appropriate use of antibiotics and the local prevalence of resistance.
The CHMP opinion will now be forwarded to the European Commission for the adoption of a decision applicable to all oral moxifloxacin-contain medicines authorized in the EU.

Reference: European Medicines Agency Presss Release, Doc. Ref. EMEA/CHMP/382927/2008. 24 July 2008. http://www.emea.europa.eu

Ezetimibe/simvastatin: safety review of cancer risk

United States of America — The Food and Drug Administration (FDA) is investigating a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of a possible association between the use of Vytorin® (a combination of simvastatin plus ezetimibe) and a potentially increased incidence of cancer.

Simvastatin (Zocor®), a “statin” class drug approved in 1991, decreases production of cholesterol by the liver and is indicated to reduce LDL-cholesterol levels and reduce the risk of cardiovascular events such as heart attack and stroke. Ezetimibe (Zetia®), approved in 2002, inhibits the absorption of cholesterol in the intestine and is indicated to reduce LDL-cholesterol levels. Vytorin®, the combination product approved in

2004, is indicated to reduce LDL-cholesterol levels.

Recently, FDA obtained preliminary results from the SEAS trial. This clinical trial tested whether lowering LDL-cholesterol with Vytorin® would reduce the risk of major cardiovascular events, including aortic valve replacement, congestive heart failure, and ischemic cardiovascular events in individuals with aortic stenosis. A lower overall cardiovascular risk was not found with Vytorin®. However, there was an additional observation that a larger percentage of subjects treated with Vytorin® were diagnosed with and died from all types of cancer combined (including skin cancer) when compared to placebo during the 5-year study.

Interim data from two large ongoing cardiovascular trials of Vytorin® — the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) — show no increased risk of cancer with the combination of simvastatin plus ezetimibe. The SHARP trial is expected to be completed in 2010. The IMPROVE-IT trial is scheduled for completion around 2012. Safety data from both of these trials are being evaluated on a regular basis by independent data safety monitoring boards. FDA has determined that, to date, these findings in the SEAS trial plus the interim data from ongoing trials should not prompt patients to stop taking Vytorin® or any other cholesterol lowering drug.

FDA is aware of previous reports suggesting a link between low on-treatment cholesterol levels and an increased risk of cancer. A 2007 pooled analysis of 16 studies with 23 statin drug arms, published in the *Journal of the American College of Cardiology*, reported an association between the level of LDL-cholesterol achieved and incident cancer in patients receiving a statin.

However, most large prospective studies of statin drugs have reported no difference in cancer incidence between the active and placebo arms. For simvastatin, the Heart Protection Study randomized 20 000 patients to a daily dose of simvastatin 40 mg or placebo for up to 5 years. The incidence rate for cancer was 7.9% in the simvastatin group and 7.8% in the placebo group, and the deaths from cancer occurred at similar rates in both groups.

References

1. Alsheikh-Ali A et al. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer. *J Am Coll Cardiol* 2007;**50**: 409-18.

2. Heart Protection Study Collaborative Group. MRC/BFH Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;**360**: 7-22.

3. FDA Early Communication about an ongoing safety review of ezetimibe/simvastatin (marketed as Vytorin®), simvastatin (marketed as Zocor®) and ezetimibe (marketed as Zetia®). 21 August 2008 at http://www.fda.gov/medwatch

Norfloxacin-containing medicines not for use in urinary infections

European Union — The European Medicines Agency (EMEA) has recommended restricting the use of oral norfloxacin-containing medicines in urinary infections. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the marketing authorizations for oral norfloxacin-containing medicines, when used in the treatment of acute or chronic complicated pyelonephritis (kidney infection), should

be withdrawn because the benefits of these medicines do not outweigh their risks in this indication. This is based on the fact that the efficacy has not been adequately demonstrated for this type of infection.

Norfloxacin is a fluoroquinolone antibiotic. Medicines containing norfloxacin are authorized in all European Union (EU) Member States under various trade names for the treatment of infections, including simple or complicated urinary tract infections, infection of the prostate, uncomplicated gonorrhoea, several types of gastroenteritis and conjunctivitis.

The CHMP review of norfloxacin medicines was initiated on the request of the Belgian medicines regulatory agency. They questioned the efficacy of oral formulations of the medicine for complicated pyelonephritis, in comparison with other fluoroquinolones. In current practice, this disease is usually treated using either injectable antibiotics, or other fluoroquinolones taken by mouth or given by injection.

Following evaluation of information provided by the companies, the CHMP, at its July 2008 meeting, noted that there was not enough clinical data to demonstrate the efficacy of oral treatment with norfloxacin-containing medicines in complicated pyelonephritis. Therefore, the CHMP concluded that the use of oral norfloxacin-containing medicines in the treatment of acute or chronic complicated pyelonephritis could no longer be supported.

The recommendation of the CHMP does not have an impact on the use of oral norfloxacin-containing medicines in other types of infection.

Doctors should not prescribe oral norfloxacin for complicated pyelonephritis and should consider switching patients already taking oral norfloxacin for this type of infection to an alternative antibiotic. Patients who are taking oral formulations of norfloxacin-containing medicines to treat complicated pyelonephritis should discuss their treatment with their doctor if they continue to have symptoms or at their next scheduled visit.

Reference: European Medicines Agency Press Release. Doc. Ref. EMEA/380260/2008. 24 July 2008. http:/www.emea.europa.eu

Ceftriaxone: fatal outcome with calcium–containing solutions

Canada — There is a risk of precipitation when ceftriaxone and calcium are administered concurrently via intravenous route. Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys have been described in neonates and infants (1–4).

Ceftriaxone is a long-acting broad spectrum cefalosporin antibiotic for parenteral use indicated for treatment of lower respiratory tract infections, renal and urinary tract infections, bacterial septicemia, skin and wound infections, bone and joint infections, gonorrhoea, intra-abdominal infections, and meningitis when caused by susceptible organisms. Ceftriaxone is also indicated for prophylaxis in patients undergoing certain surgical procedures.

Although there are no reports to date of intravascular precipitations in patients, other than neonates, the theoretical possibility exists for an interaction between ceftriaxone and calcium-containing solutions in other patients.

- In patients aged less than 10 weeks, IV Ceftriaxone and IV calcium-containing solutions should not be administered within 5 days of each other.

- In all other patients, IV Ceftriaxone and IV calcium-containing solutions should not be administered within 48 hours of each other.

- Ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusion such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites

Although most cases occurred with simultaneous administration of the two products, the interaction has also been reported when ceftriaxone and calcium-containing products were administered at different times and through different infusion lines. This explains the recommended interval between the administration of the two products because ceftriaxone remains in circulation for a certain time after its administration (5).

References

1. Rapp RP, Kuhn R. Clinical pharmaceutics and calcium ceftriaxone. Ann pharmacother 2007;41:2072. Epub 6 nov 2007. DOI 10.1345/aph.1K410.

2. Gin AS, Wheateon H, Dalton B. Comments: Clinical pharmaceutics and calcium-ceftriaxone. Ann pharmacother 2008;42:450-51. Epub 29 January 2008. DOI 10.1345/aph.1K410a.

