WHO Drug Information

Contents

Announcement

The 14th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Health Sciences Authority, Singapore, in collaboration with the World Health Organization

The ICDRA will take place in Singapore from 30 November to 3 December 2010

Updated information is available at:
http://www.icdra2010.sg
http://www.who.int/medicines/icdra

Prequalification of Medicines Programme

WHO Prequalification of Medicines Programme: facts and figures for 2009

The WHO Prequalification of Medicines Programme was launched in 2001 in partnership with UNAIDS, UNICEF and the UN Population Fund, with support from the World Bank. Its focus is on tackling the quality problems commonly associated with medicines for treating HIV/AIDS, malaria and tuberculosis. In 2006, the Programme also laid the groundwork for prequalifying medicines and commodities for reproductive health. This was in response to the fact that, in many developing countries, the need for family planning and reproductive health services remains urgent.

Evaluation of medicines by the Programme includes assessment of data and information on safety, efficacy and quality. In addition, inspections are performed to ascertain compliance with good manufacturing practices. Inspection activities expanded in 2003 to include manufacturers of selected active pharmaceutical ingredients and, in 2004, to include clinical sites and contract research organizations. These are also inspected to verify compliance with good laboratory practices and good clinical practices.

Prequalification of medicines success in 2009

In 2009, a record 44 medicinal products were prequalified of which 39 are generic. By the end of 2009, the WHO list of prequalified medicines totalled 237 products manufactured in 16 countries. WHO prequalification “firsts” included three reproductive health products as well as generic lopinavir/ritonavir, generic oseltamivir, generic tenofovir, ciprofloxacin infusion, generic ceftriaxone and generic abacavir oral solution.

Three medicines quality control laboratories (QCLs) were also prequalified: one in Kenya and two in Singapore. At the end of 2009, a total of 11 QCLs had been prequalified and a further 29 were working towards becoming prequalified.

Updated invitations for expressions of interest to manufacturers to submit product dossiers for prequalification were issued for antimalarial medicines, antituberculosis medicines, HIV/AIDS-related medicinal products, influenza-specific antiviral medicines and medicinal products and reproductive health products. The updated invitations incorporate additional products and/or take into account revisions made to WHO treatment guidelines.

Assessment activities

The pace of dossier submission and assessment from previous years was maintained. Eighty-four dossiers were submitted for evaluation and 53 dossiers were accepted for evaluation. Seven dossier assessment sessions were held in Copenhagen, during which 898 assessment reports were produced: 528 for HIV/AIDS-related products; 197 for antituberculosis medicines; 110 for antimalarial medicines; 28 for influenza-specific antiviral medicines and 35 for reproductive health products. The Copen-

hagen sessions include a training component for assessors from developing countries and are enabling a growing number of these to acquire stringent regulatory expertise. The Copenhagen sessions also incorporate consultations between assessors and applicants so that the latter can discuss technical issues relating to their dossiers. The consultations benefit from the presence of a range of assessors with considerable experience. Applicants pay their own costs to attend consultations and must be committed to the prequalification process.

Problems continue to be seen regarding antituberculosis products: the number of related dossiers continues to be low and their quality is often poor. The Programme has therefore initiated a study to review dossier deficiencies for these products and determine which deficiencies are most commonly observed at each evaluation stage. (Study results will be published and guidance on how to avoid deficiencies developed.) Additionally, members of the Programme team and the WHO China country office worked to secure funding from the Bill & Melinda Gates Foundation for a project to provide technical support on quality issues to manufacturers of fixed-dose combination antituberculosis products. It is hoped that this will lead to increased dossier submissions for these products.

Inspections

Programme inspectors carried out 50 inspections in seven countries: 27 of finished pharmaceutical product manufacturing sites; seven of active pharmaceutical ingredient (API) manufacturing sites; ten of contract research organizations (CROs) and six of pharmaceutical QCLs. The majority of inspections were carried out in India, followed by China.

A number of manufacturers were contacted in late 2009 and requested to submit their inspection reports from stringent regulatory authorities together with a report of corrective action they had implemented following these inspections. The Prequalification of Medicines Programme is investigating the possibility of conducting a “desk review” of these documents and of any relevant quality review reports prepared by the manufacturers. Such review would be in lieu of an on-site inspection by WHO subject to specified conditions. The aim is to avoid duplication of site inspections and to optimize use of inspection resources. In the event, only two cases were found in which the inspection reports and corrective actions were considered to meet the requirements set by the inspection team for allowing postponement of an on-site inspection by WHO. An amendment to the WHO procedure for prequalification of pharmaceutical products is now being considered to make provision for this new process.

Advice and assistance

WHO assessors continued to provide scientific advice to manufacturers during 2009. This included review of bioequivalence study protocols and responding on a daily basis to specific questions relating to quality, efficacy and safety. New guidance was issued on *Submission of Documentation for Prequalification of Multisource (generic) Finished Pharmaceutical Products approved by Stringent Regulatory Authorities*, and an alternative procedure for accepting second-line TB product dossiers for assessment.

The Programme organized ten technical missions to pharmaceutical manufacturers and QCLs in seven different countries. Missions focused principally on good manufacturing practice but also on dossier preparation and quality systems in QCLs. It also organized 12 training workshops and co-organized or supported a further five workshops for nearly 800 participants. Workshops ranged from introductory workshops on WHO Prequalification and how to meet requirements, assessment of multisource inter-

changeable medicines, and to the planning, implementation and assessment of stability studies.

Testing of medicines quality
The pilot phase of an activity to sample and monitor the quality of paediatric and second-line antiretrovirals and sulfamethoxazole-trimethoprim for treating HIV/AIDS was completed. Nearly 400 medicines samples produced by 24 manufacturers were collected, mostly from treatment centres. Only three samples failed quality testing and none of the failures were life-threatening for patients. The results underscore that, provided procurement and distribution practices are sound, medicines prequalified by the Programme can be viewed with confidence by health workers and patients alike.

The quality of antimalarial medicines was surveyed in six African countries for artemisinin-based combination therapy and sulfadoxine-pyrimethamine oral dosage forms. Over 900 medicines samples were collected from all levels of the distribution chain and informal market and were screened using "minilabs" in cooperation with the relevant national medicines regulatory authority. Thereafter, 306 samples were fully tested in the laboratory: 74 samples were non-compliant and demonstrated a range of quality problems, including absence of the API in two samples. A quality survey was also initiated in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine and Uzbekistan. It focuses on antituberculosis medicines containing rifampicin, isoniazid, kanamycin and ofloxacin. Testing is ongoing for the 291 samples collected.

Norms and standards relevant to WHO prequalification activities
The 44th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted seven monographs for HIV and related conditions, five monographs for antimalarial medicines, six monographs for antituberculosis medicines and one monograph for an influenza-specific antiviral medicine. The Committee also adopted: an update of good practices for quality control laboratories; a guideline for the preparation of a CRO master file; a guideline on requalification of prequalification dossiers; various updates and revisions of good manufacturing practice texts; and an update of good distribution practices for pharmaceutical products. Each of these norms and standards is of direct relevance to the Programme's activities.

Improving Prequalification of Medicines Programme services
A business plan for the Prequalification of Medicines Programme was completed in August 2009. It analyses the current mandate and functions, maps performance, estimates resources required for coming years and makes recommendations on how the Programme can improve organization and management. The plan projects an economic return on investment of 170:1 for the Programme for the period 2009–2013. The projection is based on: projected availability of global funding for procuring medicines for treating HIV/AIDS, TB and malaria; projected prequalification of 105 additional medicines (around 90% of which will be generic medicines); and projected estimated impact on additional volume of medicines that can be purchased as a result of increased competition among generics.

Survey of manufacturers
In late 2009, work started on development of a first survey of manufacturers. The aim is to obtain feedback on the services provided by the Programme and to analyse where and how improvements to those services might be made.

Further information on the WHO Prequalification of Medicines Programme, including the full list of medicines prequalified by WHO can be found at: http://www.who.int/prequal

Regulatory Harmonization

Updating medicines regulatory systems in sub–Saharan African countries

An effective medicines regulatory system ensures that all pharmaceutical products on the market are safe, effective and consistently meet approved quality standards (1). The World Health Organization (WHO) works with its Member States in assessing national regulatory systems to identify gaps, develop strategies for improvement and support countries in their commitment to build national regulatory capacity.

The WHO report, *Assessment of medicines regulatory systems in sub-Saharan African countries* (2), synthesizes the findings of rapid assessments performed over the last eight years of national medicines regulatory authorities (NMRAs) in 26 African countries: Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Chad, Democratic Republic of Congo, Cote d'Ivoire, Djibouti, Ethiopia, Gabon, Ghana, Kenya, Malawi, Mali, Mozambique, Niger, Nigeria, Rwanda, Senegal, South Africa, Sudan, United Republic of Tanzania, Uganda, Zambia. Although the emphasis of the missions was on capacity-building rather than a standardized comparison of indicators, the findings give a useful insight into the regulatory situation in Africa and potential areas for collaboration. The report sheds light on the urgent need for regulatory capacity strenghtening in African countries and proposes action for sustainable progress. A summary of the report is set out on the following pages.

Medicines regulation in developing countries

Medicines are essential to health care and should be available to the inhabitants of every country. Medicines regulation aims to ensure that medicines circulating in national markets and international commerce are safe, effective and of good quality, are accompanied by complete and correct product information, and are manufactured, stored, distributed and used in accordance with good practices.

Affordable products are now available with the potential to dramatically reduce morbidity and mortality in resource-constrained countries. Although African countries import most of their pharmaceuticals, the African Union has recently started to promote local manufacture of medicines in Africa.

Globalization of commerce and the merging of pharmaceutical companies has led to an increasing breakdown of national boundaries in medicines supply. Substandard and counterfeit pharmaceutical products are now reported from all parts of the world (3). The problem is greatest in developing countries, which have insufficient funds for medicines procurement, and even fewer resources to enforce quality standards and protect the medicines supply chain.

Norms and standards for medicines quality are becoming more sophisticated and make the assessment of new chemical entities especially challenging. WHO continues to develop international norms and standards to serve as guidance for national regulatory systems. In practice however, medicine quality standards are subject primarily to the requirements in

force in the country of destination (4). Regulating the increasingly complex channels of medicines supply requires constant vigilance, adaptation and considerable organizational capacity and resources.

Aim of the WHO report

Assessments of medicines regulatory systems in sub-Saharan African countries presents assessments of regulatory systems conducted in 26 sub-Saharan African countries over the past eight years. It identifies regulatory gaps and suggests priority activities to strengthen regulatory capacity.

At the request of each country, national medicines regulatory authority (NMRA) assessments were carried out between 2002 and 2009 by teams composed of WHO experts, staff from NMRAs and/or external consultants. Written terms of reference and an agenda for the visits were agreed beforehand with the regulatory authority being assessed. The duration of the visits varied depending on the complexity of the country's regulatory functions, most visits took approximately three to five working days.

