

WHO Drug Information

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Announcement

**The 15th International Conference
of Drug Regulatory Authorities (ICDRA)
will be hosted by the State Agency for
Medicines, Estonia, in collaboration with the
World Health Organization**

**Tallinn, Estonia
23 – 26 October 2012**

**Information and registration at:
<http://www.icdra.ee>
<http://www.who.int/medicines/icdra>**

Regulatory Harmonization

Regulator prequalification of medicines: a future concept for networking

Presented below is the first draft of a concept paper for discussion which is aimed at solving international procurement needs for quality assured essential medicines beyond what is today covered by the WHO Prequalification of Medicines Programme (PQP). It is hoped that this concept paper, developed by the Quality Assurance and Safety: Medicines (QSM) Team in the WHO Department of Essential Medicines and Health Products, may offer solutions to several existing problems in assuring the availability of essential medicines that meet international quality standards for international procurement. In particular:

- It offers a potential strategy for sustainability of prequalification of medicines in light of increasing globalization and humanitarian procurement demands.
- It builds on activities of both WHO and other parties and uses existing tools — such as the WHO assessment tool for regulatory authorities — and other approaches. (For example, vaccines prequalification which is linked to the maturity of medicines regulatory authority functions.) Henceforth, the medicines regulatory authority will carry out all necessary prequalification activities and have full responsibility for the product offered for international procurement.
- It focuses on developing certain regulatory capacities based on a modular approach by allowing functions to reach the desired level in a step-wise manner. This does not exclude countries from building additional modules themselves, with or without the help of WHO.
- It allows uncoupling of the quality standards of products available on the internal market from those to be offered for international procurement. Products targeted for international procurement must meet international standards and the approval process must comply with international transparency requirements, i.e., publicly-available inspection and assessment reports. For the internal market, it is anticipated that prequalification activities will have a spill-over effect and improve the quality of products nationally.
- It links the functions of assessing generic medicines for registration/marketing authorization to the desired level of standard, i.e., generics will be assessed and inspected against international standards.
- Its long-term ambition is to assemble procurement quality assurance initiatives which have become far too numerous and duplicative and place them where they belong. As a consequence, medicines regulatory authorities will do what they are mandated to do and procurers will no longer take on functions for which they are not designed: thus removing the potential for sacrifice of quality over price.

Comments and suggestions on this paper are most welcome and will facilitate further discussion on this concept. They should be sent to Angela Lopes at lopesa@who.int

Regulatory prequalification for quality medicines

Although coverage levels can still be improved (1), medicines are now available in low- and middle-income countries in numbers never before imagined. As an example, roughly four million people had access to antiretroviral therapy in sub-Saharan Africa in 2009: up from less than 50,000 in 2002 (2). Further, the number of artemisinin combination courses procured for malaria increased from 11 million in 2005 to 158 million in 2009 (3). In general, the increase in available medicines correlates with an explosion in global health funding in the last 10–15 years (4) and a concomitant proliferation of treatment initiatives for various infectious diseases.

In the case of AIDS specifically, the phenomenon also reflects a shift in public health thinking: where treatment has an equally important role to play as prevention (5). Well-known examples are the WHO/UNAIDS 3 by 5 initiative (5), the 2005 G8 pledge to work towards universal access to ARVs by 2010 (5) and, more recently, the WHO/UNAIDS-sponsored Treatment 2.0 (6).

The surge in available medicines is a tremendously positive development for global health and all efforts must now be focused on providing medicines of quality. At the beginning of the decade, when availability began to improve, quality assurance of medicines was difficult to set in place for many low- and middle-income countries, mainly through lack of regulatory capacity. Neither were procurement agencies staffed for this purpose.

As a consequence, WHO identified an urgent need for a quality assurance mechanism and established the Pre-qualification of Medicines Programme (PQP) in 2001 (7). Through PQP, medicines are reviewed and certified for quality so that procurers and medicines regulatory authorities can have access to

scientific guidance on the quality aspects of medicines which they purchase.

PQP has so far been extremely successful. However, due mainly to resource constraints its reach has remained targeted to public health priorities such as treatments for HIV, TB, malaria, reproductive health and diarrhoea (8). Meanwhile, where prequalification product information is lacking, some donors have gone on to develop their own criteria (9). This is problematic because it introduces a tension between price and quality. It is not uncommon for donors/procurers to purchase medicines at very low prices — creating a situation where insufficient emphasis is placed on quality aspects.

In the years ahead, there is no doubt that demand for generic medicines will increase, especially as efforts to treat noncommunicable diseases ramp up (10). WHO has prequalified hundreds of medicines (11) but the question now is whether it will have the resources to continue at an increased or even similar pace. Much of PQP is currently financed with global health aid which may, in all possibility, face a decline in the future (12). Limited resources are also an issue for other assurance programmes such as the President's Emergency Plan for AIDS Relief (PEPFAR) (13) Tentative Approval Initiative (14). Both PQP and PEPFAR espouse programmatic goals of country ownership. This means that countries will ultimately need to take over the responsibility of assuring quality medicines for themselves.

In conclusion, the present landscape has improved over what it was before PQP began operating but for the reasons described above future prospects are currently limited and operations may be difficult to sustain in the long term.

A global regulatory prequalification network

The present concept proposal develops a sustainable alternative to the current

landscape in the form of ***a global network of low- and middle-income country regulatory authorities to pre-qualify quality generic essential medicines for international procurement.***

The concept is based on six key features:

- Creation of a global network of low- and middle-income country medicines regulatory authorities.
- Gradual transfer of responsibility for prequalification of medicines from WHO to medicines regulatory authorities.
- Prequalification of medicines to be based on uniform quality standards.
- A focus on prequalifying generic medicines in the first instance with expansion to vaccines, blood and other biological products and medical devices, as necessary and appropriate.
- Prequalification of all generic essential medicines, both for adults and children.
- Offer of prequalified medicines which meet the criteria for international procurement.

There are many benefits to establishing a global network of low- and middle-income country regulatory authorities. A network can pool resources and particularly those of inspection. In the developing world, where regulatory capacities are not uniform or evenly distributed, countries could work together to identify who is good at a specific regulatory function and let that, or those, countries take the lead. This is especially important for small countries who may not be able to muster expertise in all regulatory areas but who can specialize in a given technical area.

As the network assumes responsibilities for prequalification and starts to be functional, it is envisioned that WHO will gradually hand over its prequalification activities. This would provide a sustainable win-win situation to all concerned players and a natural and beneficial evolution to PQP efforts. Regulators can

assume responsibility for assuring quality within their country, which is where the responsibility rightfully belongs, and WHO can refocus on its primary duties as a standard-setting organization and provider of scientific expertise and consensus.

Uniform quality standards would be a key feature of the network. This has implications for capacity building since some countries already have certain capacities needed to participate in the network and will be eager to showcase them. Other countries will need to improve to meet the standards of the network but, in doing so, will be strengthened.

All countries will benefit from learning from each other and from the external stakeholders providing support to the network — namely, WHO and stringent regulatory authorities. Uniform quality standards will also foster local manufacturing capacity, which is increasingly a goal of development-minded organizations like the African Union (15). Although meeting uniform quality standards may initially pose a considerable challenge, the reward for achieving prequalification will be access to the international procurement market. This will offer a major incentive for manufacturers to meet the network's quality standards and inspire their own regulatory authority to build the capacity necessary to assure products for international procurement.

An initial focus on prequalification of generic medicines is a key feature of the network. Where capacities are limited across the regulatory continuum, as they are in many low- and middle-income countries, a focus on assuring quality generics will develop a specific set of skills — but will not make too immediate a demand on regulators. There is a place for focused, objective-oriented capacity building and progress can be measured in very concrete ways, e.g., having in place functional regulatory modules and the capacity to assess, inspect, and ensure post-approval regulatory oversight

based on international standards, etc. If the network can master this process, it would be possible to consider expanding its focus to other areas beyond generics, including vaccines and other biological products, and potentially medical devices.

One of the most important outcomes of the network will be a dramatically improved access to quality-assured medicines. By aiming to prequalify all generic essential medicines rather than just a focused group, procurers and countries will be able to purchase many more medicines at generic prices, thereby ensuring treatment for illnesses beyond infectious diseases, including diabetes and hypertension.

A final key feature of the network is that the medicines it prequalifies will meet the requirements for international procurement. Currently, some of the largest initiatives like PEPFAR and The Global Fund to Fight AIDS, TB and Malaria (16) stipulate that the medicines they buy must be approved by stringent regulatory authorities or prequalified by WHO. As the network gains the trust of the international community, it could also be considered “stringent” with respect to prequalifying generic medicines. This is a positive move for several low- and middle-income countries that have aspirations to scale up regulatory capacity and be considered stringent within the limits of pre-defined regulatory functions such as assessment, inspection, approval and post-approval oversight of generic medicines.

There is also a potential benefit to programmes like PEPFAR which currently rely on the Food and Drug Administration (FDA) to tentatively approve antiretroviral medicines. FDA is proud of the contribution it has made but the effort requires money and staff resources and does not cover all the generics on the WHO Model List of Essential Medicines or those needed for the PEPFAR programme. A sustainable alternative is thus for the

network of regulators to prequalify generic medicines themselves.

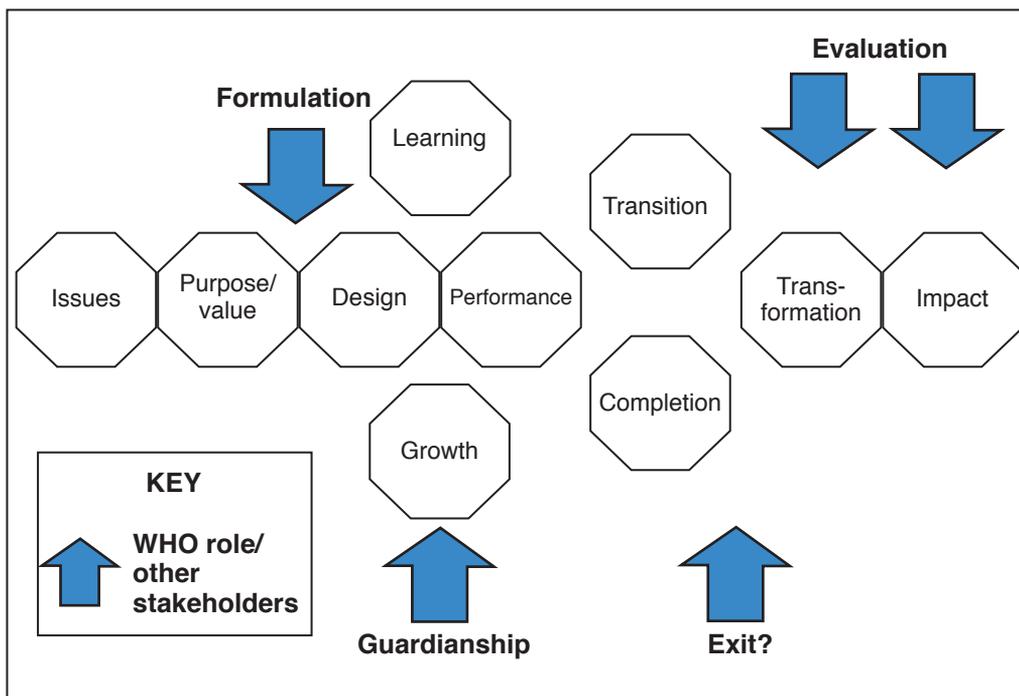
Political Support

There is a growing confluence of political support for regulatory capacity-building in the developing world. This need has recently been highlighted in a US Institute of Medicine report entitled, “Ensuring safe foods and medical products through stronger regulatory systems abroad” (17). It suggested ways that the international community could put regulatory system strengthening on the global health and development agenda. Also, there are a number of high-profile regulatory capacity building initiatives, either already under way, or planned in the future. The Pan American Health Organization (PAHO) is working with partners to assess regulatory systems in the Americas towards the goal of designating authorities as “regional references”. It has also launched an electronic platform to exchange regulatory system information between these countries (18).

The Bill & Melinda Gates Foundation (19) has funded the African Medicines Registration Harmonization Initiative (AMRH) (20) and is working with partners such as WHO, the New Partnership for Africa’s Development (NEPAD) (21), and the World Bank to help countries speed up product registration and implement appropriate unified product registration standards.

Looking towards the future, a 2012 UNAIDS Issue Brief entitled “AIDS dependency crisis: sourcing African solutions” proposes a single African medicines regulatory agency for the whole of Africa (22) and the African Union’s 2012 “Roadmap on shared responsibility and global solidarity for AIDS, TB and malaria response in Africa” (23) has called for this as well.