3. Minutes of “Commission Nationale de pharmacovigilance” meeting, January 31, 2006. http://afssaps.sante.fr/htm/1/pharmaco/cr060101.pdf. Accessed 2008-06-23.

4. Information for healthcare professionals. September 2007. www.fda.gov/cder/drug/InfoSheets/HCP/ceftriaxone.htm. Accessed 2008-06-23.

5. Communication from Medeffect, 31 July 2008. http://www.hc-sc.gc.ca

Safety review of tumour necrosis factor blockers

United States of America — The Food and Drug Administration (FDA) is investigating the possible association between use of tumor necrosis factor (TNF) blockers (marketed as Remicade®, Enbrel®, Humira®, and Cimzia®) and the development of lymphoma and other cancers in children and young adults. These individuals were treated with TNF blockers for Juvenile Idiopathic Arthritis (JIA), Crohn disease or other diseases. JIA is the new name for what was called Juvenile Rheumatoid Arthritis (JRA).

FDA is investigating approximately 30 reports of cancer in children and young adults submitted to FDA’s Adverse Event Reporting System over a ten-year interval, beginning in 1998 after approval of the first TNF blocker, and extending through 29 April 2008. These reports described cancer occurring in children and young adults who began taking TNF blockers (along with other immunosuppressive medicines such as methotrexate, azathioprine or 6-mercaptopurine), when they were aged 18 or less, to treat Juvenile Idiopathic Arthritis (JIA), Crohn disease or other diseases. Approximately half the cancers were lymphomas and included both Hodgkin and non-Hodgkin lymphoma. Lymphoma is not a recognized complication of JIA or of Crohn disease. Other cancers reported included leukaemia, melanoma, and solid organ cancers.

FDA is also aware of the risk of hepatosplenic T cell lymphoma in children and young adults with Crohn disease treated with Remicade® and immunosuppressive drugs such as azathioprine or 6-mercaptopurine. This risk was described in the Remicade® prescribing information in 2006.

FDA has requested the manufacturers to provide information about all cases of cancer reported in children taking TNF blockers. The manufacturer of Cimzia® is required to conduct a study to assess long-term risks of the product, including lymphoma and other cancers.

Reference: *FDA Advise of safety review*, 4 June 2008. http://www.fda.gov/medwatch/

Recombinant human bone morphogenetic protein: life–threatening complications

United States of America — The Food and Drug Administration (FDA) has received reports of life-threatening complications associated with recombinant human bone morphogenetic protein (rhBMP) when used in the cervical spine. It is of note that the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated and these products are not approved by FDA for this use.

FDA has received at least 38 reports of complications during the last 4 years with the use of rhBMP in cervical spine fusion. These complications were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck. Some reports describe difficulty swallowing, breathing or speaking. Severe dysphagia following cervical spine fusion using rhBMP products has also been reported in the literature.

Anatomical proximity of the cervical spine to airway structures in the body has contributed to the seriousness of the events reported and the need for emergency medical intervention. The mechanism of action is unknown, and characteristics of patients at increased risk have not been identified.

Most complications occurred between 2 and 14 days post-operatively with only a few events occurring prior to day 2. When airway complications occurred, medical intervention was frequently necessary. Treatments needed included respiratory support with intubation, anti-inflammatory medication, tracheotomy and most commonly second surgeries to drain the surgical site.

Since the safety and effectiveness of rhBMP for treatment of cervical spine conditions has not been demonstrated, and in light of the serious adverse events described above, FDA recommends that practitioners either use approved alternative treatments or consider enrolling as investigators in approved clinical studies.

Both rhBMPs are contraindicated for all uses in patients who are skeletally immature (<18 years of age) or pregnant, and in those with a known hypersensitivity to the specific rhBMP, bovine Type 1 collagen or to other components of the formulations.

Reference: FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion. 1 July 2008. http://www.fda.gov/medwatch

Electronic medical devices malfunction: computed tomography scanning

United States of America —The Food and Drug Administration (FDA) is alerting users to the possibility that x-rays used during computed tomography (CT) examinations may cause some implanted and external electronic medical devices to malfunction, and to provide recommendations to reduce the potential risk.

The FDA has received a small number of reports of adverse events in which CT scans may have interfered with electronic medical devices, including pacemakers, defibrillators, neurostimulators, and implanted or externally worn drug infusion

pumps. In these reports, the following adverse events were likely to have been caused by x-rays from CT scans:

- Unintended “shocks” (i.e., stimuli) from neurostimulators
- Malfunctions of insulin infusion pumps
- Transient changes in pacemaker output pulse rate

Note that malfunctions of this kind, which can result from direct exposure of the medical device to the high x-ray dose rates generated by some CT equipment, are different from those related to MRI scanning, which are caused by strong electric and magnetic fields.

Reference: *FDA Preliminary Public Health Notification*: Possible Malfunction of Electronic Medical Devices Caused by Computed Tomography (CT) Scanning, 14 July 2008 at http://www.fda.gov/cdrh/safety.html.

Desmopressin and hyponatraemia

Australia — Desmopressin (Minirin®, Octostim®) is a synthetic analogue of the natural antidiuretic hormone (ADH) arginine vasopressin and is currently available in nasal spray, nasal solution, tablet, sublingual wafer, and injection form. Desmopressin nasal spray and tablets are indicated for primary nocturnal enuresis (where an enuresis alarm has failed or is contraindicated) and cranial diabetes insipidus; desmopressin nasal solution and tablets are indicated for cranial diabetes insipidus and certain blood disorders.

Desmopressin acts on the ADH receptors in the kidneys, mimicking the effects of ADH and therefore preventing excessive loss of water. In the presence of excessive fluid intake in patients taking desmopressin, dilutional hyponatraemia can occur. If this occurs quickly then lack of adaptation can result in a shift of water intracellularly and cerebral oedema, which may present with anorexia, nausea and vomiting, difficulty concentrating, confusion, lethargy, agitation, headache, and seizures.

The risk of hyponatraemia is greater with desmopressin intranasal preparations than with the oral forms. In 2007, the TGA amended the indications for desmopressin nasal spray to restrict use only when it is not feasible to use an oral formulation. Sponsors were also required to amend all desmopressin product information documents to strengthen precautionary statements relating to the potential for hyponatraemia and to provide information on this potentially serious reaction (1).

To date, ADRAC has received 68 reports of adverse reactions associated with the use of desmopressin, including 17 reports of convulsions (with or without reported hyponatraemia), and 10 further reports of hyponatremia alone. Of 12 reports of convulsions or hyponatremia following the use of desmopressin nasal spray, 7 involved children under 13 years of age.

Prescribers are reminded that desmopressin nasal spray and tablets should be used in the treatment of nocturnal enuresis only when an enuresis alarm has failed or is contraindicated, and that tablets should be used in preference to intranasal preparations because of a possible increased risk of hyponatremia. Avoidance of excessive fluid intake should be advised during treatment with desmopressin. The ongoing need for these products should be reviewed periodically in patients taking desmopressin long-term.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 27, Number 4, August 2008

Reference

1. Ferring Pharmaceuticals Pty Ltd. Product Information for: Minirin Nasal Spray, Minirin Tablets, Minirin, Octistim.

Micro-bubble contrast agents

United States of America — The Food and Drug Administration (FDA) has issued an alert to healthcare professionals about changes that were made to the prescribing information for micro-bubble contrast agents.