Data were collected by interviewing personnel, reviewing documents (manuals, records, reports, files), analysing data and/or observing activities. Findings were recorded on a comprehensive data collection tool developed by WHO (5) which has since been complemented by a detailed guidance document (6). A draft report was submitted to the regulatory authority after the visit together with a drafted proposal for a plan of action. The main aim of the visits, and the design of the tool itself, were geared towards identifying priorities for strengthening regulatory capacity. They were not intended to provide comparable indicators of regulatory capacity over time.

The strengths and weaknesses identified by the country reports are a reflection of their technical judgement of the authors together with the views expressed by relevant national regulatory officials.

Country profiles

The 26 countries included in the report represented 88% of the population of sub-Saharan Africa in 2007. Key economic and health-related data are also summarized in the report (2).

Pharmaceutical sector data contained in country reports indicated that African countries generally had:

- Limited pharmaceutical production capacity, while most depended mainly on imports.
- Some pharmaceutical manufacturing activity catering mainly for domestic and regional demand. However there were some exporting countries.
- A diverse distribution chain, with various types of unauthorized outlets suggesting the presence of an informal market.

In virtually all countries included in the report, limited public funds were available for law enforcement in general and for medicines regulation in particular. Additionally, there were indications of the presence of parallel, unregulated medicines markets, posing a serious risk to individual and public health.

Nevertheless, differences did exist in the efficiency of the measures implemented among countries. This illustrates the impact of political commitment and level of resources allocated to medicines regulation.

Regulatory framework

Legislation

Written laws, Acts or Statutes enacted by Parliament give the NMRA the power to control medicines. Regulations prepared under the authority of an Act provide directions on how regulatory functions are

to be carried out. Guidelines are also needed to interpret legislation and advise on how to comply with a regulation. The way in which these legal and explanatory texts are drafted affects the efficiency of medicines regulation.

The legal framework should allow effective implementation and provide adequate powers to the NMRA. Legislation should cover all products for which medicinal claims are made as well as related manufacture and trade activities in the public and private sectors. Countries should update their medicines legislation and regulations regularly to reflect national realities and to address new pharmaceutical issues as they arise (1).

Key findings

- In most countries, legislation had evolved over many years. In only three countries had a medicines regulation Act been adopted later than 2000.
- Successive regulations and decrees had created a complex legal framework with overlaps and grey areas.
- Regulations for specific regulatory functions were missing in some countries, especially where the NMRA was undergoing transformation.

Regulatory scope

In the last few decades, expansion of regulatory scope has been considered in many countries (7). A medicine has been defined as “Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient” (8). In addition to conventional medicines for human use, this definition also includes biological medicines (including vaccines and blood products), veterinary medicines, and traditional and herbal medicines, although the latter category is challenging to define and to regulate (9).

All types of medicines should be regulated by the NMRA. At the same time, implementation of medicines regulation should not be compromised by other, non-regulatory activities exerted by the NMRA.

Key findings

- Seventeen of 26 NMRAs (65%) had the mandate to control veterinary medicines. In four countries veterinary medicines were controlled by another Ministry, such as the Ministry of Agriculture or Livestock.
- Eighteen of 26 NMRAs (69%) had some policy or provisions to deal with traditional or herbal medicines. While eleven of these registered traditional or herbal medicines, another two were about to start doing so.
- NMRAs in eleven countries (42%) regulated a wide scope of products, which included foods, poisons, pesticides, bottled water, cosmetics and/or animal food supplements.
- In seven countries, the NMRA was involved in designing and implementing national medicines strategies, implementing legislation or coordinating public sector medicines supply; in one case a clearly distinguished unit was in charge of policy issues.

Organizational forms

One central authority should be accountable for the overall effectiveness of medicines regulation. It should have government backed legal power to acquire and use resources, recruit and dismiss staff, and make independent decisions. The choice of a specific organizational form will have an impact on the autonomy, visibility and accountability of an NMRA and would affect efficiency in medicines control.

Key findings

Historically, most NMRAs in Africa started life as departments under the Ministry of Health. Organizations of this type have little autonomy. They cannot recruit their own staff, nor can they offer adequate salaries to attract and retain qualified experts. With the maturation of regulatory systems, some countries are moving away from this model and are establishing their NMRAs as autonomous bodies or as centralized parastatal agencies with their own management structures.

- Seventeen of 26 authorities (65%) were departments of the Ministry of Health, with very little or no autonomy to manage their own funds and human resources.
- Seven NMRAs (27%) were in transition or not formally constituted at the time of the visit.

Regulatory functions
NMRA responsibilities should cover all medicines regulatory functions and should be performed in a balanced fashion.

If functions are distributed between different authorities, either horizontally (e.g., ministry of health, ministry of agriculture) or vertically (federal, state/regional and local governments), a central coordinating body should be accountable for all aspects of medicines regulation in the country (1).

Key findings

- Four of the 26 NMRAs (15%) carried out functions of marketing authorization, licensing, inspection, quality control and pharmacovigilance together under one umbrella.
- Seventeen NMRAs (65%) had access to a functional national regulatory quality control laboratory, while seven of these laboratories were part of the NMRA. In one of the remaining countries, there was an NMRA laboratory which had ceased to function.
- Most countries had fragmented regulatory systems. Gaps and overlaps of responsibilities were common, especially in licensing (involving the Ministry of Public Health or Ministry of Trade) and inspection (involving pharmaceutical councils, regional authorities or public health inspectorates).
- Decentralization and cooperation between authorities was problematic; 12 reports highlighted the lack of communication at operational level.
- In many cases, regulatory functions were not operational and in some cases authorities were not legally delegated.

Structure and management

Funding
Sustainable funding for NMRAs should be derived from various sources:

- Fees, which contribute significantly to operational costs without being too high to discourage applications.
- Public funding, to ensure a certain independence from the parties that MNRAs are mandated to regulate.
- Donations to supplement limited public funds.

NMRAs should have the autonomy to retain and use the fees collected for services provided for their own purposes.

Key findings

- Most NMRAs derived their funding from more than one source, although the proportions varied from one country to another.

- Fees were commonly charged for initial marketing authorization, renewal and retention. More rarely, fees were charged for importation of medicines, inspection, analysis of samples and registering persons and premises.

- Generally, the fees were lower than the cost of services rendered, and were not retained or redistributed in full.

- Nine NMRAs depend on government funding, with all fees paid directly to the treasury and not redistributed. Four NMRAs also receive donor funding. Funds allocated by the states were not always released on time.

- None of the NMRAs assessed had adequate and sustainable funding to cover operations.

Human resource management
Personnel engaged in medicines regulation should be individuals of integrity and be appropriately trained and qualified.

Human resource development programmes should be made available to enable staff to keep up with developments in pharmaceutical science and technology.

Key findings

In general, human resource management was virtually non-existent. This was the case especially where an NMRA was not given importance by the Ministry of Health. As a result, lack of qualified staff affected critical regulatory functions while specific shortcomings included the following.

- Only two of the 26 NMRAs (8%) had a human resource development plan, which was however not specific to the tasks of the NMRA. Specific training needs and difficult access to sources of current information were noted in most countries.

- Job descriptions for key personnel were described as absent in five countries, and as unclear or outdated in four. Four reports mentioned the absence of an organigram.

- In some authorities, responsibilities were not assigned appropriately. One NMRA director was at the same time the director of the national laboratory, resulting in an unmanageable workload. Three others were simultaneously in charge of public sector medicines supply or tenders, creating a potential conflict of interest.

- Four reports mentioned the absence of a legal adviser on the NMRA's payroll.

Quality management systems
NMRAs perform critical and sensitive functions such as handling and assessing marketing application dossiers containing confidential information, inspecting facilities and handling site master files. A quality management system (QMS) should ensure that the operations of an NMRA are carried out to defined, uniform standards, and that each step of the regulatory process is identified and documented.

Key findings

- Four NMRAs (15%) were in the process of implementing a QMS and had elements of the system in place, two others were drafting a system.

- None of the NMRAs had implemented a comprehensive QMS.

Impartiality and transparency
Medicines regulation is a public policy that regulates private sector activities in order to attain the promotion of public health. Conflicting interests therefore need to be recognized and managed appropriately.

To provide credible regulatory services, NMRAs must have specific measures in place to avoid conflict of interest in decision-making, to ensure confidentiality, to make their rules and decisions transparent, and to consult with stakeholders.

Key findings

- Nine of the 26 NMRAs had a dedicated web site. Five of these were in need of updating, one was not functioning correctly at the time of the visit. As at November 2009, seven additional sites were identified (10).

- Consultation with stakeholders took place in most countries, although it tended to be limited to specific issues or groups.

- Current information was not always publicly available: lists of approved products or establishments were often missing and/or outdated. Little information was made public on decision-making.

- Twenty-three of 26 NMRAs (88%) had no written declaration of interest or confidentiality agreements in place, although some had general rules of conduct such as a code for civil servants. In the three countries which did have a specific written system, this did not apply to all technical staff involved.

Medicines registration

A core regulatory function is the authorization of medicines based on a scientific assessment of their safety, efficacy and quality.

To assess applications for marketing authorization, NMRAs need:

1. Legislation giving the NMRA the power to grant, renew, vary, suspend and withdraw marketing authorizations.

2. Guidelines for applicants setting out the conditions, content and format of applications, and the detailed technical requirements against which dossiers will be assessed, based on international guidelines (11–13).

3. Standard operating procedures (SOPs) to assess submissions, and standard formats to communicate and publish the outcomes.

4. Involvement of an advisory committee and expert assessors in adequate numbers with specific, current expertise.

5. Logistics for management, secure storage, retrieval and exchange of data with other regulatory departments, as well as access to current scientific and technical information.

6. Mechanisms to consider decisions from more stringent NMRAs.

Key findings

- Some evaluation of technical documents was performed in 19 of 26 countries (73%) to varying degrees of stringency, at least for generic medicines.

- The technical standard of evaluations was generally not in line with WHO standards. For example, in at least four countries, guidelines did not exist. At least three NMRAs did not require the manufacturer to have GMP certification. At least six NMRAs did not assess summaries of product characteristics (SPC).

- The capacity to assess applications for new innovator products was almost non-existent.

- NMRAs in seven countries conducted only an administrative review of documents, or no review at all at the time of the assessment.

Legal basis and regulations

- Eighteen of 26 NMRAs (69%) operated within a legal basis which empowered them to assess applications for marketing authorization, with regulations that briefly outlined the requirements or listed the components of dossiers to be submitted for different types of products.
- Provisions for renewal of marketing authorizations were in place, usually every five years.
- Seven countries had provisions which exempted wide ranges of products (such as public sector imports or donations) from registration or from specific requirements irrespective of quality risk. For example, in one country, all oral solid-dose anti-infectives were exempt from in vivo bioequivalence studies.

Guidelines

Some countries had guidelines which described the required content of submissions and gave brief instructions, but did not give sufficient guidance on technical issues such as bioequivalence and stability. Others described the administrative steps and others provided only checklists. A specific format for submissions was not required in any of the countries.