While a global prequalification network should not supplant other capacity building programmes, there are similarities

Diagram 1. Network Overview ⁽²⁵⁾

and synergies in rationale and approach which provide opportunities for leveraging. In fact, a 2012 World Bank paper was explicitly supportive of many of the features of the proposed global network, as well as the idea that activities should be leveraged. It said that the long-term goal of international donor aid for regulatory capacity should be “for developing countries to take the lead in ensuring the health of their citizens... [and] harmonization, coordination, and optimal leveraging of existing approaches may help national regulatory authorities to strengthen their own capacity to better control their markets, including registering products according to stringent standards” (24).

Network overview

Designing a network is a complex task and it is important to have a framework or some theoretical guidance when doing so. Diagram 1 sets out the key elements of a network and points out the role that

WHO and other external stakeholders should consider playing. This concept paper addresses all the pieces of the diagram except those covered by evaluation (transition, completion, transformation, impact) which is beyond its present scope.

Network design: functions

In keeping with its focus on prequalifying generic medicines, the proposed global network will initially perform at least the following core functions:

1. Assessment of generic product dossiers.
2. Assessment of generic product efficacy/safety.
3. Inspection of generic manufacturing plants.
4. Utilization of prequalified quality control laboratories for quality monitoring.

5. Transparent communication of pre-qualification information in general and about each individual product to the public and to other regulators in the network. In the case of regulator-to-regulator communication, this can also include information that goes beyond public information, depending on the given confidentiality arrangement.
6. Utilization of this information to make procurement decisions and national decisions about product approval (8). An implied function of the network is that it will also be doing capacity building, both by members as they work and learn together, and by external stakeholders who provide capacity building assistance and expertise where needed.

The regulatory functions of the network correspond to well-established scientific principles for regulation of generic medicine, i.e., a generic medicine must be the same as the original product (comparator) in terms of efficacy, safety, and quality and it should be therapeutically and pharmaceutically equivalent (8).

Bioequivalence, the standard for therapeutic equivalence, is evaluated by comparing the difference between a generic and comparator in a pharmacokinetic study with human subjects (8). In scientifically justifiable cases a biowaiver procedure is allowed in which bioequivalence is proven based on in vitro comparative dissolution tests. Additionally, inspection of the manufacturing plant or conducting laboratory quality control tests to assure pharmaceutical quality and equivalence alone are not sufficient. Rather, all processes involved in the manufacture of the active pharmaceutical ingredient and finished dosage form need to be accounted for (8). Thus, the entire product dossier must be reviewed prior to prequalification according to international standards for both format and content (8). WHO uses the International Conference on Harmonisation of Technical Require-

ments for Registration of Pharmaceuticals for Human (ICH) Common Technical Document (CTD) format (26) for dossiers in its prequalification programme and it is anticipated that the network will use the CTD format as well.

Network design: membership

The proposed network will be comprised of low- and middle-income country medicines regulatory authorities. Participation in the network will be voluntary and dependant on the ability to meet standards in regulatory support functions such as governance, IT, human resources and quality management, as well as standards in regulatory processes necessary for prequalifying generic drugs such as those mentioned in Figure 1.

Standards will be set by expert committees, such as the WHO Expert Committee on Specifications for Pharmaceutical Preparations, and can draw upon the work carried out by other international bodies such as ICH and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) (27), as well as standards and guidance published by convening bodies such as WHO. The ability to meet standards will be assessed by impartial teams of international experts. If a medicines regulatory authority has already met standards for membership in the framework of "certification" activities carried out by other relevant organizations such as PIC/S and WHO, it may be possible to consider its inspectorate and quality control laboratory as qualified, respectively.

Once a medicines regulatory authority is qualified for having all the necessary functions in place and is operating according to international standards, manufacturers can apply for prequalification with the regulatory authority on a product-by-product basis. When products are approved in the context of the network, the assessing authority has to make public its assessment and inspection reports in the format and content prescribed by the network. In cases where the product

Figure 1. Network functions for prequalification of generic medicines ⁽³¹⁾

<p>1. Assessment of generic product dossiers</p> <ul style="list-style-type: none"> • API specifications and characteristics • Development pharmaceuticals • Manufacturing, process controls, process validation • Excipients • FPP specifications and analytical methods • Container closure systems • Stability data • Product labelling • Other miscellaneous quality deficiencies <p>2. Assessment of generic product efficacy/safety</p> <ul style="list-style-type: none"> • Clinical study information • Bioanalytical information • Pharmaceutical/statistical analysis • Audit/monitoring information <p>3. Inspections</p> <p>4. Utilization of prequalified quality control laboratories</p> <p>5. Communication of prequalification information</p> <ul style="list-style-type: none"> • Be transparent in terms of communication information to the public and in terms of communication within the network, such as communication of information of a technical or confidential nature <p>6. Utilization of information for procurement and national decisions about product approval</p>

formerly approved by the medicines regulatory authority does not meet the international standards of the network, the applicant must submit the missing parts of documentation for assessment in compliance with international standards.

Network formulation: role of WHO and stakeholders

The role of WHO in formulating the network will be very important and primarily focus on two areas: as a convener and guardian. Its role as convener will necessitate that it put forward the process of network formulation to external stakeholders such as donors and medicines regulatory authorities and then gain endorsement and support.

Its role as guardian will mean that the network exists under the auspices of WHO, but with a very different role than

that of the current prequalification programme. Rather than actually doing the prequalification itself, WHO will only establish procedures to join the network, provide guidance and oversight in the proposed network, and perform such functions as suspending or dequalifying a product and, in those cases where it is needed, a regulatory authority.

Given the level of support to go forward with the concept, WHO will be the body to convene technical experts for standard-setting and for procedures and standards for assessment of regulatory authorities to join the network. As WHO will publish a roster of qualified medicines regulatory authorities or individual components, its trusted name will be an invaluable asset when political sensitivities arise relating to whether or not countries meet standards for the network. If something goes wrong

in the network, such as with one of the medicines it prequalifies, the respective authority must initiate a complaint procedure and report the results to WHO and the public in a timely manner.

The role of stringent regulators in the network is also important to consider. It is not proposed that they participate in the network as members but this is not explicitly precluded — especially if they want to prequalify a generic product for the network. Rather, they will provide technical expertise and help build up regulatory capacities through activities like coaching and mentoring. It is also envisaged that they will be part of standard-setting groups and standard-assessment teams.

Financing

Financing for the network must be considered in phases. Funds will be required to get the network up and running and this will provide an opportunity for intervention by the donor community. Funding will also be required to sustain the network. This is a place for potential application of small user fees for manufacturers in order to compensate for the work of national regulators and the network.

Network performance: how it should work

Formal processes will be put in place explaining how a medicines regulatory authority will join the network. In general, they will forward an expression of interest to WHO and then agree to be evaluated for membership. The process governing a manufacturer request for regulatory assistance will be developed more formally as well. However, in general it will entail a manufacturer approaching either the regulator of interest or WHO for assistance with prequalification. In the event that a manufacturer asks for assistance from an authority that has not gained membership to the network, it may be possible to carry out a guided prequalification, where WHO and other experts work closely with the regulator to perform the requisite functions of prequalification.

When a manufacturer has identified a regulatory authority or authorities within the network, the process will be similar to WHO prequalification: the regulator will perform a dossier assessment, inspections, and make a prequalification decision. Once the product is prequalified, it will go on a list of prequalified medicines accompanied by the public assessment and inspection reports as prescribed by network procedures. International procurers can then be assured that these medicines are of requisite quality to purchase for treatment programmes.

As a valuable spin-off from the procedure, it may also be possible to design a mechanism with countries participating in the network to automatically grant approval/marketing authorization to a medicine once it has been prequalified. This would eliminate some barriers to approval in individual countries and speed access to needed treatments.

Regulators participating in the network will also perform a maintenance function to make sure that the medicines that have already been prequalified — and the manufacturers that make these medicines — continue to meet the quality standards of the network. This will mean that all the participating authorities have to implement and enforce unified variations guidelines, have sampling strategies in place for post-approval quality control, and follow complaint procedures as prescribed by the network in order to handle potential quality complaints from all concerned third-parties effectively. It is also anticipated that the authorities participating in the network will have surveillance systems in place to be able to monitor the safety of prequalified products.

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WHO Prequalification of Medicines Programme

WHO Prequalification of Medicines Programme rotational fellowships

In assessing pharmaceutical product dossiers for prequalification, the dossier assessment team of the WHO Prequalification of Medicines Programme (PQP) evaluates product data in close cooperation with inspectorates and other experts. PQP draws from the expertise of a pool of assessors from a variety of regulatory environments, including countries with sophisticated pharmaceutical industries and countries where prequalified medicines are used.

To build regulatory capacity in the latter environments, PQP invites assessors for a three-month rotational period at the World Health Organization (WHO) in Geneva, Switzerland. Since 2006, 16 assessors from nine different countries have completed a rotation. This article describes the setting of the PQP rotational fellowship programme, summarizes the benefits and challenges of the rotations as described in feedback received from former fellows, and highlights the impact on building regulatory capacity, which has helped to increase patient access to good quality medicines.

Setting

Unified dossier assessment standards

The standard procedure for prequalification of medicines relies on dossier assessment and inspection of manufacturing and clinical testing sites (1). PQP dossier assessors evaluate product dossiers according to principles and practices agreed by the world's leading regulatory agencies and adopted by the WHO Expert Committee on Specification for Pharmaceutical Preparations (2). A comprehensive set of guidelines and model formats is published regularly in annexes to the Expert Committee's *Technical Report Series* (TRS) for use in prequalification and regulatory practice. The guidelines incorporate state-of-the-art regulatory principles. For example, the common technical document (CTD) format for registration applications, introduced as part of the International Conference on Harmonization (ICH) process

to harmonize submissions and facilitate good review practices, is required for prequalification submissions (3).

International pool of experts

To assess dossiers, PQP brings together regulatory experts from some of the national regulatory authorities of Australia, Canada, the European Union, and Switzerland, as well as from the developing countries where prequalified medicines will be used. Assessors meet in Copenhagen, Denmark, every other month to evaluate submissions for prequalification.

Between the regular assessment sessions, PQP core staff in Geneva review product quality data submitted in support of applications for prequalification of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), as well as variations (changes) to already prequalified FPPs and APIs. Data for the purpose of requalification of FPPs are also reviewed.

Rotations

To build regulatory capacity in the countries where prequalified medicines are predominantly used, PQP invites assessors from its pool of experts for three-month rotations to work on ongoing assessment tasks alongside PQP core staff.

The rotational fellows are introduced to WHO experts on pharmacovigilance, quality control testing, development of the *International Pharmacopoeia* and other fields. They also participate in a good manufacturing practices (GMP) inspection as observers. As PQP follows an integrated approach in evaluating submissions, its dossier assessors work in close cooperation with the PQP inspectorate and other experts.

As at June 2012, 16 assessors had completed a rotation at PQP; 11 were still working at their regulatory authorities

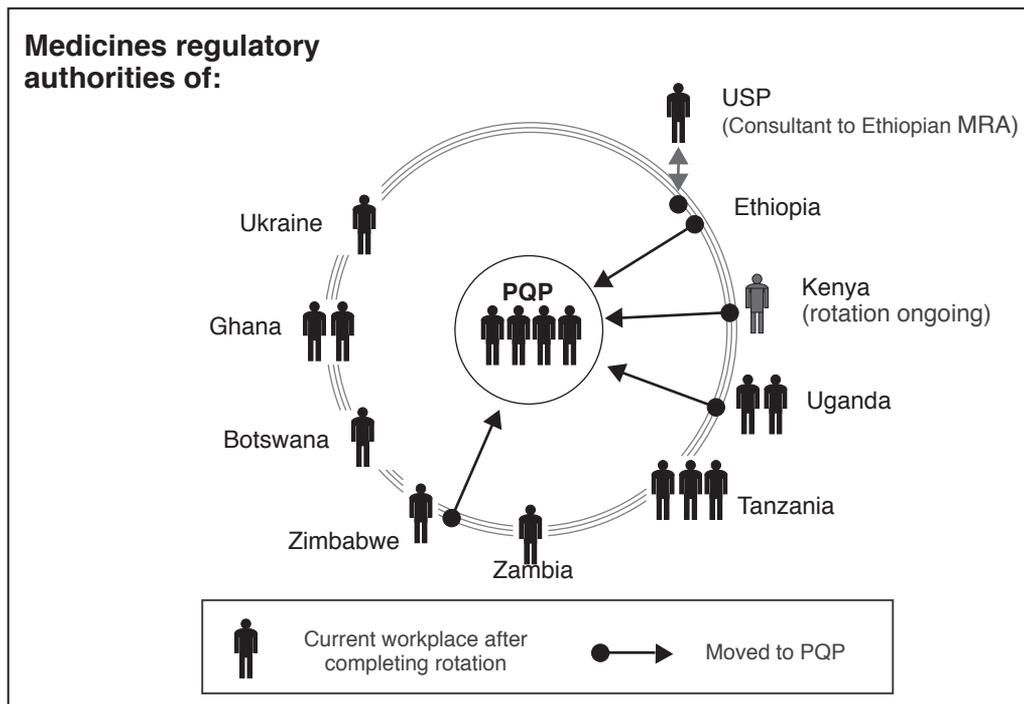
of origin (see Figure 1). Of these, one became director of his organization some time after the rotation and one became acting head of the medicines department. The other nine returned to their positions in drug registration, three as heads of the registration section, one as assistant head and five as regulatory officers. This article gives an overview of changes in regulatory practice implemented in countries, based on feedback received from twelve of the sixteen former rotational fellows. The other four did not respond to the invitation to provide feedback within the time available.