The revised boxed warning and warnings continue to highlight the risk of serious cardiopulmonary reactions during or within 30 minutes following the administration of these products and recommend that high risk patients with pulmonary hypertension or unstable cardiopulmonary conditions be closely monitored during and for at least 30 minutes post administration of these contrast agents. Concurrent with these labelling changes, the FDA has required that manufacturers of micro-bubble contrast agents conduct clinical studies to more thoroughly assess the risks for serious cardiopulmonary reactions.

Reference: Information for Healthcare Professionals. Micro-bubble Contrast Agents (marketed as Definity® (Perflutren Lipid Microsphere) Injectable Suspension and Optison® (Perflutren Protein-Type A Microspheres for Injection). *FDA Alert,* 17 July 2008 at http://www.fda.gov/medwatch

Simvastatin used with amiodarone: rhabdomyolysis

United States of America — The Food and Drug Administration (FDA) has issued an alert to healthcare professionals about the risk of a rare condition of muscle injury called rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone.

This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. A revision of the simvastatin labelling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily.

However, the FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin, particularly with simvastatin doses greater than 20 mg daily. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

Reference: Information for Healthcare Professionals. Simvastatin (marketed as Zocor® and generics), Ezetimibe/Simvastatin (marketed as Vytorin®), Niacin extended-release /Simvastatin (marketed as Simcor®), used with Amiodarone (Cordarone®, Pacerone®). *FDA Alert,* 8 August 2008 at http://www.fda.gov/medwatch

Naltrexone injection site reactions

United States of America — The Food and Drug Administration (FDA) has issued an alert to healthcare professionals about the risk of adverse injection site reactions in patients receiving naltrexone (Vivitrol®). Physicians should instruct patients to monitor the injection site and contact them if they develop pain, swelling, tenderness, induration, bruising, pruritus, or redness at the injection site that does not improve or worsens within two weeks. Physicians should promptly refer patients with worsening injection site reactions to a surgeon.

FDA has received 196 reports of injection site reactions including cellulitis, indura-

tion, haematoma, abscess, sterile abscess, and necrosis. Sixteen patients required surgical intervention ranging from incision and drainage in the cases of abscesses to extensive surgical debridement in the cases that resulted in tissue necrosis.

Naltrexone is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. Naltrexone is administered as an intramuscular (IM) gluteal injection. Naltrexone should not be administered intravenously, subcutaneously, or inadvertently into fatty tissue. Healthcare providers should ensure that the naltrexone injection is given correctly with the pre-packaged needle that is specifically designed for this drug.

Reference: Information for Healthcare Professionals. Naltrexone Injection Site Reactions [naltrexone for extended-release injectable suspension (marketed as Vivitrol®)]. *FDA Alert,* 12 August 2008 at http://www.fda.gov/medwatch

Adalimumab: hepatosplenic T–cell lymphoma

United Kingdom — The manufacturer of adalimumab (Humira®) is advising healthcare professionals of new safety information. Adalimumab is a TNF alpha blocker authorized in adult patients for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn disease and psoriasis.

- From launch in December 2002, three postmarketing reports of hepatosplenic T-cell lymphoma (HSTCL), which is a rare aggressive form of non-Hodgkin lymphoma with a poor prognosis, have been reported in patients receiving adalimumab.

- Two of these three patients were young men also receiving azathioprine or 6-mercaptopurine for inflammatory bowel disease. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with adalimumab cannot be excluded.

- HSTCL should be considered in the event that a patient receiving adalimumab develops symptoms of lymphomas and / or hepatosplenomegaly with or without peripheral lymphadenopathy or significant peripheral blood lymphocytosis.

- A warning will be added to the product information (SPC/Package Leaflet) as a risk minimization measure.

Reference: Direct Healthcare Professional Communication on reports of hepatosplenic T-cell lymphoma in patients treated with Humira® (adalimumab). Abbott Ltd. at http://www.mhra.gov.uk

Serious Risks/New Safety Information

United States of America — The Food and Drug Administration (FDA) has published a table listing the names of products and potential signals of serious risks/new safety information that were identified for these products during the period January – March 2008 in the Adverse Event Reporting System (AERS) database (see table on page 199).

The appearance of a drug on this list does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a potential safety issue, but does not mean that FDA has identified a causal relationship between the drug and the listed risk. If after further evaluation the FDA determines that the drug is associated with the risk, it may take a variety of actions including requiring changes to the labelling of the drug, requiring development of a Risk Evaluation and Mitigation Strategy (REMS), or gathering additional data to better characterize the risk.

Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS), January – March 2008

Product Name: Active Ingredient (Trade), New or Product Class	Potential Signal of Serious Risk/ Safety Information
Arginine Hydrochloride Injection (R-Gene 10®)	Paediatric overdose due to labelling / packaging confusion
Desflurane (Suprane®)	Cardiac arrest
Duloxetine (Cymbalta®)	Urinary retention
Etravirine (Intelence®)	Haemarthrosis
Fluorouracil Cream (Carac®) and Ketoconazole Cream (Kuric®)	Adverse events due to name confusion
Heparin	Anaphylactic-type reactions
Icodextrin (Extraneal®)	Hypoglycaemia
Insulin U-500 (Humulin R®)	Dosing confusion
Ivermectin (Stromectol®) and Warfarin	Drug interaction
Lapatinib (Tykerb®)	Hepatotoxicity
Lenalidomide (Revlimid®)	Stevens Johnson Syndrome
Natalizumab (Tysabri®)	Skin melanomas
Nitroglycerin (Nitrostat®)	Overdose due to labelling confusion
Octreotide Acetate Depot (Sandostatin LAR®)	Ileus
Oxycodone Hydrochloride Controlled-Release (Oxycontin®)	Drug misuse, abuse and overdose
Perflutren Lipid Microsphere (Definity®)	Cardiopulmonary reactions
Phenytoin Injection (Dilantin®)	Purple Glove Syndrome
Quetiapine (Seroquel®)	Overdose due to sample pack labelling confusion
Telbivudine (Tyzeka®)	Peripheral neuropathy
Tumor Necrosis Factor (TNF) Blockers	Cancers in children and young adults

FDA wants to emphasize that the listing of a drug and a potential safety issue on this Web site does not mean that FDA is suggesting prescribers should not prescribe the drug or that patients taking the drug should stop taking the medication. Patients who have questions about their use of the identified drug should contact their health care provider. FDA will complete its evaluation of each potential signal/new safety information and issue additional public communications as appropriate.

Reference: 5 September 2008 at http://www.fda.gov

Deferasirox: hepatic failure

United Kingdom — In agreement with European Union regulatory authorities, the manufacturer of deferasirox (Exjade®) has advised healthcare professionals of updated safety information. Deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions, or when desferrioxamine (Desferal®) is contraindicated or inadequate:

- Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with deferasirox. The role of deferasirox as a contributing or aggravating factor cannot be excluded.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase are checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, deferasirox should be interrupted (see section 4.8 of revised SPC, attached).

- Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during deferasirox therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse event is suspected.

- Cases of renal tubulopathy (Fanconi syndrome) have been reported in patients treated with deferasirox. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.

Reference: Communication from Novartis Pharmaceutical UK Ltd, EXJ08000052, July 2008 at http://www.Mhra.gov.uk

Abacavir: hypersensitivity reactions

United States of America — The Food and Drug Administration (FDA) has issued an alert to healthcare professionals about serious and sometimes fatal hypersensitivity reactions (HSR) caused by abacavir therapy which are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*5701. Abacavir HSR is a multi-organ syndrome characterized by 2 or more clinical signs or symptoms that can include fever, rash, gastrointestinal symptoms, respiratory symptoms and constitutional symptoms.

FDA has reviewed data from 2 studies that support the recommendation for pre-therapy screening for the presence of the HLA-B*5701 allele and the selection of alternative therapy in positive subjects. Genetic tests for HLA-B*5701 are already available and all patients should be screened for the HLA-B*5701 allele before starting or restarting treatment with abacavir or abacavir-containing medications. Avoidance of abacavir therapy in HLA-B*5701 positive patients will significantly decrease the risk of developing clinically-suspected abacavir HSR. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only under exceptional circumstances when the potential benefit outweighs the risk.

Development of clinically-suspected abacavir HSR requires immediate and permanent discontinuation of abacavir therapy in all patients, including patients negative for HLA-B*5701. This new safety information will be reflected in updated product labelling.

Reference: Information for Healthcare Professionals. Abacavir (marketed as Ziagen®) and Abacavir-containing Medications. *FDA Alert,* 24 July 2008 at http://www.fda.gov/medwatch

Fluoroquinolones: risk of tendinitis and tendon rupture

United States of America — The Food and Drug Administration (FDA) has notified manufacturers that a boxed warning is necessary in the labelling for fluoroquinolones concerning the increased risk of tendinitis and tendon rupture. The agency also determined that it is necessary for manufacturers of the drugs to provide a Medication Guide to patients about possible side effects.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in people older than 60, in those taking corticosteroid drugs, and in kidney, heart, and lung transplant recipients.

Reference: *FDA News*, 8 July 2008. http://www.fda.gov/medwatch

Colchicine: fatal interactions and reactions

Australia — Colchicine is indicated for the treatment of acute gout, but it has a narrow therapeutic index with significant potential for toxicity and severe drug interactions. In mid-2007, the Therapeutic Goods Administration (TGA) required updates to the Colgout® and Lengout® product information to limit colchicine usage to only where NSAID treatment is contraindicated, has failed or has caused unacceptable side effects; and to limit the maximum cumulative dose to 6 mg over 4 days in otherwise healthy adults (with washout intervals of at least 3 days if additional treatment is needed). Alternative treatments should be considered in the elderly and those with renal or hepatic impairment, but if colchicine is to be used in these patients the cumulative dose should not exceed 3 mg over 4 days.

The Adverse Drug Reactions Advisory Committee (ADRAC) has previously warned of the potential for severe or fatal toxicities with colchicine especially in overdose and in those with renal impairment (1). Toxic effects of greatest concern include blood dyscrasias due to bone marrow suppression, multi-organ failure and, more rarely, myopathy and rhabdomyolysis (which tend to occur in patients with impaired renal or hepatic function on long-term treatment with prophylactic doses of colchicine).

Since colchicine is metabolized mainly by CYP3A4, prescribers should be aware that drugs that inhibit this enzyme may increase blood colchicine concentrations and therefore increase the potential for colchicine toxicity. The CYP3A4 inhibitor, clarithromycin, was used concomitantly in 4 cases of severe colchicine toxicity reported to the TGA, 3 of which described a fatal outcome. In one of the fatal cases, clarithromycin was being used as part of "triple therapy" for *Helicobacter pylori* eradication in a patient undergoing treatment for gout with colchicine; this patient subsequently developed massive myelosuppression and multi-organ failure. Cases of fatal interactions between colchicine and clarithromycin have also been published (2, 3).

To date, the TGA has received 243 reports for colchicine, including 53 describing blood dyscrasias such as neutropenia (15 reports), thrombocytopenia (10), pancytopenia (10), leukopenia (8) and agranulocytosis (4 reports), and an additional report describing sepsis and extensive severe maculopapular rash. Of these cases, 21 had not recovered at the time of reporting and 9 described a fatal outcome associated with renal failure, multi-organ failure or overwhelming sepsis. Colchicine was the sole suspected drug in 16 of the reports of blood dyscrasia but other drugs were also suspected in all of the reports that described a fatal outcome.

Prescribers are reminded that colchicine can be associated with significant toxicity and the risk-benefit should be considered on a case-by-case basis. In most cases, it should be used for short-term periods and only where NSAID therapy is contraindicated or has failed. Colchicine is best avoided if patients are taking drugs that inhibit CYP3A4 or have significant renal or hepatic impairment.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 27, Number 5, October 2008

References

1. ADRAC and Kubler PA. Fatal colchicine toxicity. *MJA* 2000; **172**: 498-490.

2. Cheng VC, Ho PL and Yuen KY. Two probable cases of serious drug interaction between clarithromycin and colchicine. *Southern Med J* 2005; **98**: 811-813.

3. Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: A retrospective study. *Clin Infect Dis* 2005; **41**: 291–300.

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Regulatory Action and News

WHO Prequalification: GMP deviations and suspension

World Health Organization — WHO's Medicines Prequalification Programme has issued a Notice of Concern letter to Sandoz South Africa Ltd. based on the results of inspections performed at their manufacturing facility in Kempton Park, South Africa. Additionally, one product (isoniazid 150 mg + rifampicin 300 mg tablet) which is manufactured at the facility was suspended from the WHO List of Prequalified Medicines.

These actions were taken as a consequence of problems documented with manufacturing processes, where significant deviations from good manufacturing practices (GMP) were documented in the manufacture and control of antituberculosis medicines during the WHO inspection in May 2008. A follow-up inspection by WHO was refused by the company, thus it was not possible to verify the implementation of corrective action and come to a conclusion on the level of GMP compliance currently on site.

These actions are proactive measures that WHO is taking to ensure that all prequalified medicinal products are manufactured according to GMP requirements. A Notice of Concern is issued to remind a manufacturer or research organization of their obligations to assure quality and to inform suppliers and procurement agencies of potential risks associated with a given product, manufacturer or organization.A Notice of Concern is not cause for public concern. If WHO identifies a public health risk, appropriate additional steps are taken to advise health professionals and the public.

Suspension from the WHO List of Prequalified Medicinal Products will halt procurement by international and national procurement agencies of the products concerned until the Medicines Prequalification Programme is satisfied that all corrective actions have been taken by the manufacturer and verified by WHO.

Based on the information currently available, the documented deficiencies in manufacturing do not relate to the specific failure of the concerned Sandoz product to meet its required specifications or to treat human illness.

WHO is advising consumers to continue taking their Sandoz medications until they can be replaced with quality assured products from other manufacturers. However, where no alternative treatment options are available, WHO strongly advises consumers not to interrupt their drug therapy, which could have serious implications for their health.