- Only three NMRAs (12%) provided detailed technical guidelines (but not in line with WHO Guidelines).

Procedures for assessment

Written SOPs for dossier assessment were either absent or they described only administrative steps such as checking the completeness of dossiers, payment of fees or inclusion of samples, or were checklists outlining elements of the assessment methodology.

- Adequate SOPs for dossier assessment were in place in only three countries.

Timeframes for assessment of applications ranged from three months to five years, depending on the complexity of assessments and available resources. Fast-track mechanisms existed for certain product types. Two reports mentioned the short preparation and meeting times available for committee members to make their decisions, meaning that they may not be able to read all documents and carry out any real assessment.

- Although overall assessment time frames were long, little time was available for an in-depth thorough assessment by experts due to scheduling difficulties and backlogs.

Expert assessors

Most NMRAs had formal advisory committees. However, not all committees were operational, bringing assessment to a halt in two countries. Eleven countries used external experts, two of them exclusively. Appointment of committee members and experts was not necessarily based on specific regulatory expertise, and provisions for confidentiality and declaration of interest were lacking in most countries.

- Twenty-four of 26 country reports (92%) mentioned the shortage of adequately qualified assessors as an obstacle to timely dossier evaluation.

Logistics

- Only four NMRAs (15%) had appropriate archiving space to store confidential data securely.
- Only six of 26 countries (23%) had coherent, networked computerized systems designed for medicines registration. Nine (35%) had only manual systems.

The latter shortcoming affected transparency and information-sharing with other

departments. Lists of registered products were not readily available, which made it difficult to verify the registration status of medicines circulating in the market and those being imported. The countries which did publish a list did not include the approved summary of product characteristics (SPC) needed to verify package inserts, information for health professionals and advertising claims.

Recognition of decisions made by other NMRAs

Certificates of pharmaceutical products (CPPs) issued under the provisions of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (14) were commonly requested as part of applications, but usually without considering the capacity of the issuing regulatory authority to certify that the data on the certificates was correct. Conversely, one report from an exporting country mentioned that the NMRA *"issues CPP without ascertaining that all prerequisites as specified by WHO are fulfilled"*.

- Only two NMRAs (8%) explicitly relied on other regulatory bodies/organizations which they considered stringent, including the WHO Prequalification Programme (15).

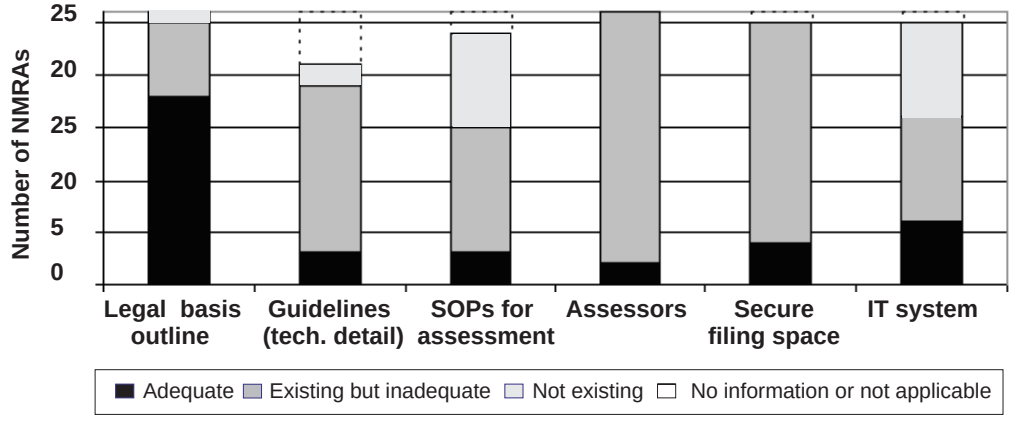
The lack of mechanisms and procedures that would enable NMRAs to benefit from the scientific assessments and inspections carried out by other well resourced and established regulators is a major cause of concern, as most of the authorities in the region have limited human resources and scientific expertise. (See Figure 1.)

Licensing of pharmaceutical establishments

Health budgets in African countries are low and a high percentage of health costs are paid out of pocket. There are many types of medicines outlets not managed by a pharmacist. Concerns about the parallel medicines market were voiced in most country reports, such as this typical statement: *"The illicit medicines market has become a real plague in the country. All therapeutic classes can be found, including psychotropic medicines, and there is no national strategy to combat this situation."*

A mandatory system of licensing manufacturers, wholesalers/distributors and retailers is essential to ensure that medicines conform to acceptable standards of quality, safety and efficacy until they reach the end user. Licensing must be complemented by inspections and market surveillance.

Figure 1. Resources for medicines registration



NMRAs should ensure that all premises and practices used to manufacture, store, distribute and supply pharmaceutical products to patients comply with current guidelines on good manufacturing practice (GMP), good distribution practice (GDP) and good pharmacy practice (GPP).

Key findings

- All countries except one had systems in place to license pharmaceutical establishments.
- Authorities other than the NMRA were involved in licensing in 16 countries (62%), resulting in overlaps, grey areas and gaps in the control of pharmaceutical activities.
- Decentralization of licensing, involving regional authorities, was not organized efficiently. Lack of coordination was commonly highlighted; lax control of licensing by local authorities was mentioned specifically in three country reports.
- Licences or renewals were granted without inspection in some instances.
- In practice, good practices requirements were poorly enforced. In one country only one of many established manufacturers was licensed.

Import and export control

With the rapid introduction of high-technology medicines into import, export and distribution networks (including e-commerce), the safety, quality and efficacy of medicines on the market are matters of considerable concern.

Setting in place a registration system should not be considered as the only mechanism to guarantee the quality of products on the market. It should be complemented by other control measures such as the authorization of each act of importation of pharmaceutical products on the basis of the product's registration status.

Products for export should be subject to the same standards as those for domestic consumption.

Key findings

- Control of imported products was weak. In at least eight countries (31%) there was no efficient system to verify the marketing authorization status and exemptions for imported products.
- Cooperation with police and customs was consistently described as problematic.
- Control of exports was not stringent. One report mentioned manufacturers' illegal practice of issuing "free sale certificates", which leaves all control to the receiving country.

Inspections

Inspections conducted on pharmaceutical facilities should enable medicines regulatory authorities to monitor whether pharmaceutical activities are carried out in accordance with approved standards and guidelines. The efficiency of inspections has a direct impact on the extent to which medicines control is enforced.

A legal basis must be in place for inspections and enforcement. Planning of routine inspections should be implemented to regularly check compliance with relevant good practices in place.

A quality management system (16) should ensure that inspections are planned, conducted, documented and followed up in a consistent way, based on risk assessment.

Sufficient qualified inspectors and logistic resources must be available to cover the area to be regulated.

Key findings

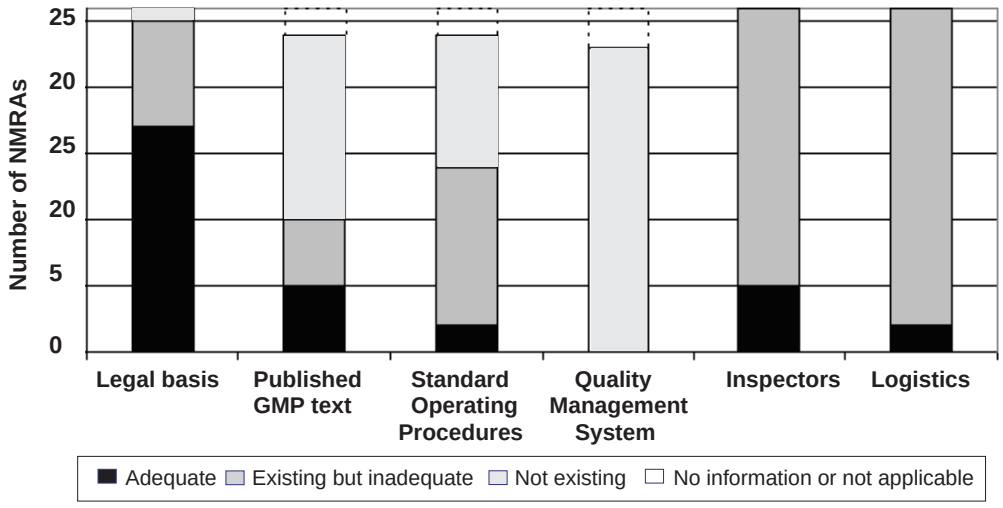
- A legal basis empowering the relevant authority to perform inspections was in place in 17 countries.
- GMP was not required in at least nine countries. In at least two countries where GMP was required, none of the established manufacturers had GMP certification.
- Only five of 26 countries (20%) had published GMP guidelines meeting WHO standards (two had national texts, and another three used the WHO text). Only one country had adequate GDP guidelines.
- SOPs for inspection, if any, were mostly in checklist format and were not comprehensive.
- No NMRA had a comprehensive quality management and planning system for inspections in place.
- Shortages of qualified inspectors were a universal problem. The need for specific training of inspectors in current GMP was commonly highlighted.
- Potential conflicts of interest were noted. Inspectors could be pharmacy technical directors or supervisors in at least three countries. Pharmacists from private retail and manufacturing facilities were used as inspectors in another.
- Inadequate logistic resources, especially means of transport and communication, were a major constraint. The effectiveness of inspections suffered from these constraints. (See figure 2.)

Quality control

Quality control (QC) aims to verify that products comply with the specifications of the marketing authorization. QC testing of pre-marketing samples can be useful to some extent, although applicants may take measures to ensure that their registration samples will not fail. However, the same quality standards may not be met by each batch of product put on the market. QC testing of post-marketing samples thus acts as a deterrent against negligent or fraudulent manufacturing and trading practices.

NMRAs should have access to a quality control laboratory with adequate capacity to undertake quality surveillance.

Figure 2. Resources for inspections



QC facilities should have sufficient qualified personnel and the necessary equipment and materials, and must operate according to established standards. A quality management system, such as ISO 17025 (17), provides a framework for QC laboratories to operate according to defined procedures and standards. WHO's good practices for national pharmaceutical control laboratories (18) and guidance on good laboratory practice (19) provides detailed advice on organizational and technical issues.

If dossiers are assessed and samples tested, good collaboration between assessors and laboratory staff needs to be in place.

Key findings

- A QMS was in place at five (29%) of the 17 functioning regulatory laboratories; three others had partial systems which were lacking essential elements and were not fully operational.
- Satisfactory staffing and equipment were in place in the majority of cases, but six laboratories were housed in inadequate buildings.

Ten reports mentioned QC testing for pre-marketing applications. However, the laboratories were not always given the relevant dossiers, manufacturer's reference materials and validated methods.

Market surveillance

Product quality monitoring

Substandard pharmaceuticals may circulate on the market if good practices in manufacturing, distribution and storage are not adhered to.

In addition, counterfeiting — the production and distribution of medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source — is becoming an increasing problem. It requires a coordinated response from different sectors both at country level and internationally (20). In both cases, the deficient products pose a risk for individual and public health.