Benefit of rotations

Networks

Networking was the first benefit that came to mind of both the rotational fellows and PQP staff. Time is saved as they can now sort out issues in a telephone call that might otherwise have taken weeks

Figure 1. Workplaces of current and former PQP rotational fellows (June 2012)



Note: USP = U.S. Pharmacopoeial Convention

or months to resolve. Knowing “the faces behind the scenes” makes it easy for regulators to contact the right person to get technical advice. More importantly, having worked together WHO staff and regulators “speak the same language”: They can understand technical questions in the same way and identify the best possible solution to the issue at hand. Networking also extends beyond PQP, to experts on vaccines, biologicals or rational use of medicines all over the world.

The big picture

Interaction with other dossier assessors and WHO experts in related fields has been described as “simply superb and very enlightening”. The rotational fellows appreciated the exposure to a wide range of medicines quality aspects, which does not usually occur within their regulatory authority to the same extent. Having followed some of the debate concerning the development and the interpretation of a comprehensive set of WHO guidelines, the assessors became aware of the main risk areas. They can now introduce risk-based strategies in medicines regulation, including dossier evaluation in context and in more depth. As they say: “we now know where to look”.

An integrated view of quality issues is particularly valuable for assessors in small organizations who evaluate submissions for a wide range of products, including diagnostics, vaccines, blood products and traditional medicines. One ex-fellow pointed out the usefulness of the rotations to acquire “knowledge, skills, exposure and experience in those complicated areas” and another ensured that a regulation of blood products became part of the authority’s plan after having met a WHO expert on biologicals.

World class standards

WHO and PQP are well known in countries where prequalified medicines are funded because products meet internationally accepted standards. Assessors returning to their countries found that the

advice they offered as “a WHO expert” and of “someone who has written pre-qualification reports” was trusted and respected.

They also gained a clearer understanding of WHO as an organization and realized their own potential and the importance of implementing WHO standards in their countries: “We find that they [WHO] look to us in countries and to what happens with our products”. By improving regulatory practice in their countries, the regulators have improved, and will continue improving, the conditions in which all medicines are produced, distributed and provided to patients.

Collaboration

Widening knowledge and networks made the rotational fellows aware that “you can’t be an expert in everything”. As a result they introduced or strengthened collaborative approaches at their organizations, notably peer review of dossier assessment reports and exchange of information with other departments, for example, the inspectorate and national quality control laboratories (NQCLs). Some of the latter also became prequalified (4) or are working towards prequalification.

The importance of staying abreast with medicines quality assurance issues was realized. Copenhagen dossier assessment and training sessions were mentioned throughout feedback as a unique platform for this purpose. One assessor who was no longer working for a regulatory authority or PQP regretted not being able to participate in these sessions any more.

Follow-up action

Training

All respondents reported having conducted training and mentoring based on WHO guidelines and systems. Topics mentioned included the CTD concept and format, general dossier assessment, active pharmaceutical ingredient (API)

and finished product specifications, excipients, formulation development, production (with a focus on solid oral dosage forms), dissolution testing, stability, packaging, GMP and good clinical practice (GCP). Training was typically provided in-house, but was also extended to manufacturer representatives in some cases.

In describing the effect of the training in their countries, respondents highlighted the need for continuous learning. One respondent said, “we are now more organized... we believe in continuous improvement. ... I do training of staff ... even after a CPH session”, while another confirmed that “the technical competence and efficiency of the officers has increased due to the constant practice and implementation of the new regulatory concepts”.

The former fellows also contributed to training on prequalification in other countries and made presentations about WHO standards and systems at national and international meetings.

Implementation of WHO-based systems

Where this was not already the case, returning assessors implemented guidelines and formats based on WHO systems. As a result, the quality of dossier assessment in their organizations improved, and converging practices facilitated collaboration (see Table 1).

Challenges

Short duration of rotation

Feedback suggested that a timeframe of three months was too short to cover the wide range of possible topics and experiences. For example, one assessor would have liked more exposure to PQP’s “currently very good” assessment management system; another pointed out that the exposure to different activities during the rotation could vary, depending on what issues were ongoing at PQP at

the time. The time-consuming challenge of finding accommodation in Geneva was also mentioned. Three respondents recommended extending the duration to six months; one suggested introducing rotational posts for inspectors as well. Unfortunately, extending the duration of the rotations is not possible for organizational reasons.

Follow-up

The respondents interviewed at PQP, including core staff and former rotational fellows, would have liked a more structured follow-up to ensure that the knowledge and skills acquired during the rotation are passed on to the regulatory authorities. For example, the seconding MRA could be requested to define objectives of the rotation and report back on how they were achieved.

One of the respondents at a regulatory authority suggested that WHO should facilitate a joint meeting every two years, for former fellows to report on progress and development. The others did not mention that concern. Rather, they were glad to provide feedback by contributing to this article, and they emphasized their reliance on PQP as a platform for ongoing joint work on medicines quality assurance. Two respondents would have liked PQP to expand its scope of priority medicines, and another concluded, “I hope that all relevant institutions will support the noble activities of PQP.”

The regulatory gap

Not surprisingly, lack of staff, finance and electronic management information systems were mentioned as challenges in implementing improvements in regulatory practice. Beyond purely material limitations, one assessor commented on the difficulty of implementing a “complete overhaul” of the registration system to bring it into line with international best practices, while two others commented that it takes a “critical mass” of people in an organization to shift towards new working modes and attitudes.

Table 1: WHO-based systems implemented after rotation

System introduced:	Stringency	Efficiency	Accountability	Transparency	Speed
Product evaluation					
Registration-related guidelines derived from WHO PQP guidelines	√		√		
Common technical document (CTD) format recommended or accepted for submissions	√	√			√
Applications screened for minimum standard before acceptance for review		√			√
Product-specific issues verified during GMP inspections	√	√			
GMP non-compliances linked to specific requirements in GMP guidelines			√	√	
Assessment reports peer-reviewed before communicating with applicants	√	√	√		
Reasons for decisions, reviewer names documented in assessment reports (a)	√		√	√	
Organization					
Information systems reorganized, information exchanged between departments		√			√
Process flow charts, meeting dates and timelines developed and published		√	√	√	
Collaboration					
Secondment of dossier assessors between regulatory authorities		√			√
Recognition of WHO-prequalification and stringent authority approval	√ (c)	√		√	√
Participation in WHO collaborative procedure for registration of prequalified products (pilot) (b)		√		√	√

Notes:

(a) In a 2011 PQP survey among registration officials, the average length of assessment reports ranged from 9-40 pages in six countries that had seconded rotational fellows, compared to 2-7 pages in ten other countries. The increased length is at least partly due to more detail being included in the reports, although it could partly be because the PQP-based format repeats the applicant's summary.

(b) Of 25 authorities approached, eight had seconded a rotational fellow. Seven of these eight, compared with three of 17 others, confirmed participation within four weeks of being informed.

(c) These initiatives accelerate registration of already stringently assessed products through a transparent process and free up resources for assessment of high risk products outside PQP's scope.

One assessor highlighted the fact that the regulatory gap is reflected at the product level, where the same manufacturer may produce a prequalified version alongside one or more non-prequalified versions of the same product for supply to different environments – a challenge which has also been experienced in NGO procurement (5).

Language barriers

As PQP's working language is English, assessors from non-anglophone countries are under-represented in the assessor pool and accordingly in the rotations. They work through other channels, such as the francophone WHO AFRO office or regional cooperation, but translation of detailed, technical guidelines and communication from English can still be a challenge.

Impact

Feedback from ex-fellows suggests that as the competence and efficiency of regulatory staff increased, the regulatory authority gained in credibility.

Management buy-in

Political commitment, recognized as a contributing factor for effective national medicines regulation (6), was described in some of the feedback received. "We are now recognized as people who know what they are doing by our superiors in the Ministry of Health", said one assessor. Another mentioned that a comprehensive action plan was under way as mandated by the relevant regulatory governance committee to implement unified medicines standards. A third authority is directed by an ex-rotational fellow and has chosen as its vision to become the best Regulatory Authority in regulating food, drugs, cosmetics and medical devices in Africa by 2015.

Client satisfaction

Application of clear standards led to more client satisfaction among applicants for

medicines registration. In one country, the introduction of a screening step before acceptance of dossiers "... has reduced [assessment] timelines, and the clients are now happy with it – initially they did not like it." Another respondent said that as a result of better quality assessment reports "manufacturers know that guidelines will be applied and assessors can defend their decisions". If this development can be sustained, it will lead to overall better quality of dossiers and subsequent shorter review cycles, benefiting both applicants and regulatory authorities.

Access to good quality medicines

Two respondents mentioned that patients have access to quality-assured medicines as a result of regulatory improvements, and one said that the authority's decisions have come to be increasingly relied upon in NGO procurement in recent years.

Indeed, there are some "best of class" regulatory authorities in Africa despite ubiquitous resource constraints (7), with implications for local medicines quality and pharmaceutical sector development. A 2011 review conducted in Zimbabwe, where almost half of the items on the national essential drugs list are available from local manufacturers, confirms that the regulatory authority has processed a commendable number of marketing authorizations despite its resource limitations, and is implementing procedures that capture the latest developments in generic pharmaceutical pre-approval best practice (8).

Harmonization

At a time when the pharmaceutical sector becomes ever more globalized and complex while resources stagnate, regulatory authorities re-define their strategies to regulate medicines effectively. They develop and share regulatory competence to use limited resources where they are needed most. Harmonization in the East African Community has benefited from

the experience of a total of seven former rotational fellows from Kenya, Uganda and Tanzania (two of whom went on to work for PQP). At the global level, PQP's unique contribution to harmonization is that it brings regulators from diverse environments together, enabling them to identify the best ways to contribute to medicines quality.

Conclusion

PQP rotations have led to improvements in regulatory practice, although it would be difficult to quantify their effect. When asked about training conducted after returning from the rotation, and approximate number of people reached, one respondent simply answered, "I do this all the time"... and explained that training could be in the form of lessons or mentoring. The same respondent clearly suggested a positive impact of the changes in regulatory practice that occurred as a result: "Clients know that in our country you have to submit good quality products supported by good quality documentation."

It is people who do things. The improvements described in this article were driven by individuals who are committed to new ways of working. These improvements must now be sustained in the regulatory authorities so that they can play their part in assuring that medicines on the market are safe, effective and of good quality.

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Prequalification of active pharmaceutical ingredients

Medicines obtained through international aid agencies, national not-for-profit procurement organizations or licensed by national medicines regulatory authorities should comply with internationally recognized quality standards.

Availability of quality medicines is assured by procurement pricing and quality assurance policies as applied by procurement organizations and medicines regulatory authorities. Recognition of the need for quality assurance policies by procurement organizations is increasingly widespread. Nonetheless, standards continue to differ between procurement organizations both nationally and internationally. Quality-driven procurement is hampered by the higher cost of quality medicines and absence of quality alternatives in certain therapeutic areas. In other situations, the quality of medicines supplied may not meet internationally recognized standards or, due to lack of product information, may be impossible to identify as compliant.

While most developed countries have implemented appropriate standards for assuring the quality of medicines and active pharmaceutical ingredients (APIs), many others still lack regulatory capacity to apply needed regulations. Consequently, they are unable to ensure access to quality medicines and are often dependent on provision by international or national procurement organizations.

Identifying quality API sources

Good-quality APIs are the essential building blocks of good-quality medicines and may represent a significant portion of the total cost of a product. However, experience has shown that production of APIs may fail to comply with internationally-accepted good manufacturing practices (GMP) (1). This is not surprising given that adoption of international GMP standards among API manufacturers is often lacking or inadequate.

Globalization of markets further complicates the availability of quality medicines. For example, API manufacturers are increasingly based in China, whereas most manufacturers who have had finished pharmaceutical products (FPPs) prequalified by the WHO Prequalification of Medicines Programme (PQP) manufacture their products in India. Thus, information asymmetry, communication problems due to lack of a common language, and trade across different jurisdictions exacerbate difficulties in sourcing good-quality APIs. These problems are acute for some diseases such as tuberculosis (TB) and manufacturers of anti-TB medicines complain increasingly of the difficulties of obtaining good-quality APIs.