Reference: *Sandoz PQ note,* 25 September 2008 at http://www.who.int/prequal

Import alert: Ranbaxy facilities

United States of America —The US Food and Drug Administration (FDA) has issued two Warning Letters to Ranbaxy Laboratories Ltd and simultaneously established an Import Alert for drugs manufactured or using materials from two Ranbaxy facilities in India at Dewas or Paonta Sahib. This means that any finished product or active pharmaceutical ingredient manufactured at these sites offered for import into the United States will be detained at the border.

The reason for these actions follows problems involving drug manufacturing

processes where significant deviation from good manufacturing practices (GMP) have been documented in manufacture and control of both finished products and active pharmaceutical ingredients during FDA inspections in early 2008 (1).

These are proactive measures that the FDA is taking to ensure that all drugs that reach the American public are manufactured according to GMP requirements. Based on the information currently available, the FDA documented deficiencies in manufacturing do not relate to the specific failure of any Ranbaxy product to meet its required specifications or to treat human illness. FDA is not recalling any product presently in distribution in the USA, but is advising consumers to continue taking their medications until they can be replaced with products from another manufacturer.

World Health Organization — Ranbaxy Laboratories Ltd has submitted several antiretroviral products for WHO prequalification since 2001. Currently 18 Ranbaxy products have been prequalified by WHO and seven products are under evaluation.

The current Import Alert issued by the FDA lists 30 products, out of which two (lamivudine and zidovudine) are present in several WHO prequalified products. The WHO Medicines Prequalification Programme has performed several inspections at the Ranbaxy Paonta Sahib site – most recently in June 2008. During each of the inspections, some non compliance with GMP was observed. However, following each inspection the company submitted corrective action plans to rectify this non compliance and in general the site was considered to be operating at an acceptable level of compliance with WHO GMP.

WHO is closely monitoring the case and planning a series of extraordinary actions in addition to its routine monitoring activities to confirm if products prequalified by WHO from Ranbaxy continue to meet all the necessary requirements to ensure quality, safety and efficacy. Additionally, the WHO Medicines Prequalification Programme:

- has written to Ranbaxy requesting clarification of the issues raised by FDA;
- is in close contact with FDA concerning the Ranbaxy products based on the confidentiality agreement between the two institutions;
- is in contact with other national regulatory authorities to follow the matter closely;
- is taking steps to identify any potential irregularities or deficiencies that may affect Ranbaxy products, either under evaluation or prequalified by WHO;
- is liaising with other UN agencies (such as UNICEF) and partners.

In the current situation, where no alternative treatment options are available, WHO strongly advises consumers not to interrupt their drug therapy, which could have serious implications for their health. Switching to non-prequalified products is not recommended as their quality has not been documented by WHO.

References

1. http://www.fda.gov/bbs/topics/NEWS/2008/NEW01886.html

2. *Ranbaxy PQ note,* 17 September 2008 at http://www.who.int/prequal

Medicines Prequalification Programme: listed products

World Health Organization —The WHO Medicines Prequalification Programme, in close cooperation with national regulatory agencies and partner organizations, was established to make quality priority

medicines available for the benefit of those in need.

This is achieved through evaluation and inspection activities and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

The list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health produced by the Programme is used principally by United Nations and other agencies to guide their procurement decisions. The list has now become a vital tool for any agency or organization involved in bulk purchasing of medicines.

List update: September 2008

HA322: Abacavir 300 mg (as sulfate) tablets Ranbaxy Ltd - India

HA393: Abacavir 300 mg (as sulfate) tablets Matrix Laboratories - India

HA396: Nevirapine 200 mg tablets Matrix Laboratories - India

HA403: Efavirenz 600 mg ablets Matrix Laboratories - India

HA404: Zidovudine 300 mg tablets Matrix Laboratories - India

HA405: Lamivudine/Stavudine 150 mg/30 mg tablets Matrix Laboratories - India

HA406: Lamivudine/Stavudine 150 mg/40 mg tablets Matrix Laboratories - India

HA407: Lamivudine/Nevirapine/Stavudine 150 mg/200 mg/30 mg tablets Matrix Laboratories - India

HA408: Lamivudine/Nevirapine/Stavudine 150 mg/200 mg/40 mg tablets Matrix Laboratories - India

HA434: Lopinavir/Ritonavir 100 mg/25 mg tablets Abbott Laboratories - Germany

Reference: WHO Medicines prequalification Programme at http://healthtech.who.int/pq/

Development of medicines for Alzheimer and Parkinson disease

European Union — The European Medicines Agency (EMEA) has released two guidelines for companies developing medicines for the treatment of Alzheimer disease and other dementias and for Parkinson disease, in light of recent scientific progress in the understanding of these diseases and conditions.

Advances in clinical science, physiopathology and molecular biology have stimulated new interest in the development of more effective symptomatic or disease-modifying treatments, i.e. early treatments that may prevent the emergence or slow down the progression of disease. The guidelines were developed in response to the need of companies developing these new types of medicines for guidance on appropriate clinical trial designs.

As life expectancy increases, neurodegenerative diseases and dementia will affect more and more people over the coming decades, and these guidelines are expected to help improve the availability of medicines to treat such diseases and conditions. The guidelines will come into effect on 1 February 2009.

Reference: *Press Release*, EMEA releases guidelines on development of medicines for Alzheimer disease and Parkinson disease. Doc. Ref. EMEA/460300/2008, 4 September 2008 at http://www.emea.europa.eu

GMP regulations for radiopharmaceuticals

European Union — Revised good manufacturing practice (GMP) requirements for the production of radiopharmaceuticals have been published by the European Commission (EC).

The updates to the annex are intended to make it compliant with GMP Part II, which laid out additional requirements for actives substances used as starting materials. In addition, the EC has sought to bring the regulations up-to-date with advances in the manufacture of radiopharmaceuticals.

An initial draft was published for public consultation in December 2006. This process has now been completed and companies have until 1 March 2009 to become compliant with the new requirements. The regulations are broken down into subcategories including quality assurance, personnel, production and documentation. These are intended to provide the necessary regulation to prevent cross-contamination, the spread of radioactive material and ensure the quality of the product.

Quality assurance is particularly important in the manufacture of radiopharmaceuticals as the half-lives of some mean they need to be administered shortly after production. Consequently there is not enough time to test the product.

Underlying all the regulations is the need for accurate, up-to-date documentation of procedures. Manufacturers must establish specifications for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications must also be put in place for any piece of equipment that could critically impact on the quality of the finished product.

The cleaning, sanitization, sterilization or maintenance of equipment should be documented to show the product name, batch number, date and time of the activity and signature for the persons involved in these activities.

Documents must be kept for a minimum of three years, unless a different timeframe is specified by national laws. Retention to ensure accountability extends to keeping sufficient samples of each batch of bulk formulated product for at least six months after expiry of the finished medicinal product.

Samples of starting materials, excluding solvents gases or water used in the manufacturing process must be kept for at least two years after the release of the product. This period can be shortened if the material has a period of stability of less than two years.