A risk-based system of inspections and sampling should be in place to monitor the quality of pharmaceutical products on the market. Manufacturers should be obliged to report complaints and quality problems to the NMRA. An effective recall procedure to remove defective products from the market should be in place.

The NMRA should coordinate an anti-counterfeiting programme with all concerned parties, including industry, customs, police and any other stakeholders involved in trade or distribution of pharmaceuticals.

Key findings

- Fourteen of 26 NMRAs (54%) lacked a quality monitoring programme altogether; seven had the capacity to test samples in case of complaints or in the framework of specific programmes, and only five (19%) had a systematic approach.
- Twenty of 26 NMRAs (77%) lacked a written procedure to organize an effective recall; of the existing six procedures three needed clarification. Five reports noted the lack of batch traceability needed to recall products. This finding is consistent with the general absence of published GDP guidelines.
- Anti-counterfeiting measures included inspections and surveillance in five countries and awareness programmes in three. No country had a specific, comprehensive programme in place at the time of the visits.

Pharmacovigilance

Pre-marketing clinical trials are usually conducted on a small number of volunteers. Not all adverse reactions can be

anticipated from these studies. NMRAs should implement a system to monitor adverse events. For this to be effective, there must be a high probability for adverse events to be identified and reported, reports must be reviewed and validated by experts, results must be fed back, and appropriate regulatory action must be taken.

Key findings

- Eight of 26 countries collected reports on adverse events, with three of the programmes being sufficiently established to contribute a sizeable number of results. Seven of the eight countries were members of the WHO Programme for International Drug Monitoring (see http://www.who-umc.org/).
- Where it existed, pharmacovigilance was generally not well integrated with other regulatory activities. Also, clinical surveillance measures implemented by specific national or NGO treatment programmes were not organized or envisaged.

Medicine promotion and advertising, provision of drug information

Information propagated through promotion and advertising can significantly influence the way in which medicines are prescribed by health professionals and used by consumers. Inaccurate and misleading information therefore poses a health risk.

NMRAs should control promotion and advertising to ensure that any claims made correspond to the approved summary of product characteristics (SPC). They should also provide independent information on medicines to the public and health professionals.

Key findings

- Most countries had some legal provisions for the control of medicines promotion. Seven of 26 countries (27%) controlled pharmaceutical promotion to varying extents.
- In 19 countries (73%) there was no control of promotion and advertising in practice, meaning that even if the regulations were in place, they were not implemented.
- At least 13 NMRAs did not provide any independent medicines information to the public.

Oversight of clinical trials

Clinical trials are an essential component of pharmaceutical research and development. They serve to establish the safety and efficacy of new medicines, and to develop new treatment uses of well known medicines. Clinical trials also include *in vivo* bioequivalence studies carried out with generic medicines to establish their therapeutic interchangeability with originator products. In all these types of studies the ethical rights and the safety of trial subjects must be protected, and the methodology must be designed in such a way as to arrive at useful, scientifically valid results.

NMRAs should control clinical trials jointly with external bodies such as national or institutional ethics committees. Trials should conform with ethical principles for medical research involving human subjects and the Declaration of Helsinki (21). Guidelines by the Council of International Organization of Medical Sciences (CIOMS) provide valuable additional information on research ethics.

WHO guidelines for GCP (22) and GLP (19) should be followed. GMP of investigational products should be verified. Other more specific guidelines on clinical research may apply.

Trials should be monitored for compliance with all applicable guidelines. Investigators should be required to report on the outcomes promptly, including any serious adverse events encountered.

Key findings

- In 18 of 26 countries (69%) clinical trials were controlled to some extent, mostly with regard to ethical review.
- Where ethics committees were involved, NMRAs retained little or no control due to lack of capacity, unclear assignment of responsibilities or non-representation in the relevant committees.
- Adherence to GLP and GCP was not a requirement in 22 countries (85%); detailed GCP guidelines were found in only two countries (8%).
- Eight reports mentioned the absence of import controls and GMP requirements for investigational products.
- Only four country reports mentioned that inspections of clinical trials were being conducted.

Conclusions

The countries included in this report had legal provisions for the most essential needs of medicines control. However, their regulatory systems presented some weaknesses. Generally, the legal framework had evolved over time, resulting in a fragmentation of responsibilities with gaps and grey areas and a multitude of provisions which were difficult to implement.

Many NMRAs were allowed little power and autonomy, and were unable to oversee the full range of regulatory functions, with few having systems for accountability or managerial commitment. Lack of sustainable funding restricted operations to a great extent. Virtually all NMRAs suffered from staff shortages. For the most part, assessors and inspectors were unable to satisfactorily attain the level of scientific and technical expertise needed to fully implement regulatory tasks. Many regulatory requirements and processes were not in line with recommended WHO standards.

As a result of these drawbacks, medicines regulation was not being carried out to the fullest extent. The findings confirm the results of a 2004 questionnaire survey conducted by WHO in 38 African Member States, which found that 90% of countries were in a situation which did not allow them to adequately carry out regulatory functions (23).

Despite the universally scarce resources and the health workforce crisis experienced throughout sub-Saharan Africa, marked differences were noted in the relative efficiency of medicines control among countries, showing that political commitment at national level can make a difference.

On the positive side, many countries were greatly committed to improving their medicines regulatory capacity: reviews of systems were invited and regulatory restructuring is being adapted. However, in many cases, the transformation process has created new administrative hurdles for effective decision-making, management and release of funding.

The follow-up assessments conducted in four countries showed progress in specific areas. However, for a sound, well-resourced national medicines regulatory system to operate within the difficult conditions imposed by African markets, commitment must be long term.

The way forward should be towards effective implementation of medicines control in practice. Political will and substantial human and financial resources will be needed for this purpose. Countries will need to take concerted action if they are to expand access to medicines of assured quality and safety for their populations. It was felt that the following approaches would be the most useful in building regulatory capacity in Africa.

WHO should:

- Encourage African countries to provide NMRAs with adequate organizational structure, sufficient autonomy and sustainable resources to enable them to carry out operations.

- Encourage and assist African countries to regularly assess their own regulatory systems in a standardized way. The WHO assessment tool and the accompanying guidance have been developed for this purpose.

Countries should:

- Consider mechanisms to share the outcomes of regulatory assessments among NMRAs.

- Work towards effective implementation of all essential regulatory functions under the umbrella of an NMRA network.

- Continuously harmonize, adapt and update the legal framework for medicines regulation based on internationally recognized norms, standards and best practices.

- Provide specific, relevant training for assessors, inspectors and other technical staff, in line with current technical requirements and good practices.

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International Nonproprietary Names

The glycosylation pattern of epoetins

The human gene for erythropoietin was cloned in the early 1980s and recombinant production processes were set up by several companies shortly thereafter. Commencing in 1989, these processes have led to the introduction of two therapeutic compounds onto the market, *epoetin alfa* and *epoetin beta.* Both of these recombinant versions of human erythropoietin are manufactured in engineered Chinese Hamster Ovary (CHO) cells.

In parallel with epoetin alfa and epoetin beta development, two other versions of epoetins have been developed. One was produced in Baby Hamster Kidney (BHK) cells and another in C127 (mouse epithelial) cells. The BHK product received the International Nonproprietary Name (INN) *epoetin omega* and the C127 product *epoetin gamma.* Neither of these two products reached the market in the European Union, North America or Japan for intellectual property reasons. Epoetin omega, developed by Elanex, has been manufactured in several developing countries and used in Latin America, India and other countries for many years under different trade names (Epomax®; Hemomax®, etc.).

Further development involved the use of a human fibroblast cell line (HT1082) producing erythropoietin by activating the endogenous erythropoietin gene. This product, under the INN *epoetin delta,* was well characterized, clinically tested, approved and distributed under the brand name Dynepo® in the European Union. Almost at the same time as Dynepo® appeared on the market, the first biosimilar epoetin products were introduced: a product developed by Sandoz was marketed under three brands (Binocrit®; Epoetin alfa®; Abseamed®) and a product developed by Stada/Hospira marketed under two brands (Silapo®; Retacrit®). Common to all biosimilar epoetins so far is the claim of similarity to *epoetin alfa* and production in CHO cells. The INN they use is rather *epoetin alfa* (Sandoz products) or *epoetin zeta* (Stada/Hospira products). A further epoetin produced in CHO cells has recently been approved in the European Union as a de novo development: *epoetin theta* from Ratiopharm (Biopoin®; Ratioepo®; Eporatio®).*

In conclusion, the majority of products on the market in the European Union, North America and parts of Asia are derived from CHO cells, while BHK derived products are available widely in developing countries. However, the C127 product never reached the market, and the only product based on a human cell system (Dynepo®) has been withdrawn from the European Union market.

Glycosylation

Glycosylation is an inherent feature of the particular cell line used for manufacturing erythropoietin and will depend on the enzymatic machinery of the cell and the growth conditions used for cultivating the cells. CHO cells in general show glyco-

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** Development of modified versions of erythropoietin, such as darbepoetin or mircera, will not be covered in this summary.*

sylation capabilities similar to human cells with some slight differences. The amino acid sequence encoded in the gene and inserted into the production cell line dictates the position (the exact amino acid) where a carbohydrate chain can be attached. The location within the sequence and, more importantly, within the three-dimensional structure of the protein influences the nature of the final carbohydrate structure.

In general there are two ways carbohydrates can be attached to proteins, either N-glycosidically on asparagine (Asn) residues or O-glycosidically on serine (Ser) or threonine (Thr) residues. Erythropoietin contains three asparagine residues in a sequence motif sufficient for N-glycosylation and one serine used for O-glycosylation. The four sites are glycosylated in human erythropoietin as well as in all recombinant epoetin products on the market. This leads to approximately 15 major carbohydrate structures (glycoforms) present in all epoetins in somewhat different quantitative distribution.

For secretory proteins like erythropoietin, the glycosylation process starts with an initial attachment of a precursor carbohydrate structure to the growing polypeptide chain. This carbohydrate structure will be further modified during the secretion process of the glycoprotein from the endoplasmic reticulum through the Golgi apparatus and finally through secretory vesicles to the outside of the cell. This process of modifying the carbohydrate chains involving numerous enzymes from the host cell during secretion is the main reason for the heterogeneity obtained in the final carbohydrate structures.

All CHO production cells, albeit developed independently, generally produce glycosylation patterns which consist of a number of CHO-typical structures with quantitative differences in the distribution of the individual structures. The glycosylation pattern of erythropoietin obtained from BHK cells, another rodent cell line used, basically shows the same structural elements as CHO, whereas other cell lines, like the human line HT1081, may show certain differences.

Nevertheless, all cells will produce a great variety of glycoprotein molecules with different carbohydrate structures which in the course of manufacturing will be further refined by selecting a subset of these molecules as the therapeutic entity. This process will further influence the actual carbohydrate heterogeneity of a glycoprotein drug. Thus, the process will finally define the end product.