FPP manufacturers are responsible for ensuring the quality of their products, including that of the constituent API. Having located a reliable API source, the FPP manufacturer must go on to verify quality and compliance with GMP. This necessitates obtaining certificates of on-site inspection(s) and conducting paper-based audits of technical documents. For manufacturers in developing countries this task can be burdensome — and if an API has been purchased through a broker this may prove even more difficult.

In 2006, the International Conference of Drug Regulatory Authorities (ICDRA) highlighted the need for high-level action aimed at improving API quality. WHO responded by developing and publishing a procedure for WHO prequalification of APIs (2).

Taking this procedure as its starting point, in October 2010, PQP launched a project to prequalify APIs. As can be seen from Table 1, the PQP evaluation procedure is open to a variety of APIs used in medicines for treating HIV, TB and malaria, and for reproductive health. APIs that are evaluated and found to be manufactured

Table 1. Active pharmaceutical ingredients proposed for WHO PQP evaluation: March 2012

Therapeutic area	API
HIV	Abacavir, Atazanavir, Darunavir, Didanosine, Efavirenz, Emtricitabine, Etravirine, Lamivudine, Lopinavir, Nelfinavir, Nevirapine, Raltegravir, Ritonavir, Stavudine, Tenofovir, Zidovudine
Anti-malarial	Amodiaquine, Artemether, Artesunate, Dihydroartemisinin, Lumefantrine, Mefloquine, Piperaquine, Pyrimethamine, Pyronaridine
Anti-tuberculosis	Sulfadoxine Amikacin, Capreomycin, Cycloserine, Ethambutol, Ethionamide, Isoniazid, Kanamycin, Levofloxacin, Moxifloxacin, Ofloxacin, Para-Aminosalicylic Acid (PAS), Prothionamide, Pyrazinamide, Rifampicin, Streptomycin, Terizidone
Reproductive health	Desogestrel, Estradiol, Ethinylestradiol, Etonogestrel, Levonorgestrel, Medroxyprogesterone, Mifepristone, Misoprostol, Norethisterone, Norgestrel, Oxytocin
Neglected tropical diseases	Diethylcarbamazine, Mebendazole

in compliance with WHO GMP are publicly listed, including on the WHO PQP web site (3).

The goal of API prequalification (API-PQ) is three-fold:

- To assist FPP manufacturers in the identification of sources of quality APIs and thereby improve the availability of quality medicines on the market.
- To raise the standard of API manufacture by providing opportunities for API manufacturers — particularly those who are new to stringent regulatory assessment — to verify compliance with GMP and quality standards
- To provide publicly accessible information regarding APIs and their suppliers that may be used by national regulators who do not have the capability to undertake API assessment themselves or who wish to avoid duplication of assessment.

Some API manufacturers struggle to meet international pharmaceutical standards. But if they are committed to improving the quality of their manufacture and produce APIs that are urgently needed, WHO PQP can provide technical assistance to enable them to deal with areas of difficulty.

WHO PQP has received a steady number of applications for API assessment since October 2010. In April 2011, the first API was prequalified and since that time a further 12 antimalarial APIs, four anti-tuberculosis and two HIV APIs have been prequalified. In addition, a further thirty-seven applications for API-PQ are currently in progress, including APIs for priority areas such as reproductive health and tuberculosis. Details can be found on the WHO PQP web site (3).

How does the process work?

The principal components of the API prequalification evaluation process are

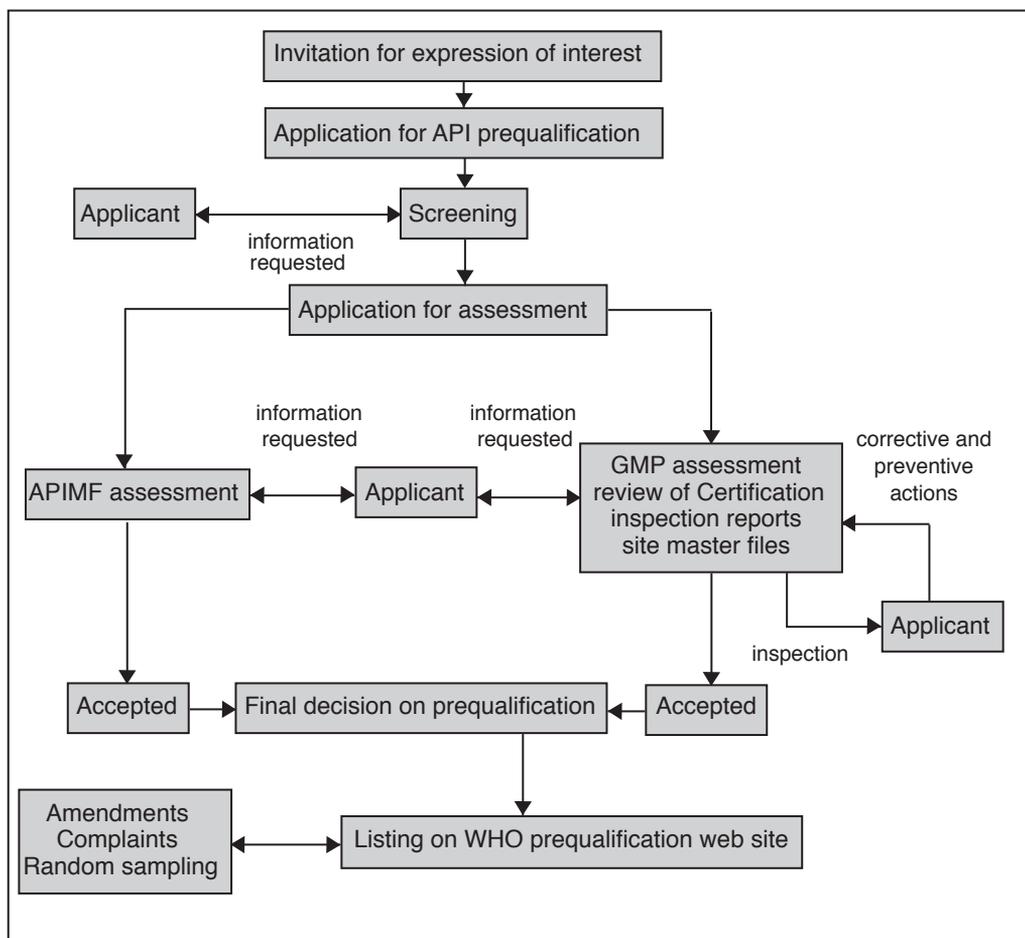
assessment of the quality components of the application, and evaluation of the GMP standards under which the API is manufactured. Full details can be found on the WHO PQP web site. Figure 1 illustrates the key steps.

The quality assessment is based upon an evaluation of the manufacturer's Drug Master File, which covers the API information requested in the International Conference on Harmonization (ICH) Module 3.2.S (4). The Drug Master File is referred to as an API Master File (APIMF) within PQP. The recently published *Guideline on submission of Documenta-*

tion for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part (5) describes information that PQP requires regarding APIs. If an API manufacturer has already submitted an APIMF, in connection with evaluation of an FPP, and the APIMF was found to be satisfactory, an abridged APIMF assessment is undertaken.

With respect to compliance with GMP, applicants can choose between submitting evidence of the GMP status of manufacture of the API undergoing assessment, or undergo WHO inspection. The evidence submitted must include:

Figure 1: Outline of the API prequalification process



- GMP certificates.
- Inspection reports.
- Corrective and preventive action reports.
- Site master files.
- Annual product review reports

Any evidence provided regarding GMP status must meet several important criteria with respect to the issuing authority, the specificity of the inspection and the date of the inspection. If the evidence provided is considered to be insufficient in terms of establishing GMP at the manufacturing site, a WHO-led GMP inspection will be necessary. A WHO-led inspection will also be necessary if evidence of GMP is unavailable. In addition, an API manufacturer can request a WHO inspection of its manufacturing site.

Subject to acceptance of the APIMF, and verification that the API is manufactured in compliance with WHO GMP, the API will be prequalified by WHO. Information about the prequalified API will be added to the publicly available WHO List of Prequalified APIs (3), including:

- WHO application number
- international nonproprietary name (INN)
- name of applicant
- site(s) of API manufacture
- APIMF version number
- API specification version number
- primary and secondary packaging components
- assigned re-test period
- recommended storage conditions.

Further useful information is available in the WHO Public Inspection Report (WHOPIR). This will have been posted on the WHO PQP web site (6) when the API manufacturing site(s) have passed WHO inspection. WHOPIRs summarize

inspection findings and are frequently consulted by procurement agencies who seek information on the operations of a manufacturer in general, as well as on an API in particular.

The API manufacturer will be issued with a Confirmation of API-PQ document. This will specify the re-test period, storage conditions, API specifications, assay test methodology and related substance test methodology accepted as part of pre-qualification. The API manufacturer may distribute this document to third parties and it could be submitted by FPP manufacturers to medicines regulatory authorities (MRAs) as supporting evidence of the quality of their API source. The primary purpose of this document is to allow API manufacturers to provide, in confidential form, the accepted API specifications, assay and related substance test methods to relevant parties.

A revised Confirmation of the API-PQ document will be issued every time there is a change in the API specifications, assay or related substance test method. The MRA or other third party can determine the validity of the presented document by comparing the date of the document with that published in the list of prequalified APIs (3).

Nonetheless, to make greatest use of the API prequalification procedure, MRAs may require further information regarding the API assessment. The API prequalification procedure allows the sharing of assessment reports with MRAs, subject to the protection of any commercially sensitive, confidential or proprietary information. To initiate this process the medicines regulatory authority should contact WHO PQP directly at prequalassessment@who.int

Avoiding duplication

WHO PQP does not seek to replicate efforts made by regulatory authorities. Applicants who have undergone a GMP inspection by an ICH member, ICH

observer or an authority with a legally binding mutual recognition agreement with an ICH member, may submit evidence of this inspection as part of their application, and in lieu of a request for inspection by WHO.

Similarly, applicants who submit an APIMF that has already been assessed and accepted by the US Food and Drug Administration (FDA) or the European Directorate for the Quality of Medicines (EDQM) can request WHO to obtain the associated assessment report for verification, in lieu of a PQP assessment of the APIMF.

Other regulatory schemes for API assessment do exist, but these do not necessarily include those APIs that are needed for manufacture of FPPs in the aforementioned public health therapeutic areas. Moreover, many regulatory schemes assess an API only if submitted in relation to an application for medicines registration. Even if an MRA does assess an API with respect to such an application, this does not necessarily include verification of compliance with GMP, or making public the details of the API if it receives approval.

So by assessing the quality of APIs, verifying the GMP compliance of manufacturers, and publishing important details of successful applications, PQP provides a unique and valuable service.

Benefits of WHO API prequalification

WHO prequalification of APIs will benefit API manufacturers, FPP manufacturers, UN organizations, other international procurers and national procurers, as well as MRAs.

For FPP manufacturers, clear identification of APIs that have been evaluated and confirmed as being manufactured in compliance with WHO GMP and for

which quality regulatory documentation is maintained, is an invaluable service by saving them both time and money in locating and registering sources of APIs.

For API manufacturers, WHO prequalification confirms that they are manufacturers who provide quality APIs, manufacture the prequalified API in compliance with GMP and maintain excellent regulatory documentation. Prequalification of APIs is of particular relevance to those API manufacturers who are currently supplying only their domestic markets, and who have limited or no experience of registering their products with stringent regulatory authorities. For these manufacturers, working with PQP is an opportunity to enhance their quality systems and regulatory documentation and assess the level of compliance with GMP.

API manufacturers who have not previously undergone a stringent regulatory authority assessment will be interested to know that they can apply for API prequalification without having to submit an associated application for FPP evaluation. This is generally not the case with MRAs. This could be an important point for API manufacturers who have not yet attracted an FPP manufacturer partner and who are nevertheless keen for FPP manufacturers to be aware that their API(s) meet(s) stringent regulatory authority requirements. PQP offers them a means of raising this awareness.

For medicines procurers, use of a prequalified API is a strong indicator that the overall quality of an FPP is acceptable, even if the FPP in question has not (yet) been prequalified by WHO.

For MRAs from developing countries, the benefits of WHO prequalification of APIs will be quickly apparent when they review an application for marketing authorization for an FPP that uses a WHO-prequalified API. Full evaluation of suppliers of APIs is a cost-intensive and resource-demand-

ing activity that only a few MRAs can afford to undertake. As a result, in-depth API assessment rarely forms part of the process of granting marketing authorizations to FPPs, and the quality and safety of marketed pharmaceutical products can be undermined. This lack of information about an API makes it difficult to verify whether an API supplier is legitimate.

The published details of WHO-prequalified APIs, together with the aforementioned Confirmation of the API-PQ (4), will enable MRAs to quickly identify whether the API details presented to them, when an FPP is submitted for registration, are identical to those relating to a WHO-prequalified API. As noted earlier, WHO's API prequalification procedure also allows for sharing of assessment reports with MRAs, subject to the protection of any commercially sensitive, confidential or proprietary information.