Reference: Communication on EMEA website, 15 September 2008, at http://www.emea.europa.eu

Pharmaceutical Distribution and Trade

WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

Quality assurance of pharmaceutical products should be based on a reliable system of marketing authorization, independent analysis of finished product quality and confirmation through independent inspection that all manufacturing operations are carried out in conformity with good manufacturing practices. In the 1960s, a large number of African and Asian countries joining the World Health Organization did not have the necessary infrastructure or trained and skilled human resources to ensure the quality of medicines imported into their territories and they requested WHO to help them by establishing the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.* This was designed as a tool for exchange of confirmatory information between medicines regulatory agencies.

At its Forty-second meeting held in October 2007, the WHO Expert Committee on Specifications for Pharmaceutical Preparations identified a number of concerns with operation of the WHO Certification Scheme. These have been documented in a background paper entitled *Proposal for improvement of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* (reproduced below).

A consultation on the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce was convened at WHO in Geneva on in July 2008 to discuss improvement of the Scheme. Final observations and recommedations are set out in the second part of this article (page 214). Comments on these proposals are now invited and should be forwarded to: Dr S. Kopp, Quality Assurance, Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, 1211 Geneva 27, Switzerland. e-mail: kopps@who.int. A final report will be presented to the WHO Expert Committee at its Forty-third meeting in October 2008.

Proposal for improvement of the WHO Certification Scheme

In 1969, WHO developed a guideline entitled *Good practice in the manufacture and quality control of drugs*. The good manufacturing practices (GMP) guideline together with the first version of the *Certification Scheme on the quality of pharmaceutical products moving in international commerce* was endorsed by the World Health Assembly (WHA) in July 1969 in resolution WHA 22.50. The 1969 Certification Scheme provided for:

(a) the exporting country to establish, after inspection, an up-to-date list of manufacturers complying with GMP which could be exchanged between governments; and

(b) the issuance of batch certificates by responsible health authorities of the exporting country.

However, six years after the Scheme was endorsed, it was realized that maintenance of the list of manufacturers complying with GMP and issuance of batch certificates by health authorities was not feasible. As a result, a revised version of the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* was adopted in 1975 by the World Health Assembly in resolution WHA 28.65. Under this scheme, maintenance of the list of manufacturers complying with GMP was dropped.

The 1975 version of the Scheme is based on certification by the responsible health authorities of the exporting country of:

(a) the registration status of a particular product in the exporting country; and

(b) GMP compliance of the responsible manufacturer.

Additionally, responsibility to issue batch certificates became that of the manufacturer.

In 1988, the World Health Assembly in resolution WHA 41.18 endorsed an expanded Certification Scheme. The amended Scheme covered drug substances and finished dosage forms intended for human use as well as veterinary products administered to food-producing animals. The Scheme also required the competent authority in the exporting country to provide copies of all approved product information and labelling as determined by the registration certificate issued by the regulatory authority in the country of manufacture.

Four years after the 1988 expanded version was adopted, the WHA endorsed a modified version of the Scheme in 1992 in resolution WHA45.29 and recommended that it be field tested in a number of WHO Member States in order to obtain feedback on its feasibility (1).

The current Scheme

Five years later the Scheme was refined, based on information gathered from field trials and was adopted in 1997 in resolution WHA50.3. Under the current 1997 Scheme, three different types of certificate can be requested by importing countries.

1. **Certificate of a Pharmaceutical Product (Product Certificate)**: issued by the competent authority when a product in question is under consideration for a product licence (registration) in the importing country or when administrative action is required to renew, extend, vary or review such a licence.

2. **Statement of Licensing Status of a Pharmaceutical Product**: issued by the competent authority of the exporting country when an importing agent is bidding in international tender.

3. **Batch Certificate of a Pharmaceutical Product**: issued by the manufacturer in case of non-biological products and by the competent authority in the case of vaccines and other biological products.

Participation in the Scheme

The Certification Scheme requires that a WHO Member State send a letter to the Director-General of WHO expressing its intention to participate in the Scheme and indicating:

- the conditions under which it will participate, i.e. (a) as exporting country, (b) as importing country, or (c) both as exporting and importing country;
- any reservations it may have;
- provision of the name(s) and address of the national drug regulatory authority (ies)/competent authority(ies) authorized to issue certificates; and

• willingness to comply with the following prerequisites of the Certification Scheme.

Prerequisites for exporting countries (countries issuing certificates)
The WHO Certification Scheme (2) states that a Member State intending to use the Scheme to support the export of pharmaceutical products should first satisfy itself that it possesses:

• an effective national licensing system not only for pharmaceutical products but also for manufacturers and distributors;

• GMP requirements consonant with those recommended by WHO to which all manufacturers of finished products are required to conform;

• effective control to monitor the quality of pharmaceutical products registered or manufactured within the country, including access to an independent quality control laboratory;

• a national pharmaceutical inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigation to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;

• the administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member States known to have imported a specific product that is subsequently associated with potentially serious quality defects or other hazard.

Discussion and conclusions

A summary of problems identified in implementation of the Scheme and measures to be taken are set out in the table on pages 210–211.

International trade in pharmaceutical products encompasses many thousands of products and the value of the global market is currently estimated to reach over US$ 600 billion. During the last few decades many pharmaceutical manufacturing industries have flourished in both developed and developing countries. Some manufacturers produce only for local consumption, whereas a large number also produce for export. Confidential information available indicates that, particularly in developing countries, there are many pharmaceutical manufacturers that do not meet WHO GMP requirements. Some of these manufacturers also operate as contract manufacturers for manufacturers in developed countries.

When the Scheme was formulated three decades ago the assumption was that it would operate in situations where a pharmaceutical product is sold directly from the country of manufacture to the country of final destination. At present such direct trade is rare and pertains only to a small sector of international trade. To a large extent pharmaceutical manufacturing/trade has taken on a global dimension in that different stages of the manufacturing activities take place in different countries of the world before the product reaches the final destination.

On the other hand, it is currently estimated that out of 193 WHO Member States about 20% are said to have a well-developed national drug regulatory system that can ensure the quality of drugs circulating in their national markets. Over 50 % of remaining countries are said to have a varying level of development and capacity to regulate their

Table. Summary of problems identified in implementation of the Scheme and measures to be taken

Problem	Measures to be taken
Exporting countries that do not fulfil the prerequisites required by the Certification Scheme issue certificates to support export	• Request countries to submit a verifiable self-assessment report before they become party to the Scheme. Alternatively: consider the possibility of ISO certification; or Certification by a well-established/ known regional drug regulatory authority cooperation/block, e.g. (ASEAN, EU, ICH, SADC). • Require governments of Member States to submit a letter declaring the competent authority meets the prerequisites set out in the Certification Scheme.
Countries not party to the Scheme issue certificates to support export of pharmaceutical products	• WHO should write a letter to the governments of those countries asking them to be party to the Scheme. • Inform authorities of importing countries of the names of those countries that issue certificates without being party to Scheme. • Advise countries not to accept certificates from countries that are not party to the Scheme.
There have been cases in which forged certificates have been supplied to competent authorities of importing countries	• Ask exporting countries to develop secured certificates by using a watermark/hologram, or any other technology. • Request each exporting country to submit to WHO samples of their certificates so that WHO can compile those certificates and distribute them to Member States with the list of names of competent authorities to serve as reference material.
Information on who released the batch for marketing is not disclosed in certificates issued by exporting countries	• Certificates should be transparent in disclosing information that has impact on quality of products. • A certificate issued for a product manufactured by a contract manufacture should indicate the name and address of (a) the product licence holder, and (b) the name and address of the contract manufacturer. • A certificate issued for a product intended for export only (not registered in the exporting country should indicate (a) the name and site address of the manufacturer who released the batch, and (b) the reason why it is not registered in the exporting country.