Carbohydrate structures of epoetins

CHO-derived products (*epoetin alfa, beta, theta, zeta*)

Three N-linked carbohydrate structures are predominantly of the tetra-antennary complex type. Characteristic for CHO glycosylation is a high degree of complex structures with LacNAc repeats (GlcNAc-Gal); there is a tendency to have smaller complex type structures (e.g., bi-antennary and tri-antennary on Asn 24, whereas Asn38 and Asn83 almost exclusively carry tetra-antennary structures with variable numbers of LacNAc repeats.

Minor structures, like high-mannose-types with phosphate groups can also be found if sophisticated analytical tools are applied, as well as hybrid-type structures.

Sialic acids (mainly NeuAc) are bound exclusively α2–3 to galactose as CHO cells lack the enzyme for the formation of α2–6 linkages found on human glycoproteins. A small percentage (approximately 1%) of the sialic acid appears as N-glycolyl-neuraminic acid (NeuGc).

There are quantitative differences in the glycosylation patterns of *epoetin alfa, beta and zeta* reflecting the actual CHO production clone and unique production

process used. The glycosylation profile of epoetin theta has not been released yet. The O-linked carbohydrate is smaller and consists of 2 to 4 sugars bound to Serine-126. (See Figures 1 and 2 below).

As an example, statements from the European Public Assessment Reports (EPAR) of two biosimilar epoetins developed using epoetin alfa (Eprex®) as the reference product describing carbohydrate similarities and differences highlight the issue of using glycosylation patterns as a discriminator for different epoetins:

Binocrit® (epoetin alfa)
"Differences were observed at the glycosylation level. Phosphorylated high mannose type structures in HX575 were detected at higher levels than in Eprex/ Erypo®".

Silapo® (epoetin zeta)
"With respect to the glycan moieties, the overall range of structures was found to be comparable. Even upon sub-fractionation of glycans of both products a very similar profile with respect to antennarity and sialylation was revealed. However, the amount of glycoforms without an O-glycan chain was slightly higher for epoetin zeta as compared to epoetin alfa. On the other hand, the amounts of undesired variants of sialic acid, N-glycolyl neuraminic acid and O-acetyl neuraminic acid were higher in the reference product as compared to epoetin zeta".

BHK derived product (*epoetin omega*)
Nimtz et al (1) reported a significant amount (2 to 4 %) of phosphorylated high-mannose type structures on the Asn-24 glycosylation site, otherwise a very similar carbohydrate pattern, as seen in erythropoietin from CHO cells, was observed. Since phosphorylated high-mannose structures are also found in erythropoietins from CHO cells (although in somewhat lower amounts) this feature does not qualitatively differentiate BHK-derived erythropoietin from CHO-derived erythropoietin.

Figure 1. Main N-linked carbohydrate structures of erythropoietin (terminal sialic acids omitted)

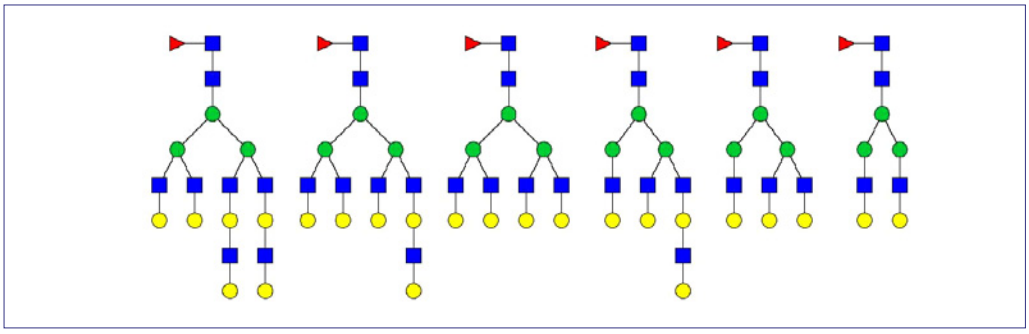
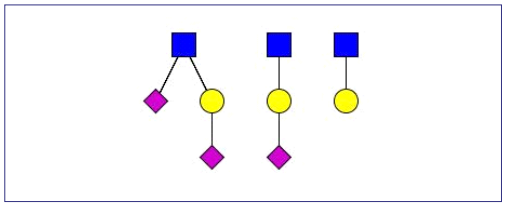


Figure 2. Main O-linked carbohydrate structures of erythropoietin



Codes

- Mannose(Man)
- N-acetylglucosamine (GlcNAc)
- Galactose (Gal)
- Fucose(Fuc)
- N-acteylneuraminic acid (NeuAc)

HT1081 derived product (*epoetin delta*)
Llop et al (2) report on the carbohydrate pattern of epoetin delta and conclude that the pattern is similar to CHO-derived epoetins with slightly less bi- and tri-antennary structures. Neu5Gc cannot be found in *epoetin delta* as humans cells cannot synthesize this sialic acid variant. But since it is only a minor component in CHO-derived products it is not suitable as a general analytical feature to distinguish CHO-derived from human-cell derived products.

Conclusion

All epoetins (regardless of INN) exhibit a glycosylation pattern which is quantitatively different from each other and mainly reflects the individual production cell clone and the unique production process. Even small differences in the glycosylation pattern may or may not have an impact on clinically relevant parameters like in vivo elimination time and safety. The complexity of the glycosylation pattern does not allow a prediction based solely on analytical data if the comparison can only be carried out at final product level. The situation is different if small changes in the glycosylation pattern can be followed over time within an established production process with all analytical and clinical data available to the manufacturer.

Even greater differences in the glycoform pattern have been observed among various epoetin products marketed outside the European Union, USA, and Japan which were developed independently without adequate proof of similarity to a reference product. These are, nevertheless, often marketed using the INN epoetin alfa (3–5).

Since both the cell line and the production processes define the glycosylation pattern, a unique INN for each independently manufactured epoetin is fully justified.

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Safety and Efficacy Issues

Didanosine: serious liver disorder

United States of America — The Food and Drug Administration (FDA) is alerting healthcare professionals to the risk of non-cirrhotic portal hypertension in patients using didanosine (Videx® or Videx EC®). Didanosine is used to treat human immunodeficiency virus (HIV) infection.

The FDA became aware of cases of non-cirrhotic portal hypertension through adverse event reports. The FDA believes the clinical benefits of didanosine for certain patients with HIV continue to outweigh its potential risks. The decision to use this drug, however, must be made on an individual basis between the treating physician and the patient. Didanosine already has a boxed warning for lactic acidosis and hepatomegaly with steatosis. Didanosine in combination with other antiretroviral agents as well as hydroxyurea or ribavirin has been associated with the development of liver toxicity.

Reference: *MedWatch Alert,* 29 January 2010 at http://www.fda.gov

Bortezomib: updated safety information

United States of America — The new label for bortezomib (Velcade®) contains important updates to the full prescribing information including dose adjustments for patients with moderate to severe hepatic impairment. Bortezomib is indicated for the treatment of patients with multiple myeloma or mantle cell lymphoma who have received at least one prior therapy.

A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely. Contraindications include hypersensitivity to bortezomib, boron, or mannitol. Velcade® should be administered under the supervision of a physician experienced in the use of antineoplastic therapy. Complete blood counts should be monitored frequently during treatment.

There have been reports of peripheral neuropathy, hypotension congestive heart failure and new onset of decreased left ventricular ejection fraction, acute diffuse infiltrative pulmonary disease of unknown etiology, reversible posterior leukoencephalopathy syndrome, nausea, diarrhoea, constipation, and vomiting, thrombocytopenia and neutropenia, gastrointestinal and intracerebral haemorrhage, tumour lysis syndrome, cases of acute liver failure.

Reference: Communication from the Takeda Oncology Company at http://www.fda.gov

Deferasirox: renal events and gastrointestinal haemorrhage

Canada — Deferasirox (Exjade®) is indicated in the management of chronic iron overload in patients with transfusion-dependent anaemias aged six years or older. The product is also indicated in the management of chronic iron overload in patients with transfusion-dependent anaemias aged two to five who cannot be adequately treated with desferoxamine.

Therapy with deferasirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

Review of adverse events for patients treated with deferasirox suggests a greater risk of kidney failure, gastrointestinal haemorrhage (potentially fatal) and deaths in patients with myelodysplastic syndrome (MDS) and in elderly patients compared to younger patients with other chronic anaemias such as α-thalassaemia and sickle cell disease. Many of the adverse events reported are common to elderly patients and patients with MDS, making it difficult to draw conclusions.

Risk factors for kidney failure include pre-existing compromised renal function, and it is therefore recommended that creatinine clearance (and/or serum creatinine) be assessed twice before initiating therapy. Weekly monitoring of creatinine clearance (and/or serum creatinine) is recommended in the first month after initiation or modification of therapy, and monthly thereafter.

Gastrointestinal haemorrhage is a known adverse reaction of deferasirox. There have been rare reports of fatal gastrointestinal haemorrhage, especially in elderly patients who had advanced haematologic malignancies and/or low platelet counts.

In the review of death cases in the MDS patient population, it was apparent that approximately two-thirds of deaths were in patients who had received less than six months of therapy, indicating that patients with advanced disease and a corresponding poor prognosis have been treated. These patients are unlikely to derive benefit from treatment with deferasirox.

Reference: Communication from Novartis Pharmaceuticals Canada Inc. dated 30 November 2009 at http://www.hc-sc.gc.ca

Sirolimus: drug monitoring assay comparison

Canada — Different laboratory assays used to measure sirolimus (Rapamune®) trough concentrations generate results that are not interchangeable. Healthcare professionals should be aware that the methods used to measure sirolimus whole blood concentration have a direct impact on the values obtained. Improper adjustment to the dose of sirolimus based on the use of differing assay methods can lead to allograft rejection (if the patient is underdosed) or toxicity (if the patient is overdosed).

Therapeutic drug monitoring is recommended for patients taking Rapamune®. Adjustments to the targeted range should be made according to the assay being used to determine the sirolimus trough concentration. Several immuno-assays have been developed that allow for rapid turnaround of results. Most immuno-assays have a positive bias of approximately 15–20% relative to the reference HPLC assay with detection by tandem mass spectrometry due to antibody cross-reactivity with sirolimus metabolites. However, it has recently come to the attention of the manufacturer that one of the more commonly used immunoassay platforms, IMx®, generally yields results with a negative bias of approximately 10% relative to HPLC/MS/MS.

Reference: Communication from Wyeth (Pfizer) dated 26 November 2009 at http://www.hc-sc.gc.ca and 20 January 2010 at http://www.hsa.gov.sg/publish/hsaportal/en/health_ products_regulation/safety_ information/DHCPL.html

Mycophenolate: pure red cell aplasia

Canada — The manufacturer of mycophenolate sodium (Myfortic®) has informed healthcare professionals of reports of pure red cell aplasia (PRCA) in patients when treated in combination with other immunosuppressive agents.