However, the primary and most important beneficiaries of WHO-prequalification of APIs will be patients. Easier identification of sources of good-quality APIs by FPP manufacturers should facilitate enterprise between API and FPP manufacturers and lead to increased volume and choice of quality medicinal products.

Further information regarding applications for WHO prequalification of APIs can be found on the WHO PQP web site (7).

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Model quality assurance system for procurement agencies: harmonized assessment tool

During its meeting in 2005 in Geneva, Switzerland, the World Health Organization's Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) adopted a Model quality assurance system for procurement agencies (MQAS). This was published in 2006 (2).

Subsequently, many procurement agencies (PAs) have implemented the recommendations presented in the MQAS. Other donor and implementing organizations have further prepared a tool to assess PAs and establish their level of implementation of the MQAS.

Article by Adriaan van Zyl Consultant to The Global Fund to Fight AIDS, TB and Malaria (1) and Joelle Daviaud and Sophie Logez, The Global Fund to Fight AIDS, TB and Malaria.

Some of these tools were presented and discussed during the WHO–Global Fund Joint Stakeholders meeting held in August 2011 in Geneva. As different organizations had established different tools to achieve the objective of assessing compliance with the MQAS, it was proposed to set up an informal, voluntary working group of representatives from among the stakeholders, facilitated by the Global Fund, that would develop a harmonized tool for better use of resources. This would be achieved by coordinating PA assessments and working towards mutual recognition of assessment findings.

Method

In December 2011, the Global Fund contracted a consultant to prepare a harmonized assessment tool based on the MQAS and to review the existing MQAS and propose changes for consideration by the ECSPP. It was considered important that an independent body be utilized for the work to be done in order to maintain confidentiality and avoid any conflict of interest. The objectives were to:

- Review the existing MQAS and make recommendations to WHO in case a need was identified to change or update the MQAS.
- Review tools used by procurement agencies in the existing MQAS.
- Prepare, through a consultative process, a harmonized tool for the assessment of procurement agencies, based on the MQAS.

An informal, voluntary working group was then established comprising representatives from QUAMED, PFSCM, UNICEF, MSF, IDA, Crown Agents, GDF, MSH, UNION, UNOPS, USAID, ICRC and CHMP (3–15). Existing tools used by the different organizations participating in the working group were evaluated to assess the level of implementation and compliance with the MQAS. At the same time, comments were invited focusing on areas

for amendment. A draft harmonized tool to be used in the assessment of procurement organizations was prepared through a consultative process. Two meetings were arranged with members of the working group to evaluate comments on the MQAS and the draft tool, and to discuss the way forward.

The work plan that was followed is presented in table 1.

Results and outcomes to date

Assessment tools

Of the 14 participating organizations, four indicated that they did not use specific tools; four did not respond (two not at all and two not on the tools used), and six indicated that they were making use of checklists/tools.

The tools covered distributors, manufacturers, wholesalers and products (all at different levels of detail).

MQAS

Organizations were of the opinion that although the MQAS was used by several PAs, it was not used as widely as was hoped. Possible reasons for this lack of use included:

- the perception by some PAs that the MQAS was too complex;
- that some PAs may not have sufficient resources (and would thus rely on work done by other parties);
- that buyers were not questioning the source of products;
- that there was no legal requirement for compliance with the MQAS;
- that there was a lack of awareness of the MQAS and/or its importance, and
- that the selection of sources of products was sometimes outside the scope of the activity/responsibility of a PA.

The working group concluded that the MQAS was a useful document and did

not require major changes. However, the group felt that it was not marketed enough in different countries. It was noted that not all procurement agencies used all the modules in the MQAS (especially not the one on prequalification). The group suggested that consideration should be given to consolidating the MQAS and to focusing more on quality assurance aspects.

Harmonized assessment tool

The working group supported development of a harmonized tool even though mutual recognition of assessments may not be an outcome. Nonetheless, assessments and assessment outcomes could be shared among members of the working group and the decision as to

whether a PA was compliant with the MQAS recommendations could still be decided individually by each organization. It was generally agreed that the tool should be based on MQAS, be easy to use, and should reflect principles of a risk-based approach.

The group further supported the idea that there should be an attempt to avoid duplication of inspections/assessments. The possibility of using a harmonized tool to avoid bias and the sharing of data (assessments and outcomes) through a data base was encouraged.

Meetings

The first meeting, arranged with all participating organizations, was held on 12

Table 1. Review work plan

Step	Time frame	Task	Status
1	Q4 2011	To review the existing assessment tools used by different organizations and to review the level of implementation and compliance with the MQAS. Liaise with relevant organizations to obtain information and discuss their approach to assess procurement agencies and experience with the tool. Compile a review report for discussion.	Completed on target
2 & 3	Q1 2012	To review the MQAS guidelines, identify areas for amendment and liaise with participating organizations. Prepare a draft report with recommendations to WHO. To organize a meeting with the working group to discuss the outcome of the review and agree on areas for harmonization.	Completed on target
4 & 5	Q2 2012	To prepare a draft harmonized tool for the assessment of procurement organizations, based on the MQAS that could be used for qualification of procurement agencies by an independent body. To organize a meeting with the working group to discuss the draft tool and finalize the recommendations on the MQAS.	Completed on target
6	Q3 2012	To finalize the draft tool and MQAS for submission to WHO.	Completed on target

Table 2. Assessment tools

Use of an assessment tool	Number of organizations
No specific assessment tool is used	4
Specified assessment tool is used	6*
No response on whether a tool is used	4
Total number of organizations:	14

*Some did not consider their checklists to be "assessment tools" and some indicated that these were not based on the MQAS. Three claimed that their tool was based on the MQAS.

March 2012 at the offices of The Global Fund in Geneva. During the meeting, it was agreed that the assessment tool would consist of questions/statements based on the MQAS and according to which compliance could be measured. The level of compliance, based on risk, might then be calculated.

In June 2012, a second working group meeting was held following discussion with WHO representatives. It was proposed that a WHO consultative process should start on the MQAS and that the assessment tool should be finalized after the pilot phase. Information would be collected by all members of the working group on use of the draft tool during the pilot phase (August to December 2012). The product questionnaire (which is included in the MQAS) would also be reviewed by a small sub-group.

Comments received on the MQAS were included in the existing MQAS. A draft harmonized assessment tool was prepared and is being used in a pilot-test phase. Both documents as well as a background document were submitted to WHO by the middle of August 2012.

The draft assessment tool will be revised as a result of further consultation for changes to the MQAS and after considering comments made on the draft tool at the end of the pilot-test phase.

Summary and conclusion

The working group considered the MQAS a valuable document which would

benefit from some updating to make it current and more user friendly. The group strongly supported development of the harmonized assessment tool based on the MQAS.

It is anticipated that the revised MQAS and a harmonized assessment tool for procurement agencies will be ready for submission to the ECSP by October 2013 following a global consultative process (16).

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Safety and Efficacy Issues

Ondansetron: QT prolongation

United States of America — The Food and Drug Administration (FDA) has informed healthcare professionals and the public that preliminary results from a recently completed clinical study suggest that a 32 mg single intravenous dose of ondansetron (Zofran®, ondansetron hydrochloride, and generics) may affect QT interval prolongation.

The updated label will state that no single intravenous dose should exceed 16 mg and that ondansetron can continue to be used in adults and children with chemotherapy-induced nausea and vomiting at the lower intravenous dose recommended in the drug label of 0.15 mg/kg administered every 4 hours for three doses. The new information on QT prolongation does not change any of the recommended oral dosing regimens for ondansetron. It also does not change the recommended lower dose intravenous dosing of ondansetron to prevent post-operative nausea and vomiting.

Electrolyte abnormalities (e.g., hypokalaemia or hypomagnesaemia) should be corrected prior to the infusion of ondansetron.

Reference: *FDA Drug Safety Communication*, 29 June 2012 at <http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm>

Extended-release and long-acting opioid medications

United States of America — The Food and Drug Administration (FDA) has approved a risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids.

Under the new REMS, companies will be required to make education programmes available to prescribers based on an FDA Blueprint. The REMS will also require companies to make available FDA-approved patient education materials on the safe use of these drugs. The companies will be required to perform periodic assessments of the implementation of the REMS and the success of the programme in meeting its goals.

Reference: *FDA News Release*, 9 July 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310870.htm>

Cefepime: risk of seizure

United States of America — The Food and Drug Administration (FDA) has reminded healthcare professionals about the need to adjust the dosage of the antibacterial drug cefepime in patients with renal impairment. There have been cases of nonconvulsive status epilepticus associated with the use of cefepime, primarily in patients with renal impairment who did not receive appropriate dosage adjustments of cefepime. Sections of the cefepime label are being revised to highlight this risk.

Cefepime is a cephalosporin antibacterial and used to treat pneumonia, urinary tract, skin, and intra-abdominal infections.

To minimize the risk of seizures, healthcare professionals should adjust the dosage of cefepime in patients with creatinine clearance less than or equal to 60 mL/min. If seizures associated with cefepime therapy occur, consider discontinuing cefepime or making appropriate dosage adjustments in patients with renal impairment.

Reference: *FDA Drug Safety Communication*, 26 June 2012 at <http://www.fda.gov/Drugs/DrugSafety/ucm309661.htm>

Vessel sealing system: torn vessels

Canada — Health Canada has received reports of incidents in which LigaSure® instruments were sticking to tissue or clamping onto tissue and not releasing. The LigaSure Dolphin Tip® laparoscopic vessel sealer/divider (LS1500) is a single-use class II medical device (IV being the highest risk class). The device is intended for use with a manufacturer-approved power source to seal vessels 7 mm in diameter or smaller, and to produce haemostasis in arteries, veins and tissue bundles.

As of March 2012, Health Canada received 24 reports of incidents suspected of being associated with the use of the LigaSure V® instrument. Incidents described in the reports included stripped insulation, malfunction of the device, pieces of the device falling into the body cavity requiring retrieval, and inadequate sealing by the device.

Extracted from Canadian Adverse Reaction Newsletter, Volume 22(3), July 2012 at <http://www.hc-sc.gc.ca>

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Strontium ranelate: serious skin reactions

Singapore — The Health Sciences Authority (HSA) has alerted healthcare professionals to the increase in local reports of serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) suspected to be associated with strontium ranelate (Protos®) leading to a benefit-risk review of the drug.

While the review demonstrated a favourable benefit-risk ratio, a risk management plan is proposed to mitigate the risks of serious skin reactions related to strontium. HSA is still working through the details of the risk management plan and will update healthcare professionals once it is finalized. Healthcare professionals are strongly advised to weigh the benefit versus risk of initiating strontium ranelate for the individual patient and to monitor patients closely for the possibility of serious skin reactions. Patients should also be educated on early recognition of these reactions.

Reference: Health Sciences Authority, 13 July 2012 at http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL.html

Aprotinin: restricted access programme

Singapore — The Health Sciences Authority (HSA) has alerted healthcare professionals to its decision to continue the restricted access programme for aprotinin (Trasylol®) following comprehensive benefit-risk assessment of data from the Canadian BART study, literature studies and international regulatory action.

Aprotinin has been made available under the restricted access programme since November 2007 in response to its world-wide suspension following an increased risk of mortality observed from an interim analysis of the BART study. The outcome of HSA's review concluded that aprotinin continues to have a place in therapy in preventing blood loss in patients undergoing cardio-pulmonary bypass who are at increased risk for blood loss and transfusion. HSA has assessed that the existing aprotinin restricted access programme has served its purpose of ensuring safe use locally and should be continued.

Reference: Health Sciences Authority, 12 July 2012 at http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL.html

Boceprevir: drug interaction

Singapore — The Health Sciences Authority (HSA) has informed healthcare professionals of important drug interaction updates on boceprevir (Victrelis®). In a pharmacokinetic study evaluating drug interactions between Victrelis® and ritonavir-boosted HIV protease inhibitors in healthy volunteers, concomitant administration of Victrelis® with ritonavir in combination with atazanavir or darunavir, or with lopinavir/ritonavir resulted in reduced exposures of the HIV medicines and Victrelis®, which may be clinically significant for patients infected with both chronic hepatitis C virus (HCV) and HIV.

Healthcare professionals treating patients for HCV and HIV should be aware of these drug interactions. Doctors who initiate Victrelis® in combination with peginterferon alfa and ribavirin in HIV-HCV co-infected patients on fully suppressive antiretroviral therapy containing ritonavir-boosted protease inhibitors should discuss these findings with their patients and monitor them for HCV treatment response and potential HCV and HIV virologic rebound.