Problem	Measures to be taken
Certificates are issued for products that are produced by manufacturers that do not comply with WHO GMP requirements	• Manufacturers producing pharmaceutical products should be required to provide a certificate of GMP compliance, e.g. issued by any known and reliable national inspectorate such as the US FDA. • Importing countries should inspect any manufacturer suspected to be non-compliant with WHO GMP requirements.
Addresses of some authorities have changed	• WHO should send a circular letter to countries asking them to reapply for participation in the Scheme. WHO should take countries off the list if they do not reapply. • Membership to the Scheme should have a time limit, i.e. renewable every five or 10 years.
Member States issue certificates for products not manufactured under their jurisdiction, i.e. in their country	• In principle Member States should not issue certificates for products that are not produced under their jurisdiction, i.e. in their country. The country where the product has been manufactured should issue the certificate. • If a certificate is issued for such a product then the name and address of the manufacturer (the one who released the batch) and the site address where the product has been manufactured should be indicated in the certificate.
Exporting countries issue other certificates such as free sale certificates	• WHO should advise importing country authorities not to request or accept free sale certificates. They should request and accept only those certificates indicated in the WHO Certification Scheme. • WHO should ask exporting countries not to issue certificates other than those men tioned in the WHO Certification Scheme. • WHO should organize seminars and work shops from time to time for drug regulatory authorities in order to promote the Scheme and give advice to countries.
Importing countries require legalization of certificates, additional stamps, etc.	• This is due to lack of confidence in the genuineness of certificates. This issue will remain until countries build up confidence in the Scheme and the certificates being issued under the Scheme. • Exporting countries should develop secured certificates and should provide samples of certificates, signature and stamp of author ity to serve as reference.

pharmaceutical markets. Around 30% of remaining countries are known to have either limited or no capacity to regulate the pharmaceutical market (9).

This means drug regulatory practices differ from country to country in their standards, emphasis, and rigour of enforcement. Consequently, certificates issued by a national regulatory authority should be accepted with caution unless there is full knowledge or proof of the competence of the regulatory authority to fulfil the prerequisites mentioned in the WHO Certification Scheme.

The Scheme is a non-binding agreement and participation of Member States is made on a voluntary basis. Although exporting countries have to fulfil certain prerequisites in order to issue certificates, the Scheme does not have an active mechanism to ensure that countries meet the requirements. Everything is left to the judgement of the individual exporting country and this loophole has encouraged non-compliant exporting countries to issue certificates.

Moreover, the provisions of the Scheme allow the authorities of exporting countries to decide which government institution will be responsible for the issuance of a product certificate. Where there is a single central drug regulatory authority that is responsible for the licensing of products and manufacturers, the situation is simple but becomes more complicated in countries with a federal system of government where state drug regulatory authorities do not carry out licensing of products and manufacturers but are authorized to issue certificates.

The fact that countries not complying with prerequisites are issuing certificates and the lack of a mechanism to verify the competence of regulatory authorities, coupled with the presence of fake certificates, have greatly eroded the confidence of importing countries in the Scheme. As a result, a large number of importing country authorities have now reverted to on-site inspection of manufacturing facilities and are conducting study tours to see how regulatory authorities operate. Information available shows that, through such inspection, importing countries have been able to detect manufacturers that do not comply with WHO GMP requirements.

Inspection by importing countries would become unnecessary or diminished if exporting countries provided importing countries with proof that they fulfil the prerequisites. This could be achieved if exporting countries submit to importing countries the results of an independent assessment of their regulatory system or if governments of exporting countries issued letters declaring that their authorities fulfil the prerequisites.

In order to make the Scheme useful and provide the expected assurance to importing countries about the quality of medicines they import, the Scheme needs to be revised, taking into account the needs of importing countries as the Scheme was originally planned and by considering the problems and weaknesses observed in implementation of the Scheme.

The circulation of counterfeit and substandard pharmaceutical products in the international market has become a serious global problem affecting both developed and developing countries. However, the problem is more serious in those countries with weak regulatory and quality assurance systems. As mentioned above, the WHO Certification Scheme cannot provide full assurance on the quality of imported products due to its inherent limitations. Countries have to establish their own operational drug regulatory system to ensure the quality of medicines circulating within their territories.

Strategies to improve use of the Certification Scheme

Revise the Certification Scheme to make it responsive to the needs of countries that rely on it

- Establish a committee composed of regulatory authorities of importing and exporting countries as well as experts with experience in the use of the Certification Scheme to review the existing document and prepare Draft I of the revised Certification Scheme.
- Circulate Draft I of the revised Certification Scheme among Member States for comment.
- Prepare Draft II of the revised Certification Scheme by incorporating comments received from Member States.
- Discuss Draft II of the revised Certification Scheme in a larger group of experts, for instance, at the next International Conference of Drug Regulatory Authorities (ICDRA) where regulatory authorities from both developed and developing countries are represented.
- Prepare Draft III by incorporating comments obtained from the ICDRA.
- Submit Draft III to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for discussion and adoption.

Revise criteria for membership to the Scheme

- WHO to write a circular letter to Member States to renew their membership and indicate that membership is valid for limited period.
- Applying countries to indicate in the letter their participation as (a) importing country (receiving certificate), (b) exporting country (issuing certificate), or (c) both exporting and importing country (issuing and receiving certificate).
- Member States (exporting drugs/issuing certificate) to submit with the application a verifiable assessment report proving that the competent authorities meet the prerequisites of the Certification Scheme, *or make a declaration that the competent authority(-ies) meet(s) the prerequisites stated in the WHO guidelines*
- Member States submit the names and address of competent authorities authorized to issue certificate.
- Submit samples of certificates with built-in security system (e.g. watermark, hologram) together with stamps and signature(s) of authorized person(s).
- Notify WHO of any change of address or any change of authorized competent authority.

Prepare a list of Member States party to the Scheme

- Prepare a list of Member States that have renewed their membership to the Scheme including the letter of application for membership and a sample of the certificate received from the Member State.
- Distribute the prepared list to Member States to serve as reference.
- Update the list every defined year. If new Member States join the Scheme then notify countries with a circular letter.

Create awareness and understanding of the Scheme

- Initiate informational and promotional programmes such as seminars or workshops, for member States to promote global implementation.
- Assess the operation of the Scheme from time to time to evaluate to what extent countries are using it.

Delisting and negative publication

- Establish a mechanism to remove Member States from the list in case of non-compliance with the provisions of the Scheme.
- Publish and circulate to Member States any fake certificate reported.