Mycophenolate sodium, an immunosuppressive agent, is currently indicated for the prophylaxis of organ rejection in

patients receiving allogeneic renal transplants, administered in combination with cyclosporine, and corticosteroids.

PRCA is a type of anaemia that develops secondary to failure of erythropoiesis. PRCA describes a condition in which RBC precursors in bone marrow are nearly absent, while megakaryocytes and white blood cell precursors are usually present at normal levels. PRCA may be idiopathic or occur as a manifestation of an underlying condition. Approximately 5% of all cases of PRCA are drug induced. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin (pallor). Anaemia is the primary clinical concern in PRCA. The degree of anaemia can range from subclinical to severe. Anaemia in acute self-limited PRCA is barely noticeable; however, profound anaemia can occur in chronic acquired PRCA and in congenital PRCA. Patients with severe anaemia have symptoms and signs of uncompensated anaemia and present with weakness, tachycardia, and dyspnoea.

As of 31 October 2009, between five and ten cases of PRCA out of an estimated cumulative worldwide exposure of 208 978 patient-years have been reported in patients receiving Myfortic® in combination with other immunosuppressive agents (such as tacrolimus, cyclosporine, corticosteroids). No cases are from Canada.

Reference: Communication from Novartis Pharmaceuticals Canada Inc. dated 21 December 2009 at http://www.hc-sc.gc.ca

Fosamprenavir: myocardial infarction and dyslipidaemia

United States of America — Fosamprenavir calcium is indicated in combination with other antiretroviral agents for the treatment of HIV infection. The manufacturer of fosamprenavir calcium (Lexiva®) has informed healthcare professionals of a potential association between fosamprenavir calcium and myocardial infarction in HIV-infected adults.

Elevations in triglyceride levels are already described in the prescribing information which has now also been modified to highlight that increases in cholesterol have occurred with treatment. This statement includes a recommendation that triglyceride and cholesterol testing should be performed prior to initiating therapy with fosamprenavir calcium tablets and oral suspension and at periodic intervals during therapy.

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Exenatide: altered kidney function

United States of America — The Food and Drug Administration (FDA) has approved revisions to the drug label for exenatide (Byetta®) to include information on post-marketing reports of altered kidney function, including acute renal failure and insufficiency.

Exenatide, an incretin-mimetic, is approved as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

From April 2005 through October 2008, the FDA has received 78 cases of altered

kidney function. Some cases occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing kidney problems.

Revisions to the drug label include:

- Byetta® should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease.
- Caution should be applied when initiating or increasing doses of Byetta® from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min).
- Patients should be monitored carefully for the development of kidney dysfunction and evaluate continued need if kidney dysfunction is suspected while using the product.

Reference: *MedWatch Alert,* 2 November 2009 at http://www.fda.gov

Drospirenone in oral contraceptives

Saudi Arabia — Recently, the Saudi Food and Drug Authority's (SFDA) National Drug and Poison Information Center (NDPIC) has received questions from patients and healthcare professionals about the safety of two combined oral contraceptive drugs Yasmin® and Yaz®.

Yasmin® is different from other birth-control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, patients with kidney, liver or adrenal disease should not take Yasmin®. Other drugs may also increase potassium and patients who are currently on daily, long-term treatment for a chronic condition should consult their healthcare provider about whether Yasmin® is safe for use and, during the first month of use, a blood test to check potassium levels should be performed.

The use of oral contraceptives is associated with increased risk of several serious conditions including venous and arterial thrombotic and thromboembolic events. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidaemias, obesity and diabetes.

Reference: *Press Release*, Saudi Food and Drug Authority, 1 March 2010 at http://www.sfda.gov.sa/En/Drug/News/697

Glucose test strips

Saudi Arabia — The Saudi Food and Drug Authority's (SFDA) National Center for Medical Devices Reporting has found that test strips to measure blood glucose by the glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) method cannot distinguish between glucose and other non-glucose sugars, including maltose, xylose, and galactose found in certain drug and biological formulations or resulting from the metabolism of a drug or therapeutic product. This leads to inaccurate readings and possibly inappropriate medical intervention.

Therefore SFDA has advised healthcare providers to refer to device labelling to confirm the used blood sugar measuring methodology. SFDA advice to the public is to stop using these strips since there are other glucose test strip methodologies not affected by the presence of non-glucose sugars.

Reference: *Press Release*, Saudi Food and Drug Authority, 22 December 2009 at http://www.sfda.gov.sa/En/Drug/News/697

HIV drug combination: safety review of clinical trial data

United States of America — The Food and Drug Administration (FDA) is reviewing clinical trial data about a potentially serious effect on the heart from the use of the antiretroviral medications saquinavir

(Invirase®) in combination with ritonavir (Norvir®). The data suggest that together the two drugs may affect the electrical activity of the heart.

Saquinavir and ritonavir should not be used in patients already taking medications known to cause QT interval prolongation or in patients with a history of QT interval prolongation.

Reference: *FDA Safety Announcement*, 23 February 2010 at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrug SafetyInformationforPatientsandProviders/ucm201221.htm

Sibutramine: ongoing safety review

United States of America — The Food and Drug Administration (FDA) has notified healthcare professionals of a review of additional data indicating an increased risk of heart attack and stroke in patients with a history of cardiovascular disease using sibutramine. Based on the serious nature of the review findings, a new contraindication has been added to the sibutramine drug label stating that sibutramine is not to be used in patients with a history of cardiovascular disease, including:

- History of coronary artery disease; stroke or transient ischemic attack; heart arrhythmias; congestive heart failure; or peripheral arterial disease.
- Uncontrolled hypertension.

Patients currently using sibutramine should talk with their healthcare professional to determine if continued use of sibutramine is appropriate and discuss any questions they may have about their treatment.

References

1. *MedWatch Alert:* Meridia® (sibutramine hydrochloride): Follow-Up to an Early Communication about an Ongoing Safety Review, dated 21 January 2010 at http://www.fda.gov

2. *MedWatch Alert:* Follow-Up to the November 2009 Early Communication about an Ongoing Safety Review of Sibutramine, Marketed as Meridia®, dated 21 January 2010 at http://www.fda.gov

Becaplermin: contraindication in patients with cancer

European Union — Following a review of the available data on a possible risk of cancer in patients using becaplermin (Regranex®), the European Medicines Agency (EMEA) has concluded that the medicine must not be used in patients who have any form of cancer. A similar restriction previously applied, but only for patients who had a skin cancer close to the area where the gel was to be applied.

Regranex® is a gel that is used together with other wound care measures to treat long-term skin ulcers in people with diabetes.

Reference: *Press Release*, http://www.emea.europa.eu and http://www.ema.europa.eu/ humandocs/PDFs/EPAR/Regranex/31245209en.pdf

ACSOM — advisory committee on safety of medicines

Australia — A new expert advisory committee on medicines safety, called the Advisory Committee on the Safety of Medicines (ACSOM), has replaced the Adverse Drug Reactions Advisory Committee (ADRAC). This new committee exists as a statutory committee in its own right and has broader and enhanced terms of reference compared to ADRAC. A key role of ACSOM will be the provision of expert advice to the Therapeutic Goods Administration (TGA) about the appropriateness of risk management plans and risk minimization strategies for new high-risk medicines.

Reference: Therapeutic Goods Administration, *Medicines Safety Update*, No.1, 2010 at http://www.tga.gov.au

Regulatory Scope

Tobacco product regulation

Regulation of tobacco products is endorsed by the WHO Framework Convention on Tobacco Control. Regulation serves public health goals by providing an understanding of tobacco products and meaningful surveillance of their manufacture, packaging, labelling and distribution. Tobacco product regulation includes regulation of the contents and emissions of tobacco products by testing, measuring and mandating disclosure of the results and regulating their packaging and labelling.

Chemical consumer products are usually regulated after a review of the scientific evidence on the hazards presented by the product, the exposure likely to occur, the patterns of use and the marketing messages of the manufacturer. Many jurisdictions require manufacturers to classify and label products according to their hazardous properties, to control the hazardous contents or to limit the advertising, promotion and sponsorship of such products. Electronic nicotine delivery systems deliver nicotine and other substances but do not contain tobacco, and smokeless tobacco is produced in 'cottage' industries or can be modified significantly by the end user. Both therefore pose a significant challenge to regulation, as they may fall outside the scope of domestic regulatory regimes for tobacco products. Nevertheless, their popularity and the fact that they are marketed as alternatives to cigarette smoking indicate the need to characterize them, regulate them and ensure that the public is properly informed of the potential health hazards of these products.

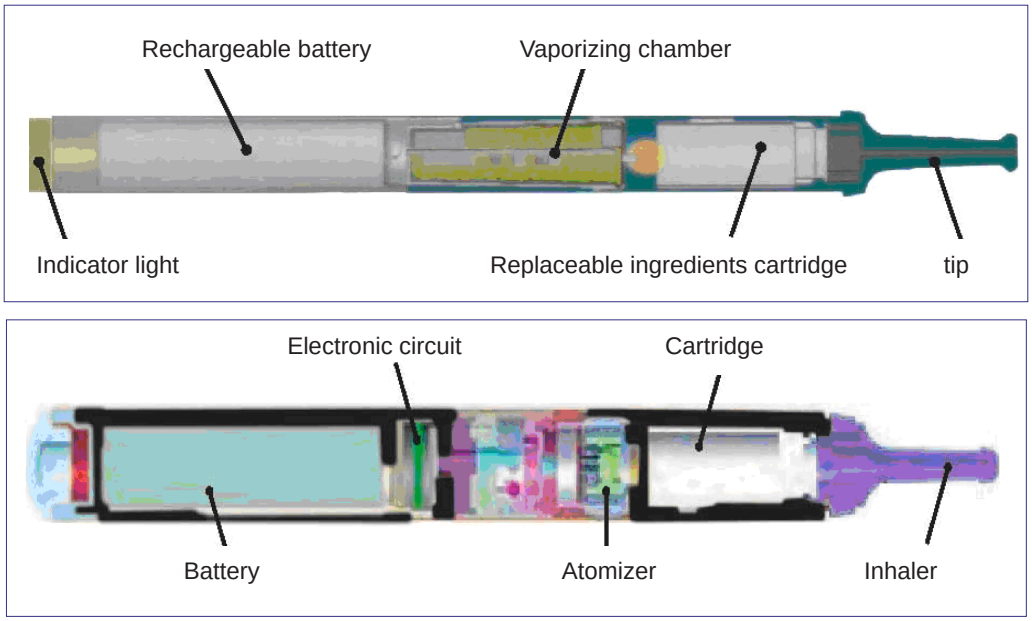
Electronic nicotine delivery systems

The WHO Study Group on Tobacco Product Regulation (TobReg) reviews the scientific evidence on topics related to tobacco product regulation and identifies the research needed to fill regulatory gaps in tobacco control. The Study Group is composed of national and international scientific experts on product regulation, treatment of tobacco dependence and laboratory analysis of tobacco ingredients and emissions.