Reference: Health Sciences Authority, http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL.html

Statins and ciclosporin: risk of myopathy

New Zealand — Patients taking a statin with ciclosporin may be at increased risk of statin-related adverse events. In patients currently taking ciclosporin, who also require lipid-lowering therapy, statins should be used with care. Prescribers should use the lowest possible dose and monitor for adverse reactions and the effectiveness of treatment.

Dyslipidaemia is common in patients who have undergone solid organ transplantation. Dyslipidaemia is estimated to occur in up to 80% of renal, pancreas, and heart transplant recipients and up to 45% of liver transplant patients. In addition, immunosuppressant therapy, including corticosteroids and ciclosporin, have all been associated with dyslipidaemia (1, 2). For these reasons, it is common for transplant patients to require statin therapy. Data indicates that approximately one third of patients taking ciclosporin are also taking a statin.

Pharmacokinetic studies confirm that ciclosporin interacts with all statins to increase the plasma levels of the statin (3, 4). Ciclosporin is an inhibitor of CYP3A4 as well as several membrane

transporters, including OATP2 and P-glycoprotein (5). The metabolic pathways of statins include CYP3A4, OATP2 and P-glyco-protein. It has been suggested that the risk of myopathy is lower with non-lipophilic statins because of their inability to enter muscle cells and to alter membrane structure (6).

Myopathies are the most severe adverse reaction to statin therapy. The risk of myopathy increases with increasing plasma levels of statins (7). Other risk factors for statin-induced myopathy include female gender, a decline in renal or hepatic function, low body mass index, hypothyroidism and a personal or family history of symptoms associated with rhabdomyolysis.

Extracted from Prescriber Update 2012; 33(2) June 2012 at http://www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUdate_June2012.pdf

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Somatropin: Increased risk of mortality?

New Zealand — Healthcare professionals are reminded that the recommended daily dose of somatropin should not be exceeded and somatropin must not be used when there is any evidence of activity of a tumour.

Somatropin is a recombinant human growth hormone. In New Zealand, somatropin is indicated in children with insufficient secretion of growth hormones, Turner syndrome, chronic renal insufficiency and Prader-Willi syndrome.

Medsafe recently conducted a review of somatropin following publication of a paper showing increased risk of mortality. Medsafe concluded that the study had significant limitations and the benefits of somatropin treatment continue to outweigh the risks when used for approved indications and at the approved doses.

A long-term population-based study in France of patients treated with somatropin during childhood found that patients receiving high doses of somatropin had a higher risk of mortality than patients on the low-dose regimen (1). The study found that bone tumour-related and cerebrovascular disease-related mortality was increased. The French study is part of a larger European study called the 'Safety and Appropriateness of Growth hormone treatments in Europe' (SAGhE).

A second paper from the SAGhE study did not support the observations of the French study. It examined mortality and cause of death in patients treated with somatropin in Belgium, The Netherlands

and Sweden (2). Not a single case of death caused by cancer or cardiovascular disease was observed in the study.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has also completed a review of the risks and benefits of somatropin (3) and concluded that the benefits of somatropin continue to outweigh the risks.

Extracted from Prescriber Update 2012; 33(2) June 2012 at http://www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_June2012.pdf

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Serotonergic medicines: cerebral vasoconstriction syndrome

New Zealand — A recent Medsafe review confirmed that cases of reversible cerebral vasoconstriction syndrome (RCVS) have been reported in association with the use of the serotonergic medicines. Cases have been reported with duloxetine, sertraline, citalopram, paroxetine, fluoxetine and sumatriptan. However, data is currently inadequate to confirm

a causal association. RCVS should be considered in the differential diagnosis of thunderclap headaches when other causes have been excluded.

RCVS is thought to be under-reported for many reasons including lack of awareness of the condition and difficulties in confirming the diagnosis. The current data on RCVS comes primarily from case series conducted in France, Taiwan, and USA (1–3). The case series include 262 patients who experienced RCVS.

RCVS is a unifying term used to describe a diverse range of conditions characterized by recurrent thunderclap headaches and reversible segmental cerebral arterial vasoconstriction on angiogram. Conditions include Call-Fleming syndrome, benign angiopathy of the CNS, postpartum angiopathy or idiopathic thunderclap headache. RCVS classically presents with sudden-onset and severe headaches that recur over a 1–3 week period (4). The headaches may be accompanied by nausea, vomiting and photophobia.

Neurological complications occur in up to 50% of patients. Complications include seizures, cortical subarachnoid haemorrhage, ischaemic stroke and intracerebral haemorrhage. The majority of patients recover fully. However, neurological deficits were found to be permanent in 3–9% of patients in a prospective case series (5).

Extracted from Prescriber Update 2012; 33(2) June 2012 at http://www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_June2012.pdf

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Ambrisentan: idiopathic pulmonary fibrosis

Canada — Healthcare professionals have been informed of new safety information regarding use of ambrisentan (Volibris®) in patients with idiopathic pulmonary fibrosis (IPF). A clinical study was prematurely discontinued due to lack of efficacy. Evaluation of the composite primary endpoint revealed higher rates of disease progression (including decreases in respiratory function, respiratory hospitalizations) or deaths in the ambrisentan group versus the placebo group.

Ambrisentan, a selective endothelin A receptor antagonist, is indicated for the treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) in patients with WHO functional class II or III symptoms who have not responded to conventional therapy.

Ambrisentan is not indicated for IPF; nonetheless, it is now contraindicated in patients with IPF, with or without pulmonary hypertension.

Reference: *Health Canada Safety Information*, 9 July 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/index-eng.php

Hepatitis B immune globulin: thrombotic events

Canada — Healthcare professionals have been informed of a theoretical risk for arterial and venous thrombosis following intravenous administration of HepaGam B® for liver transplantation. This may exist because of procoagulant (factor XIa) activity in HepaGam B®. The significance of this is being evaluated.

Caution should be exercised when administering immune globulins, including HepaGam B®, to patients with risk factors for thrombotic events.

HepaGam B® is authorized for hepatitis B post-exposure prophylaxis, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg positive persons and household exposure to persons with acute HBV infection.

Reference: *Health Canada Safety Information*, 11 June 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/index-eng.php

Human immune globulin: haemolytic reactions

Canada — Healthcare professionals have been informed of cases of haemolysis following the administration of intravenous human immune globulin (Privigen®). Since first being marketed on 8 January 2009, at least 70 cases of suspected haemolytic reactions have been reported in Canada.

Privigen® is indicated for patients with primary immune deficiency (PID) and secondary immune deficiency (SID) and the treatment of patients with immune thrombocytopenic purpura to rapidly raise platelet counts to prevent bleeding.

Delayed haemolytic anemia can develop due to enhanced RBC sequestration, and acute haemolysis, consistent with intravascular haemolysis, has been reported.

Increased vigilance is recommended for non-O blood group patients receiving high doses for non-PID/SID indications. Haemolysis has rarely been reported in patients given replacement therapy for PID/SID.

Reference: *Health Canada Safety Information*, 29 May 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/index-eng.php

Denosumab: severe hypocalcaemia

Canada — Healthcare professionals have been informed of new safety information related to hypocalcaemia associated with denosumab (Xgeva®). Denosumab is indicated in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours for reducing the risk of developing skeletal-related events (SREs). Denosumab is not indicated in patients with multiple myeloma. It is administered as a single 120 mg subcutaneous injection given once every four weeks.

Post-marketing cases of severe symptomatic hypocalcaemia have occurred at an estimated rate of 1–2%, including some cases which were fatal. Signs and symptoms of these cases included altered mental status, tetany, seizures and QTc prolongation. If severe symptomatic hypocalcaemia occurs, the benefit of continuing the treatment in these patients should be reassessed.

Reference: *Health Canada Safety Information*, 28 May 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/index-eng.php

Calcitonin medicines: limit long-term use

European Union — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has

recommended that calcitonin-containing medicines should only be used for short-term treatment because of evidence that long-term use of these medicines is associated with an increased risk of cancer.

Doctors should no longer prescribe calcitonin-containing medicines as nasal spray for the treatment of osteoporosis. Calcitonin will only be available as a solution for injection and infusion and should only be used for:

- Prevention of acute bone loss due to sudden immobilization, with treatment recommended for two weeks with a maximum duration of four weeks.
- Paget disease in patients who do not respond to alternative treatments or for whom such treatments are not suitable, with treatment normally limited to three months.
- Hypercalcaemia caused by cancer.

Taking into account the limited efficacy of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the CHMP concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in this indication. As the nasal spray is only used in osteoporosis, the CHMP recommended that this formulation be withdrawn.

For all other approved indications the CHMP considered that the benefit-risk balance remains positive, but recommended that calcitonin treatment should be given for the shortest possible time. For the treatment of patients with Paget disease, the CHMP also recommended limiting the use of calcitonin to a second-line indication in patients who do not respond to alternative treatments or for whom such treatments are not suitable.

Reference: *European Medicines Agency Press Release*, EMA/CHMP/483874/2012, 20 July 2012 at <http://www.ema.europa.eu>

Doripenem: dosing review for nosocomial pneumonia

European Union — The European Medicines Agency (EMA) has provided new advice for the treatment of patients with nosocomial pneumonia. A review of available data raises concerns that the currently approved dose of doripenem (Doribax®) of 500 mg every 8 hours may not be sufficient.

Nosocomial pneumonia is caused by bacterial infection, and doripenem is one of a limited number of medicines available to treat this life-threatening disease. For the treatment of patients with augmented renal clearance and/or with infections with non-fermenting Gram-negative pathogens, the Agency's Committee for Medicinal Products for Human Use (CHMP) is recommending that doctors double the dose to 1g every 8 hours. The Committee also advised doctors that a longer treatment period (10–14 days) is required in patients with nosocomial pneumonia, including ventilator-associated pneumonia.

Doctors should exercise particular caution in patients for whom non-fermenting Gram-negative pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* are suspected or confirmed as the cause of infection. In some of these patients, doctors should consider initiating concomitant treatment with an aminoglycoside antibiotic.

Reference: *European Medicines Agency Press Release, EMA/CHMP/413801/2012, 22 June 2012 at <http://www.ema.europa.eu>*

Dabigatran: positive benefit-risk balance

European Union — The European Medicines Agency (EMA) has recommended updating the product information for dabigatran etexilate (Pradaxa®) to give clearer guidance to doctors and patients on how to reduce and manage the risk of bleeding. Bleeding is a well-known complication of all anticoagulant medicines and Pradaxa® has therefore been kept under close review by the Agency's Committee for Medicinal Products for Human Use (CHMP) since its initial authorization.

Dabigatran is prescribed to adults who have had hip or knee replacement surgery to prevent venous thromboembolic events and also to patients with non-valvular atrial fibrillation to prevent stroke and systemic embolism.

On the basis of the available evidence, the CHMP concluded that the benefits of Pradaxa® continue to outweigh its risks and that it remains an important alternative to other blood-thinning agents. However, the advice to doctors and patients should be updated and strengthened to give clearer guidance on the best use of the medicine.

The Agency has produced a question-and-answer document for patients and for healthcare professionals that provides more detailed information on the Committee's recommendations.

Reference: *European Medicines Agency Press Release, EMA/CHMP/337406/2012, 25 May 2012 at <http://www.ema.europa.eu>*

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

Regulatory Action and News

Pharmacovigilance Risk Assessment Committee

European Union — The European Medicines Agency (EMA) has convened its first meeting of the newly formed Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC will play a major role in overseeing the safety of medicines in the European Union. Its establishment is one of the main deliverables of the new pharmacovigilance legislation that came into operation on 1 July 2012.

In addition to its role in the protection of public health, the PRAC will operate under unprecedented levels of transparency. There will be much more proactive publication of information on safety issues, the PRAC will have the possibility of holding public hearings, and agendas and minutes of its meetings will be published.

The European Commission has appointed six independent scientific experts who will also serve as members.

Reference: *European Medicines Agency Press Release, EMA/CHMP/487397/2012*, 19 July 2012 at <http://www.ema.europa.eu>

Online publication of suspected side-effect reports

European Union — The European Medicines Agency (EMA) has begun publishing suspected side-effect reports for medicines authorized in the European Economic Area (EEA) on a new public web site: <http://www.adrreports.eu>. The reports come directly from the European Union (EU) medicines safety data base EudraVigilance and are one of the many types of data used by regulators to monitor the benefits and risks of a medicine

once authorized. The launch of the new web site is part of the Agency's continuing efforts to ensure EU regulatory processes are transparent and open and is a key step in the implementation of the EudraVigilance access policy.

The information published relates to approximately 650 medicines and active substances authorized through the centralized procedure, which is managed by EMA. Information on the web site is presented in the form of a single report per medicine or active substance. Each report pulls together the total number of individual suspected side effect reports submitted to EudraVigilance by Member States and marketing authorization holders. These aggregated data can be viewed by age group, sex, type of suspected side effect and by outcome. Within a year, the Agency aims to additionally publish suspected side effect reports for common drug substances used in nationally authorized medicines.