Strengthen national regulatory system

- Support countries with a weak regulatory system to have their own quality assurance system by developing human resources and providing technical and administrative assistance.

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Consultation on improvement of the Certification Scheme

The Forty-second Expert Committee on Specifications for Pharmaceutical Preparations discussed and identified a number of perceived problems with the operation of the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce*. These were set out in a background document *Proposal for improvement of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce,* (reproduced on previous pages), together with potential solutions. Thie present text is offered for consultation before being presented to the Forty-third Expert Committee on Specifications for Pharmaceutical Preparations.

The Forty-second Expert Committee recommended that a group be formed to consider the recommendations in the document and feedback received upon its circulation. together with that given by the Expert Committee. A WHO consultation met in Geneva 22–24 July 2008:

- to consider the problems stated, suggestions and feedback received in response to the document *Proposal for improvement of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*; and

- to make recommendations for consideration by the Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The following text constitutes a summary of the meeting conclusions.

Major discussion points
Participants recognized the value of the Certification Scheme in assuring the quality of pharmaceutical products and the benefits it brought to international commerce. However, they also recognized that the Scheme had some limitations. In considering these matters the participants were guided by proposals set out in the background document. The group identified nine key issues.

1. Issuing ("exporting") countries that do not fulfil the prerequisites required by the Certification Scheme issue certificates to support export. In some countries, certificates are issued for products that are produced by manufacturers that do not comply with WHO good manufacturing practices (GMP) requirements.

Recommendations:

- Membership of the Scheme should not be open-ended. It should be renewable, every five years.
- A mechanism of independent assessment of drug regulatory authorities (DRAs) should be in place to ensure that the prerequisites stated in the Scheme are met by participating "certificate-issuing" Member States.
- WHO should encourage countries to perform self-assessment of DRAs periodically.
- In addition, when necessary, Member State regulatory capacity should be further strengthened, e.g. through WHO, regional and international collaboration.
- Importing countries should consider inspecting any manufacturer suspected to be non-compliant with WHO GMP requirements.

Responsibilities:

WHO:

- Inform Member States about the Scheme and its prerequisites, including monitoring the period of validity of the Scheme's membership.
- To provide tools for DRA assessment.
- To enhance international collaboration among DRAs, and assist in capacity building.

Member States:

- To improve on regulatory infrastructure by strengthening DRAs.

2. Countries not party to the Scheme issue certificates to support export of pharmaceutical products.

Recommendations:

- Promote the Scheme – extend invitation to officially join the Scheme to countries that are issuing certificates but which are not party to the Scheme.
- To advise importing countries, when products are imported into their country, to include a requirement for a valid CPP of a country that is party to the Scheme.

Responsibilities:

WHO:

- Promote the Scheme.

Member States:

- Abide by the Scheme.

3. Information on who released the batch for marketing is not disclosed in certificates issued by exporting countries.

Recommendations:

- Certificates should be transparent in disclosing information that has an impact on the quality of products.

- The certificate should include batch release site information in item 2A.3 (Status of product-licence holder) of the model CPP (World Health Assembly resolution WHA50.3) ["option c" will become new "d" and a new "c" will be created.]

Responsibilities:

WHO:

- When the Scheme is modified, new information on batch release site should be introduced in item 2A.3 of the model CPP and footnotes 8 and 9 to CPP suitably changed.

Member States:

- To issue information regarding batch release.

4. Member States issue certificates for products not under their jurisdiction, e.g. for products not authorized for marketing in their countries or not manufactured in their countries.

Recommendations:

- Member States should not issue certificates for products that are not under their jurisdiction, i.e. for products not authorized for marketing in their countries or not manufactured in their country, unless there is a legal provision put in place for medicines produced for "export only".

Responsibilities:

WHO:

- To provide information on the Scheme.

Member States:

- To correctly operate the Scheme.

5. The list of competent authorities is out of date; details of some authorities have changed. The current list of countries that participate in the Scheme in its present form is not readily available.

Recommendations:

- WHO should send a circular letter to participating countries asking them to update the contact details and to specify if the country is the using and/or issuing body.

- An updated list of competent authorities should be compiled from the responses to the letters of those countries actually participating in the Scheme, with appropriate contact addresses of DRAs (competent authorities) responsible for issuing certificates and for all communications related to the operation of the Scheme. In case of lack of response WHO should send reminders to countries.

- The list should be published as a standalone publication and also made available on the WHO web site.

Responsibilities:

WHO:

- To send letters, update the list, publish and distribute.

Member States:

- To respond to the circular letter.

6. The Scheme is at present directed to individual Member States, whereas regulatory and procurement groupings of multistate organizations (e.g. European Medicines Agency (EMEA) and Organization of Eastern Caribbean States/ Pharmaceutical Procurement Service (OECS/

PPS)) also need to be able to operate within the Scheme; this applies to both issuing and receiving parties.

Recommendation:

- Revise the Scheme to allow for those parties to join the Scheme in their respective official functions.

Responsibilities:

WHO and its Governing Bodies to revise the Scheme.

7. There have been cases in which forged certificates have been supplied to competent authorities of importing countries.

Recommendations:

- Encourage issuing ("exporting ") countries to develop secured certificates by using a watermark, hologram, or any other technology.
- Include a unique numbering system for ease of identification.
- Competent authorities should provide a mechanism for specimen of certificates.
- If a certificate is "suspicious" then contacts between the DRA and suspecting party (procurement/DRA) are encouraged.
- Avoid use of photocopies; only original CPP or identical copies clearly marked as "duplicate" can be accepted.

Responsibilities:

Medicines regulatory authority

- See above.

WHO:

- To consider including provision of serial number system when revising the Scheme.

8. Exporting countries issue other certificates such as free sale certificates.

Recommendations:

- WHO should advise accepting ("importing") country authorities not to request or accept free sale certificates and issuing ("exporting") countries not to issue certificates other than those mentioned in the WHO Certification Scheme.
- Use of other certificates other than the ones included in the Scheme should be avoided.

Responsibilities:

WHO and **Member States** should organize seminars and workshops from time to time for DRAs in order to promote the Scheme and give advice.

9. Importing countries require legalization of certificates, additional stamps, etc.

Recommendation:

- Revise the current guidelines of the Scheme in order to strengthen it and to emphasize that legalization of the CPP is not required and in many instances is of little value.

Responsibilities:

WHO should promote this part of the Scheme in training seminars and to take the above into account in the revision process.

Member States should not request such legalization.

Proposed next steps
Implementation of recommendations, proposed time-scale and steps towards action:

- Recommendations reported to 13th ICDRA in September 2008 for information and possible feedback.

- Report and recommendations presented to 43rd WHO Expert Committee meeting in October 2008 with a view to adoption.

If these recommendations are adopted, the following steps will be:

1. WHO Secretariat will follow up with a circular letter to Member States party to the Scheme requesting information as outlined in point 5, and informing them that revision of the Scheme is being considered.

2. Any new applicants to the Scheme will be informed by the WHO Secretariat that revision of the Scheme is being considered.

3. The proposal for revision of the Scheme and modified guidelines should be presented to the WHO Executive Board and World Health Assembly.