At its fifth meeting, the Study Group addressed regulation of electronic cigarettes, smokeless tobacco toxicants, 'roll-your-own' products, products marketed as cessation aids, particles in smoke and menthol. The meeting followed a WHO press release in 2008, which asserted that WHO does not consider electronic cigarettes to be a legitimate tobacco cessation therapy.

The TobReg recommendations address electronic nicotine delivery systems (ENDS) designed for nicotine delivery to the respiratory system. This designation encompasses products that contain tobacco-derived substances but in which tobacco is not necessary for their operation. ENDS are marketed under a variety of brand names and descriptors, including 'electronic cigarettes', 'ecigarro', 'electro-smoke', 'green cig' and 'smartsmoker'. ENDS pose significant public health issues and raise questions for tobacco control policy and regulation because:

Figure 1. Prototype e-cigarette devices



- Manufacturers have not fully disclosed the chemicals used in ENDS;
- There are few data on emissions or actual human exposure;
- The health effects have not been studied;
- Marketing and use could undermine public smoking bans, which are important tobacco control interventions;
- Products could also undermine smoking cessation efforts by proposing unproven devices for smoking cessation in the place of products of proven efficacy.
- ENDS might also undermine the prevention of tobacco use because of their appearance and marketing as safe alternatives to tobacco products for non-tobacco users, including children.

ENDS fall into a regulatory gap in most countries, escaping regulation as drugs and avoiding the controls levied on tobacco products. An important regulatory consideration is the validity of the marketing claims made for the products, which include statements that ENDS are smoking cessation aids and that they deliver safer nicotine but at variable levels compared to those in cigarettes.

ENDS are a category of consumer products designed to deliver nicotine to the lungs after one end of a plastic or metal cylinder is placed in the mouth, like a cigarette or cigar, and inhaled to draw a mixture of air and vapours from the device into the respiratory system (see figure 1). They contain electronic vaporization systems, a rechargeable battery and charger, electronic controls and replaceable cartridges that may contain nicotine and other chemicals. Some brands are claimed to deliver a range of nicotine concentrations or no nicotine at all, and some are claimed to provide sensory experiences similar to those obtained with major cigarette brands. The

chemicals used to produce the odours and flavours that simulate those of cigarettes have not all been identified, although some products claim to include 'menthol'. Some devices have light-emitting diodes, to reproduce the appearance of a burning cigarette tip. The premise stated by some marketers of the products is that ENDS provide nicotine that would otherwise be obtained by tobacco use.

The United States Food and Drug Administration recently analysed the chemicals in 18 varieties of ENDS cartridges marketed with two different brands and found significant variation in contents and deliveries. Several contained "detectable levels of nitrosamines, tobacco-specific compounds known to cause cancer". The Administration's testing also revealed that the nicotine levels were inconsistent with the information on the cartridge labels and that some cartridges that were stated not to contain nicotine actually did.

Delivery of nicotine to the lung raises concern about safety and addiction that go beyond that related to currently approved nicotine replacement therapy. Concern about the safety of ENDS is associated with the probable exposure of the lung to repeated dosing, perhaps hundreds of times a day for many months, if these products are used as a smoking cessation aid, or for years, for smokers who use them as long-term cigarette substitutes. An added concern is the safety of the chemical combinations in various ENDS cartridges, which have not been evaluated for either short-term or long-term safety. It is possible that at some time in the future ENDS might be developed as smoking cessation aids. However, currently, the evidence is insufficient to conclude that any of the ENDS products is an effective smoking cessation aid.

In summary, claims for the effectiveness of ENDS for smoking cessation and other health effects must be substantiated by rigorous studies of pharmacokinetics, trials of safety and efficacy and review and approval by major drug regulatory authorities. The types of data and studies that would be required include:

- Complete listing of the chemicals used in ENDS products.
- Listing and reporting of the concentrations of chemicals delivered to the consumer.
- Comparisons of the effect of ENDS on smoking cessation with that of approved nicotine replacement therapies and placebo.
- Adverse effects of these products.

Reference: World Health Organization. WHO Study Group on Tobacco Poduct Regulation. *Technical Report Series*, No. 955 (2009).

Regulatory Action and News

Influenza vaccines: 2010–2011 northern hemisphere

World Health Organization — Pandemic influenza A(H1N1) viruses emerged in March 2009 and remain globally predominant, while seasonal influenza A(H1N1), A(H3N2) and B viruses circulated at very low levels in many countries during the period September 2009 to January 2010.

Pandemic A(H1N1) 2009 viruses were antigenically and genetically similar to A/California/7/2009. Vaccines containing A/California/7/2009 antigen stimulated anti-HA antibodies of similar titres against the vaccine virus and recent pandemic A(H1N1) 2009 viruses.

Very few seasonal influenza A(H1N1) viruses were reported. Of these, the majority were antigenically and genetically similar to the (previous northern hemisphere) vaccine virus A/Brisbane/59/2007.

It is recommended that the following viruses be used for influenza vaccines in the 2010–2011 influenza season (northern hemisphere):

- an A/California/7/2009 (H1N1)-like virus;
- an A/Perth/16/2009 (H3N2)-like virus (A/Wisconsin/15/2009 is an A/Perth/16/2009 (H3N2)-like virus and is a 2010 southern hemisphere vaccine virus);
- a B/Brisbane/60/2008-like virus.

As in previous years, national or regional control authorities approve the composition and formulation of vaccines used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine.

Reference: Recommended viruses for influenza vaccines for use in the 2010–2011 northern hemisphere influenza season. *Weekly Epidemiological Record*, **85**:10 (2010).

European Medicines Agency: new organizational structure and visual identity

European Union — The European Medicines Agency officially unveiled a package of changes on 8 December 2009 with the launch of a new organizational structure and new visual identity.

Among the highlights of the new organizational structure is the integration of human pre- and post-authorization activities into one unit, to guarantee seamless lifecycle-management of medicines. The creation of a new unit for patient health protection further strengthens the Agency's focus on safety-monitoring of medicines. In addition, a dedicated group for the management of product data and documentation will improve the efficiency of data management processes throughout the Agency.

A new public web site for the Agency is nearing the end of development and will be launched in the coming months. With the current website being visited more than 700 000 times each month, the new site is being designed with the needs of the public in mind, offering improved navigation and search functionality, providing better access to information on public-health issues.

Reference: *Press Release*, EMA/704918/2009, 8 December 2009 at http://www.ema.europa.eu/

Risk management systems for medicinal products

Australia — In April 2009 the Therapeutic Goods Administration (TGA) formally adopted the European Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

Applications for the registration of certain higher risk prescription medicines (new chemical entities, applications for paediatric use, new dosage forms, new routes of administration and significant extensions of indication) are now required to include a Risk Management Plan as part of the application.

The Risk Management Plan is meant to document not only what is known about the safety of the medicine at that particular point in time (termed the Safety Specifications), but also potential risks that require further elucidation and how the sponsor intends to investigate those risks.

Reference: Therapeutic Goods Administration, *Medicines Safety Update*, No.1, 2010 at http://www.tga.gov.au

Relative effectiveness assessments: joint action

European Union — The European Medicines Agency and representatives from the European network for Health Technology Assessment (EUnetHTA) Joint Action met in London on 11 February 2010 for the first of a series of workshops. This initiates a new collaboration, in which the European Medicines Agency and EUnetHTA will be considering how the European Public Assessment Report (EPAR) could make a better contribution to the assessment of relative effectiveness by health technology assessment bodies in the EU Member States.

Relative effectiveness assessments are increasingly used in the European Member States to help policy makers to identify the most valuable medicines.

Reference: CHMP assessment templates and guidance at http://www.ema.europa. eu/htms/human/chmptemplates/artemplates.htm

NIH and FDA: fast-track innovations

United States of America — The Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have unveiled an initiative designed to accelerate the process from scientific breakthrough to the availability of new, innovative medical therapies for patients.

The initiative involves two interrelated scientific disciplines:

- Translational science, the shaping of basic scientific discoveries into treatments.

- Regulatory science, the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality.

Both disciplines are needed to turn biomedical discoveries into products that benefit people.

As part of the effort, the agencies will establish a Joint NIH-FDA Leadership Council to spearhead collaborative work on important public health issues. The Joint Leadership Council will work to ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process.

In addition, the NIH and the FDA will jointly issue a Request for Applications, making US$ 6.75 million available over three years for work in regulatory science.

Reference: *FDA – NIH News Release*, 24 February 2010 at http://www.fda.gov and http://.www.nih.gov4.

Orciprenaline sulphate: registration cancelled

Saudi Arabia — The Saudi Food and Drug Administration (SFDA) has announced the cancellation of orciprenaline sulphate (Alupent®) registration due to its hazards to the heart and the availability of more safe alternative drugs.

Accordingly, the Drug Products and Manufacturers' Registration Committee decided to cancel registration of this product and recall it from the market. SFDA also asked the manufacturer to recall any available stocks from the local market to protect the health of the public. SFDA requests all concerned to use other alternative drugs.

Reference: Communication dated 15 February 2010 at www.sfda.gov.sa/ar/drug

Peramivir IV: emergency use authorization

United States of America — The Food and Drug Administration (FDA) has notified healthcare professionals that, in response to a request from the Centers for Disease Control and Prevention, it has issued an emergency use authorization (EUA) for the investigational antiviral drug peramivir in certain adult and paediatric patients with confirmed or suspected 2009 H1N1 influenza infection who are admitted to a hospital. IV peramivir is authorized only for hospitalized adult and paediatric patients for whom therapy with an IV drug is clinically appropriate.

Given that limited safety data are available on peramivir, mandatory reporting requirements are in place for this unapproved drug.

Reference: *FDA News*, 23 October 2009 http://www.fda.gov

Carisbamate: withdrawal of marketing authorization application

European Union — The manufacturer of carisbamate (Comfyde®) has notified the European Medicines Agency () of its decision to withdraw its application for a centralized marketing authorization for the medicine Comfyde®.

This medicine was intended to be used for adjunctive treatment of partial onset seizures with or without secondary generalization in patients aged 16 years or older.

The decision to withdraw the application was based on feedback from the Committee on Human Medicinal products (CHMP) indicating that the Committee is unlikely to reach a favourable opinion without additional efficacy data, which at this time cannot be provided.

Reference: *Press Release*, EMA/32401/2010, 20 January 2010. http://www.ema.europa. eu/

Benfluorex withdrawal

European Union — The European Medicines Agency has recommended the withdrawal of all medicines containing benfluorex in the European Union because their risks, particularly the risk of heart valve disease, are greater than their benefits.

Doctors should stop prescribing benfluorex-containing medicines and consider alternative treatments. Because heart valve disease can develop some years after treatment, patients who have taken benfluorex in the past should tell their doctor so that they can be checked

for the signs and symptoms of heart valve disease.

Benfluorex is approved for use in overweight patients with diabetes, combined with an appropriate diet.