The Agency has launched the web site in all official EU languages.

Reference: *European Medicines Agency Press Release, EMA/CHMP/258738/2012*, 31 May 2012 at <http://www.ema.europa.eu>

Emtricitabine/tenofovir disoproxil fumarate approved for HIV

United States of America — The Food and Drug Administration (FDA) has approved emtricitabine/tenofovir disoproxil fumarate (Truvada®), to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. Taken daily, Truvada® is to be used for pre-exposure

prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually-acquired HIV infection in adults at high risk.

Truvada® was previously approved for use in combination with other antiretroviral agents for the treatment of HIV-infected adults and children 12 years or older. Truvada® for PrEP must only be used in individuals confirmed to be HIV-negative prior to prescribing the drug and at least every three months during use. It is contraindicated for PrEP in individuals with unknown or positive HIV status.

Truvada® for PrEP is being approved with a Risk Evaluation and Mitigation Strategy (REMS) to minimize the risk to uninfected individuals of acquiring HIV infection and to reduce the risk of development of resistant HIV-1 variants.

The most common side effects included diarrhoea, nausea, abdominal pain, headache, and weight loss. Serious adverse events in general, as well as those specifically related to kidney or bone toxicity, were uncommon.

Reference: *FDA News Release*, 16 July 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm>

Mirabegron approved for overactive bladder

United States of America — The Food and Drug Administration (FDA) has approved mirabegron (Myrbetriq®) to treat adults with overactive bladder, a condition in which the bladder muscle cannot be controlled, squeezes too often or squeezes without warning.

Mirabegron, as an extended-release tablet taken once daily, improves the storage capacity of the bladder by relaxing the bladder muscle during filling. The most common side effects observed in the trials were increased blood pressure, nasopharyngitis, urinary tract

infection, constipation, fatigue, tachycardia and abdominal pain. Mirabegron is not recommended for use in those with severe uncontrolled high blood pressure, end stage kidney disease or severe liver impairment.

Reference: *FDA News Release*, 28 June 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310096.htm>

Lorcaserin approved for overweight or obese adults

United States of America — The Food and Drug Administration (FDA) has approved lorcaserin hydrochloride (Belviq®) for chronic weight management in addition to a reduced-calorie diet and exercise.

Lorcaserin is approved for use in adults with a body mass index (BMI) of 30 or greater (obese), or adults with a BMI of 27 or greater and who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia.

Lorcaserin activates the serotonin 2C receptor in the brain. The approved labelling recommends that the drug be discontinued in patients who fail to lose 5% body weight after 12 weeks of treatment as these patients are unlikely to achieve clinically meaningful weight loss with continued treatment.

Lorcaserin should not be used during pregnancy. Treatment may cause serious side effects, including serotonin syndrome, particularly when taken with certain medicines that increase serotonin levels or activate serotonin receptors. These include, but are not limited to, drugs commonly used to treat depression and migraine. Lorcaserin may also cause disturbances in attention or memory.

Reference: *FDA News Release*, 27 June 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm>

Alipogene tiparvovec approved for lipoprotein lipase deficiency

European Union — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the marketing authorization of alipogene tiparvovec (Glybera®). It is intended to treat lipoprotein lipase (LPL) deficiency in patients with severe or multiple pancreatitis attacks, despite dietary fat restrictions.

LPL deficiency is an ultra-rare inherited disorder affecting no more than one or two people per million. Due to a defective gene, patients cannot produce enough LPL. So far, management of patients with the disorder consists of strict reduction of dietary fat to less than 20% of the daily caloric intake. It is very difficult to comply with such a dietary regimen and as a consequence many patients experience life-threatening pancreatitis attacks.

Alipogene tiparvovec is the first gene therapy medicine to be recommended for authorization in the European Union. It uses an adeno-associated virus vector as the delivery vehicle to add working copies of the LPL gene into muscle cells.

Reference: *European Medicines Agency Press Release*, EMA/CHMP/474664/2012, 20 July 2012 at <http://www.ema.europa.eu>

Teduglutide approved for short bowel syndrome

European Union — The European Medicines Agency (EMA) has recommended approval of teduglutide (Revestive®) for the treatment of adult patients with short bowel syndrome. This is the first medical treatment recommended for approval in Europe in this rare but seriously debilitating condition.

Short bowel syndrome is a condition in which nutrients are not properly absorbed, due to severe intestinal disease or the surgical removal of a large portion

of the small intestine. There are currently no medical treatments available. Most patients with the syndrome rely on full or supplemental parenteral nutrition. However, this has a significant impact on the quality of life of the concerned patients and is often associated with serious complications.

In clinical trials, Revestive® has demonstrated that it can additionally reduce parenteral nutrition requirements in patients with short bowel syndrome.

A review by the Agency's Committee for Medicinal Products for Human Use (CHMP) showed that most adverse events under treatment with teduglutide were mild or moderate in severity, and mainly affecting the gastrointestinal system. However, about one third of the adverse events were considered to be severe, most of them related to hepatobiliary and pancreatic events.

Reference: *European Medicines Agency Press Release*, EMA/CHMP/409283/2012, 22 June 2012 at <http://www.ema.europa.eu>

Tolperisone: restricted use

European Union — The European Medicines Agency (EMA) has recommended restricting the use of tolperisone, a muscle relaxant authorized to treat a variety of different conditions, including spasticity due to neurological disorders and muscle spasms associated with diseases of the spine and large joints in several European Union countries since the 1960s.

The review by the Agency's Committee for Medicinal Products for Human Use (CHMP) was initiated by Germany following concerns over several post marketing reports of hypersensitivity reactions and insufficiently demonstrated efficacy in some indications. Taking into account that the risk of hypersensitivity reactions is more significant than previously identified and due to uncertainties

in relation to its efficacy in the different indications, the Committee concluded that the benefits of tolperisone outweighed its risks only in the treatment of adults with post-stroke spasticity and as an oral formulation.

Reference: *European Medicines Agency Press Release*, EMA/CHMP/406866/2012, 22 June 2012 at <http://www.ema.europa.eu>

Trimetazidine-containing medicines: restricted use

European Union — The European Medicines Agency (EMA) has recommended restricting the use of trimetazidine-containing medicines in the treatment of patients with angina pectoris to second-line, add-on therapy. For all other indications the Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines were not sufficiently demonstrated and did not outweigh the risks. The CHMP therefore recommended their deletion from the marketing authorization.

Doctors should no longer prescribe trimetazidine for the treatment of patients with tinnitus, vertigo or disturbances in vision. However, they can continue to prescribe trimetazidine for the treatment of angina pectoris, but only as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies.

The review was initiated by France, mainly because of concerns that the efficacy of trimetazidine was not sufficiently demonstrated. It also looked at reports regarding the occurrence of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors and gait instability associated with the medicine.

Doctors are advised not to prescribe the medicine to patients with Parkinson disease, parkinsonian symptoms,

tremors, restless leg syndrome or other related movement disorders, nor to patients with severe renal impairment. They should exercise caution when prescribing to patients with moderate renal impairment and to elderly patients and consider dose reduction in these patients.

Trimetazidine should be discontinued permanently in patients who develop movement disorders such as Parkinsonian symptoms.

Reference: *European Medicines Agency Press Release*, EMA/CHMP/417861/2012, 21 July 2012 at <http://www.ema.europa.eu>

Semuloparin sodium: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified of the manufacturer's decision to withdraw its application for a centralized marketing authorization for the medicine semuloparin sodium (Mulsevo®), 20 mg, solution for injection. Semuloparin was intended to be used for the primary prophylaxis of venous thromboembolism (VTE) in cancer patients receiving chemotherapy for locally-advanced or metastatic solid tumours.

In its withdrawal letter, the company stated that they have decided to withdraw all applications globally following comments by regulatory agencies.

Reference: *European Medicines Agency Press Release*, EMA/CHMP/450866/2012, 9 July 2012 at <http://www.ema.europa.eu>

Tesamorelin: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified of the manufacturer's decision to withdraw its application for a centralized marketing authorisation for the medicine tesamorelin (Egrifta®), 2 mg powder for solution for injection. Egrifta® was intended to be

used for the treatment of excess visceral adipose tissue (VAT), defined as a level greater than 130 cm² by imaging procedures, in treatment-experienced HIV-infected patients.

The company decided to withdraw the application because the CHMP considers that the provided data do not allow it to conclude on a positive benefit-risk balance.

Reference: *European Medicines Agency Press Release, EMA/CHMP/431454/2012, 26 June 2012 at <http://www.ema.europa.eu>*

Lenalidomide: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified of the manufacturer's decision to withdraw

its application for a centralized marketing authorization for the medicine lenalidomide (Revlimid®) for an extension of the therapeutic indication in patients with newly diagnosed multiple myeloma and for the addition of new pack sizes.

The company decided to withdraw its application because the CHMP considers that additional, more mature data are required for it to reach a clear benefit-risk conclusion.

Revlimid® is currently indicated in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy.

Reference: *European Medicines Agency Press Release, EMA/CHMP/416782/2012, 21 June 2012 at <http://www.ema.europa.eu>*

Essential Medicines

Paediatric morphine dosage

New dosage recommendations are now available in the *WHO Guidelines on the pharmacological treatment of pain in children with medical illnesses*, published earlier in 2012 (1). The new guidelines have a more cautious approach and replace the dosage recommendations in the *WHO Model formulary for children* (2010) (2). In view of this, the dosage recommendations for morphine and other opioid analgesics in children in future editions of other relevant publications — text books and hand books, etc. — may need to be reconsidered.

WHO has no recently published guidelines on use of opioid analgesics in adults but the following may also apply to prescription in adults.

Pain treatment with strong opioids should be based on a low initial dosing.

(See tables 1 to 3 for paediatric starting dosages.) Titration of the dosage should be based on a regular assessment of the pain level which is discussed in the guidelines. After a starting dose according to the dosages mentioned in the guidelines, the dosage should be adjusted to the level that is effective (with no ceiling or maximum dose) but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient, increasing to the level that is effective.

The preferred route is oral. If oral administration is not possible, subcutaneous administration or other parenteral routes can be considered, but intramuscular administration should be avoided as it is painful. It should be noted that due to the first pass effect parenteral administration is about twice as potent as oral administration.

Table 1. Starting dosages for opioid analgesics in opioid-naive neonates

Medicine	Route of administration	Starting dose
Morphine	IV injection ^a	25–50 mcg/kg every 6 hrs
	SC injection	
	IV infusion	Initial IV dose ^a 25–50 mcg/kg then: 5–10 mcg/kg/hr
Fentanyl	IV injection ^b	1–2 mcg/kg every 2–4 hrs ^c
	IV infusion ^b	Initial IV dose ^c 1–2 mcg/kg then: 0.5–1 mcg/kg/hr

^a Administer IV morphine slowly over at least 5 minutes.

^b The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for non-ventilated neonates.

^c Administer IV fentanyl slowly over 3–5 minutes.

Table 2. Starting dosages for opioid analgesics in opioid-naïve infants (1 month –1 year)

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	80–200 mcg/kg every 4 hrs
	IV injection ^a	1–6 months: 100 mcg/kg every 6 hrs
	SC injection	6–12 months: 100 mcg/kg every 4 hrs (max. 2.5 mg/dose)
	IV infusion ^a	1–6 months: Initial IV dose: 50 mcg/kg then: 10–30 mcg/kg/hr 6–12 months: Initial IV dose: 100–200 mcg/kg then: 20–30 mcg/kg/hr
	SC infusion	1–3 months: 10 mcg/kg/hr 3–12 months: 20 mcg/kg/hr
Fentanyl ^b	IV injection	1–2 mcg/kg every 2–4 hrs ^c
	IV infusion	Initial IV dose 1–2 mcg/kg ^c then: 0.5–1 mcg/kg/hr
Oxycodone	Oral (immediate release)	50–125 mcg/kg every 4 hours

^a Administer IV morphine slowly over at least 5 minutes.

^b The intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information.

^c Administer IV fentanyl slowly over 3– 5 minutes.

The dose titration schedule mentioned above also applies to most other strong opioids but not to methadone because of its long half-life. Details for titrating methods for methadone that avoid accumulation can be found in the guidelines.

In case of overdosage of opioids, the antagonist naloxone can be administered. Occurrence of dependence is often not well understood. On adequate treatment of pain, it is rare, if occurring at all. However, if opioids are withdrawn abruptly in chronic treatment, severe withdrawal symptoms will be precipitated. Therefore, when stopping treatment, the patient should be weaned gradually: after short-

term therapy (7–14 days), the dose can be decreased by 10–20% of the original dose every 8 hours increasing gradually the time interval between doses. After long-term therapy, the dose should be reduced not more than 10–20% per week.