Reference: *Press release*,EMA/CHMP/815033/2009, 18 December 2009 at http://www.ema.europa.eu/

Ethyl eicosapent: withdrawal of marketing authorization application

European Union — The manufacturer of ethyl eicosapent (Ethyl Eicosapent®), 500 mg soft gelatine capsules has notified the European Medicines Agency of its decision to withdraw its application for a centralized marketing authorization.

Ethyl eicosapent was expected to be used for the long-term stabilization of symptoms in patients with Huntington disease, a hereditary neurological disorder of the central nervous system that causes progressive degeneration of cells in the brain.

Withdrawal of the application was based on preliminary comments which indicate that the CHMP is unlikely to conclude a favourable opinion without additional efficacy information.

Reference: *Press Release*, EMA/796337/2009, 8 December 2009 at http://www.ema.europa.eu/

Olanzapine approved in adolescents

United States of America — The Food and Drug Administration (FDA) has approved of the use of oral olanzapine (Zyprexa®) in adolescents (ages 13–17).

Olanzapine is indicated for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential for weight gain and hyperlipidaemia.

It is recommended that medication therapy for paediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both paediatric schizophrenia and bipolar I disorder should be part of a total treatment programme that includes psychological, educational and social interventions.

The types of adverse events observed in adolescents were similar to those seen in adult patients. However, the magnitude and frequency of some events were greater in adolescents than in adults. Compared to patients from adult clinical trials, adolescents were likely to gain more weight and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels, and sedation.

Reference: *FDA News*, 24 October 2009 http://www.fda.gov

Lisuride: withdrawal of marketing authorization application

European Union — The manufacturer of lisuride (Nenad®) has notified the European Medicines Agency of its decision to withdraw its application for a centralized marketing authorization for the Nenad®, 2.5 and 5.0 microgram/h transdermal patch. Nenad® was expected to be used in adults with moderate-to-severe idiopathic restless legs syndrome.

Withdrawal of the application was based on the CHMP's view that the data pro-

vided do not allow the Committee to conclude on a positive benefit-risk balance in the claimed indication.

Reference: *Press Release*, Doc. Ref. EMEA/781919/2009. 3 December 2009 at http://www.ema.europa. eu/

Velaglucerase alfa approved for Gaucher disease

United States of America — The Food and Drug Administration (FDA) has approved velaglucerase alfa for injection (VPRIV) to treat children and adults with a form of the rare genetic disorder, Gaucher disease.

VPRIV provides long-term enzyme replacement therapy for Type 1 Gaucher disease, the most common form of the genetic disorder. It is an alternative to imiglucerase (Cerezyme®), another enzyme replacement therapy.

The most common adverse reactions to VPRIV are allergic reactions. Other observed adverse reactions with VPRIV are headache, dizziness, abdominal pain, back pain, joint pain, nausea, fatigue/weakness, fever, and prolongation of activated partial thromboplastin time, a measure of clotting time.

Reference: *FDA News Release*, 26 February 2010 at http://www.fda.gov and http://www.ninds.nih.gov/disorders/gauchers/gauchers.htm 2

Pneumococcal 13–valent conjugate vaccine approved

United States of America — The Food and Drug Administration (FDA) has approved Prevnar 13®, a pneumococcal 13-valent conjugate vaccine for infants and young children ages 6 weeks through 5 years. Prevnar 13® will be the successor to Prevnar®, the pneumococcal 7-valent conjugate vaccine licensed by the FDA in 2000 to prevent invasive pneumococcal disease (IPD) and otitis media. The new vaccine extends the protection to six additional types of the disease causing bacteria.

Prevnar 13® is approved for the prevention of invasive disease caused by 13 different serotypes of the bacterium *Streptococcus pneumoniae*. It also is approved for the prevention of otitis media caused by the seven serotypes shared with Prevnar®. The bacterium can cause infections of the blood, middle ear, and the covering of the brain and spinal cord, as well as pneumonia.

Common adverse reactions reported after administration of Prevnar 13® were pain, redness and swelling at the injection site, irritability, decreased appetite and fever.

Reference: *FDA News Release*, 24 February 2010 at http://www.fda.gov

Monoclonal antibody products approved for chronic lymphocytic leukaemia

United States of America — The Food and Drug Administration (FDA) has approved the monoclonal antibody rituximab (Rituxan®) to treat certain patients with chronic lymphocytic leukaemia (CLL), a slowly progressing blood and bone marrow cancer.

Rituximab, an anti-cancer drug, is intended for patients with CLL who are beginning chemotherapy for the first time and for those who have not responded to other cancer drugs for CLL. Rituximab is administered with two other chemotherapy drugs, fludarabine and cyclophosphamide.

FDA approved ofatumumab (Arzerra®) in October 2009 for patients whose cancer is no longer being controlled by other forms of chemotherapy and bendamustine (Treanda®) in March 2008 for

patients with CLL who had not received prior treatment.

Rituxan® carries a boxed warning for infusion reactions. A decrease in normal white blood cells was also commonly observed in patients enrolled in the clinical trials. Other boxed warnings for Rituxan® include rashes and sores in the skin and mouth; progressive multifocal leukoencephalopathy (PML); and tumour lysis syndrome.

Reference: *FDA News Release*, 2 February 2010 at http://www.fda.gov

Rosuvastatin: new indication approved

United States of America — The Food and Drug Administration (FDA) has approved the cholesterol-lowering medication rosuvastatin (Crestor®) for some patients who are at increased risk of heart disease but have not been diagnosed.

The new indication is for reducing the likelihood of a heart attack or stroke or the need for a procedure to treat blocked or narrowed arteries in patients who have never been told they have heart disease but are nevertheless at increased risk of a cardiac event.

Specifically, this includes men 50 years of age and older and women 60 years of age and older who have an elevated amount of a substance known as high sensitivity C-reactive protein in their blood and at least one additional traditional cardiovascular risk factor such as smoking, high blood pressure, a family history of premature heart disease, or low amounts of high-density lipoprotein or HDL cholesterol.

Reference: *FDA News Release*, 9 February 2010 at http://www.fda.gov

Influenza A/H1N1: collection–to–detection assay

United States of America — The manufacturer of Longhorn Influenza A/H1N1-09 Prime RRT-PCR Assay® has been granted Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) for a ready-use assay that requires no mixing prior to use.

The device includes PrimeStore®, a clinical collection and transport solution that preserves the released nucleic acids, including labile RNA for testing and contains an internal positive control, providing the first specimen collection solution to contain an internal RNA control capable of tracking the degradation of the sample from the point of collection.

Reference: Longhorn Vaccines & Diagnostics, *New Release,* 22 February 2010 at http://www.lhnvd.com

Recent Publications, Information and Events

TSE tissue infectivity distribution update

The data reported in the World Health Organization (WHO) *Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies* were originally assembled by an expert group appointed during a WHO Consultation held in 2003 and subsequently updated during a later Consultation held in 2005. As new information became available, the tables were updated and now reflect the current status of knowledge about infectivity in body tissues, secretions, and excretions of humans with sporadic or variant Creutzfeldt-Jakob disease (CJD); cattle with typical or atypical bovine spongiform encephalopathy (BSE); sheep with scrapie and, (for the first time), deer or elk with chronic wasting disease (CWD).

It is not the purpose of the document to revise the current *WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies* published in 2006, which remain valid, but new information on tissue infectivity distribution is important in the context of potential transmission of variant CJD through human blood and blood products, as well as through medicinal products prepared with bovine-derived materials, and may have implications for future recommendations.

Since the publication in 2006 of *Major Categories of Infectivity,* Annex 1 in the *WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies*, some tissues (ovary, uterus, mammary glands/udder, skin, adipose tissue, and heart/pericardium) and body fluids (saliva, milk, urine, and faeces) in which infectivity had not been detected, have since been found to contain infectivity or PrPTSE and therefore have been moved from the category of ‘‘tissues with no detectable infectivity’’ ’’ to the category of ‘‘lower-infectivity tissues.’’

The inclusion of infectivity data in CWD in these Tables was considered important for three reasons:

- CWD is continuing its spread to new regions of North America.
- Infectivity has been convincingly demonstrated in several bodily secretions and excretions of infected deer.
- CWD is the only form of animal transmissible spongiform encephalopathy (TSE) that exists in the wild and, although not presently considered to be an important concern for humans, could pose serious problems of control in the future, especially as a potential source of infection in other animal species.

Reference: World Health Organization. *Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies*. WHO/EMP/QSM/2010.1 at http://www.who.int/medicines

Restricted availability of opioids for cancer patients

A report regarding the regulations and restrictions preventing cancer patient access to medication to relieve strong cancer pain has been released by the European Society for Medical Oncology (ESMO) and the European Association for Palliative Care (EAPC).

The study, published online in *Annals of Oncology*, collected data from twenty-one

eastern European countries and twenty western European countries to evaluate the availability of official lists of allowed opioid drugs (formulary) for the management of strong pain, the cost of opioid medication to patients and the regulatory barriers that can make it more difficult, if not impossible, for cancer patients and their doctors to get access to these medications in a timely manner.

The study found that in many European countries (particularly in eastern Europe) the balance between enabling cancer patients to receive the pain relief that they need, while, at the same time, preventing prescription drugs being diverted for substance abuse in illicit drug markets, is weighted too much in favour of the latter.

References

1. Annals of Oncology, at http://www.oxfordjournals.org/our_journals/annonc/press_releases/freepdf/mdp581.pdf

2. European Society for Medical Oncology, at http://www.esmo.org

3. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative. *Annals of Oncology*, **21**: pp 615-626, 2010 DOI: 10.1093/annonc/mdp581

4. Access to therapeutic opioid medications in Europe by 2011? Fifty years on from the Single Convention on Narcotic Drugs. *Palliative Medicine*, **24**: pp109-110 DOI: 10.1177/0269216309360103

Transparency and the public pharmaceutical sector

The Assessment Tool for Measuring Transparency in the Public Pharmaceutical Sector represents the first step of a three-phase approach within The World Health Organization's Good Governance for Medicines (GGM) Programme started in late 2004. The goal of the GGM programme is to contribute to health systems strengthening and prevent corruption by promoting good governance in the pharmaceutical sector.

The purpose of the national assessment is to provide countries with a comprehensive picture of the level of transparency and potential vulnerability to corruption of the following eight functions of the pharmaceutical sector:

- Registration of medicines.
- Control of medicines promotion.
- Inspection of establishments.
- Control of clinical trials.
- Licensing of establishments.
- Selection of essential medicines.
- Procurement of medicines.
- Distribution of medicines.

The methodology probes the perception of pharmaceutical policy makers and other stakeholders about transparency and provides both qualitative and quantitative information on the level of transparency present in the eight areas.

The assessment should be viewed as a starting point for investigating weaknesses and strengths in the national medicine regulatory and supply management systems. It represents the beginning of a process aimed at bringing long-lasting changes through efforts to strengthen the national health systems. Twenty-six countries have adopted the GGM and conducted the assessment.

Reference: *Assessment Tool for Measuring Transparency in the Public Pharmaceutical Sector*. http://www.who.int/medicines/areas/policy/goodgovernance/