Pharmacological profiles for morphine and several other opioid and non-opioid analgesics, as well as for the antagonist naloxone can be found in Annex 1 of the Guidelines (page 63). The Guidelines can be downloaded from the web free of charge. The printed guidelines package also contains a pocket dosing-card and pain-assessment scales for children.

Table 3. Starting dosages for opioid analgesics in opioid-naïve children (1–12 years)

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	1–2 years: 200–400 mcg/kg every 4 hrs 2–12 years: 200–500 mcg/kg every 4 hrs (max 5 mg)
	Oral (prolonged release)	200–800 mcg/kg every 12 hrs
	IV injection ^a	1–2 years: 100 mcg/kg every 4 hrs
	SC injection	2–12 years: 100–200 mcg/kg every 4 hrs (max 2.5 mg)
	IV Infusion	Initial IV dose : 100–200 mcg/kg ^a then: 20–30 mcg/kg/hr
	SC Infusion	20 mcg/kg/hr
Fentanyl	IV injection	1–2 mcg/kg ^b repeated every 30–60 mins.
	IV Infusion	Initial IV dose 1–2 mcg/kg ^b then: 1 mcg/kg/hr
Hydro-morphone ^c	Oral (immediate release)	30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)
	IV injection ^d or SC injection	15 mcg/kg every 3–6 hrs
Methadone ^e	Oral (immediate release)	100–200 mcg/kg every 4 hrs for the first 2–3 doses, then every 6–12 hrs (max 5 mg/dose initially) ^f
	IV injection ^g and SC injection	
Oxycodone	Oral (immediate release)	125–200 mcg/kg every 4 hours; (max 5 mg/dose)
	Oral (prolonged release)	5 mg every 12 hours

a Administer IV morphine slowly over at least 5 minutes.

b Administer IV fentanyl slowly over 3–5 minutes.

c Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another. In converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose.

d Administer IV hydromorphone slowly over 2–3 minutes.

e Due to the complex nature and wide inter-individual variation in the pharmacokinetics of methadone, methadone should only be commenced by practitioners experienced with its use.

f Methadone should initially be titrated like other strong opioids. The dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation. From then on dosage increases should be performed at intervals of one week or over and with a maximum increase of 50%.

g Administer IV methadone slowly over 3–5 minutes.

References

1. World Health Organization. *WHO Guidelines for the pharmacological treatment of persisting pain in children with medical illness*. 2012 at http://www.who.int/medicines/areas/quality_safety/guide_on_pain/en/index.html and http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf
2. World Health Organization. *WHO Model Formulary for Children*, (pp. 23 and 291) 2010 at http://www.who.int/Selecion_medicines/list/WMFc.pdf

Recent Publications, Information and Events

Pharmacovigilance: towards a safer use of medicines

It is generally agreed that no drug is 100% safe for 100% of the population and in 100% of cases. Adverse drug reactions can be an important cause of disease and death, particularly for the most vulnerable. This edition, in Spanish, of *Pharmacovigilance: towards a safer use of medicines (Farmacovigilancia, hacia una mayor seguridad en el uso de los medicamentos)* highlights the importance of addressing adverse drug reactions within a public health context.

The book is addressed to clinicians and physicians — both general practitioners and specialists — pharmacists and other healthcare professionals. It offers operational concepts in pharmacovigilance, with current examples of risk-benefit assessment and impact on regulation of medicines and includes discussion on the present and future role of spontaneous reporting in regulatory decisions and public perception. It also sets out the main characteristics of collaborative activities with the World Health Organization's International Drug Monitoring Programme and the Uppsala Monitoring Centre.

In a user friendly format and written in fluent and plain language, it aims to provide a useful tool in the dissemination of basic concepts and methods while highlighting the contribution of pharmacovigilance to patient safety.

Reference: *Farmacovigilancia, hacia una mayor seguridad en el uso de los medicamentos*. Edited by Raquel Herrera Comoglio and Luis Alesso in collaboration with the Uppsala Monitoring Centre. ISBN 978-987-28104-0-5. Sociedad Argentina de Farmacovigilancia, <http://www.safv.org.ar>

Patent searches on essential medicines

The United Nations Development Programme (UNDP) has published *Patent information and transparency: a methodology for patent searches on essential medicines in developing countries*. The main aim is:

- To set out the technical aspects of the rationale for the methodology.
- To describe how it should be developed as a tool for stakeholders, including health authorities and procurement agencies in developing countries — which may not necessarily have extensive legal and patent expertise — to quickly search for patents on medicines from publicly available and free sources of information.

Reference: United Nations Development Programme. *Patent information and transparency: a methodology for patent searches on essential medicines in developing countries* at <http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/a-methodology-for-patent-searches-on-essential-medicines-in-deve.html>

HIV treatment in twenty-three countries

A report published by Médecins Sans Frontières/Doctors Without Borders (MSF) indicates that while the governments of 23 key countries have made improvements to get better antiretroviral (ARV) treatment to more people, implementation of innovative community-based strategies is lagging in some countries.

The study used 25 indicators in each of the 23 countries where MSF has HIV projects. Eleven of the 23 countries surveyed have reached ARV coverage

but six countries are still reaching only a third of people in need.

Of the 18 sub-Saharan African countries in the study, 11 allow nurses to start ARV therapy, with Kenya, South Africa, Swaziland, Uganda, Zambia and Zimbabwe having changed their policies in the last two years to allow this. Conversely, Mozambique, with the highest HIV prevalence of the countries in the study, still does not allow nurses to initiate and manage ARV treatment. Additionally, only 14 of the 23 countries allow non-clinician lay workers to provide basic HIV services like prevention, testing and treatment adherence counseling.

Reference: Médecins Sans Frontières. AIDSmeds. *Study explores treatment improvements, challenges in 23 countries*, at http://www.aidsmeds.com/articles/hiv_global_msf_1667_22734.shtml

Procurement of reproductive health supplies

The Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies is now available in Spanish. The toolkit is designed to help public sector country procurement agencies strengthen their capacity and is the first comprehensive resource to focus exclusively on the procurement process for reproductive health products. It organizes the public-sector supply process for reproductive health commodities into three phases-programme planning, procurement process and performance — and ten essential steps within these three phases.

Reference: Quality of RH medicines project. *The procurement capacity toolkit: tools and resources for procurement of reproductive health supplies*, at <http://www.path.org/publications/detail.php?i=1652>

Assessing risk of resistance in antimalarial compounds

The Medicines for Malaria Venture (MMV) has developed a framework to evaluate the risk of resistance for the antimalarial compounds in its portfolio. A paper based on this work: *A framework for assessing the risk of resistance for antimalarials in development* has been published in the *Malaria Journal*.

Cross-resistance testing using a panel of multi-drug-resistant strains of the parasite checks for pre-existing resistance liability and ensures that none of MMV's compounds are cross-resistant with other drugs.

The framework also includes selection experiments in the laboratory that measure how easy it is for the parasite to develop resistance. This is achieved by measuring the minimal inoculum for resistance. Although this is already being done, the framework offers a standard, systematic method.

This new framework will result in a fully profiled portfolio for MMV in terms of resistance and could also be used by other malaria researchers to assess their compounds, measure the genetic ability of parasites to develop resistance and the intensity of the resistance.

References

1. *MMV Press release*. MMV develops framework to assess risk of resistance for antimalarial compounds. 22 August 2012 at <http://www.mmv.org>
2. A framework for assessing the risk of resistance for antimalarials in development. *Malaria Journal* at <http://www.malariajournal.com>

Consultation Documents

The International Pharmacopoeia

4. Reference substances and reference spectra

Draft proposal for the supplementary information section of *The International Pharmacopoeia* (June 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidh@who.int). Working documents are available for comment at <http://www.who.int/medicines>.

[Note from the secretariat: The chapter proposed will be part of the supplementary information section of The International Pharmacopoeia, which provides the user with texts for guidance and information and will not constitute part of the standards.]

4.1 International Chemical Reference Substances

4.1.1 Introduction

International Chemical Reference Substances (ICRS) are primary chemical reference substances for use in physical and chemical tests and assays described in The International Pharmacopoeia or in other WHO quality assurance documents adopted by the Expert Committee on Specifications for Pharmaceutical Preparations. ICRS are used to identify and determine the purity and the assay of pharmaceutical substances and preparations.

This chapter describes principles to be applied during the establishment and use of ICRS, which guarantee that the reference substances are suitable for their intended purpose. This chapter is not applicable to WHO International Biological Reference Preparations.

4.1.2 Terminology

Chemical reference substance

The term chemical reference substance, as used in this text, refers to an authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

Primary chemical reference substance

A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context, and whose assigned content when used as an assay standard is accepted without requiring comparison with another chemical substance.

Secondary chemical reference substance

A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

4.1.3 Purpose of ICRS

The purpose of establishing ICRS is to provide users of The International Pharmacopoeia or other WHO quality assurance documents adopted by the Expert Committee on Specifications for Pharmaceutical Preparations with authenticated substances for reference. Many analytical tests and assays are based on comparison of physical or chemical properties of a sample with those of a reference standard. ICRS serve as such reference standards and thus enable the analyst to achieve accurate and traceable results. Furthermore, ICRS may be used to assess system suitability during analyses and to calibrate analytical instruments.

ICRS may also be employed to establish secondary reference substances according to the WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances. In cases of doubtful results or dispute, however, the tests performed using ICRS are the only authoritative ones.

4.1.4 Establishment of ICRS

All operations related to the establishment and distribution of ICRC should be carried out according to the relevant guidelines. Among these, the WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances* and International Organization for Standardization (ISO) Guide 34 (including related guides) have a prominent position.

Production

Source material for the establishment of ICRC is usually batches selected from the normal pharmaceutical production provided that the purity and homogeneity are suitable. Compliance with the relevant tests of the corresponding monograph as published in The International Pharmacopoeia is required where applicable. WHO encourages pharmaceutical manufacturers to donate suitable candidate material and thus to contribute to the availability of ICRC.

Reference standards are dispensed into containers under appropriate filling and closure conditions, to ensure the integrity of the reference material. The containers employed are preferably single use in order to minimize the risk of decomposition, contamination and water uptake.

Analytical characterization

The source material should be tested with suitable analytical techniques aiming to characterize the relevant quality attributes. In general, the mass balance approach is used to assign a content. Following this approach, the cumulative percentage of all

* World Health Organization. Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-fifth Report. Annex 3. Technical Report Series, No. 567. 1975.

components determined (main component, organic and inorganic impurities, water and residual solvents) should yield 100%. The identity is confirmed, the purity is determined and the content is assigned, usually based on results obtained with the validated methods of the respective monographs. Absolute methods (for example, volumetric titrations, differential scanning calorimetry) should be used to complement and verify the results of methods where the properties of a sample are compared with those of a reference substance (relative methods, for example chromatographic methods).

The extent of testing and the number of laboratories involved in characterizing the material depend on the intended use of the reference standard to be established. If required, assay standards are characterized in interlaboratory trials to increase the accuracy of the assigned value and to determine the associated uncertainty.

In general, assay ICRS are assigned a content value calculated according to the following formula:

$$\text{assigned content (on an «as is» basis)} = 100 - \text{water \%} - \text{residual solvent \%} - \text{organic impurities \%} - \text{inorganic impurities \%}$$

When applying this formula the user has to make sure that all values subtracted are expressed as percentages of the “as is” amount of the reference substance, i.e. the substance without any prior treatment or correction for volatiles or other components. Organic impurities are often determined by chromatographic methods, based on the calculation of individual peak areas as a percentage of the total area of all peaks. To refer a chromatographic purity to the “as is” basis of the compound it has to be multiplied with the term: $(100 - \text{water \%} - \text{residual solvent \%} - \text{inorganic impurities \%})/100$.

Instead of measuring the content of water and residual solvent loss on drying may be determined.

Labelling

The labelling should bear all information necessary to use the reference substance as intended, i.e. the name of the reference substance, the batch number, storage conditions, etc. If intended for quantification the assigned content or potency (for biological or microbiological assays) is also given. The accompanying leaflet is considered to be part of the labelling.

Storage and distribution

ICRS are stored and distributed under conditions suitable to ensure their stability.

The stability of ICRS is monitored by regular re-examinations. The frequency and extent of the retesting is based on the:

- liability of the material to degradation
- container and closure system
- storage conditions
- hygroscopicity
- physical form
- intended use.

The analytical methods employed are often chosen among those performed during the establishment of the reference standard. The maximum permitted deviation from the assigned value should be predefined and, if exceeded, the batch should be re-established or replaced.

Release and adoption

ICRS are established and released under the authority of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Committee adopts new ICRS lots as being suitable for use as described in The International Pharmacopoeia or in other WHO quality assurance documents.

4.1.5 Use of ICRS

The letters RS after the name of a substance in a test or assay described in The International Pharmacopoeia or in other WHO quality assurance documents adopted by the Expert Committee on Specifications for Pharmaceutical Preparations indicates the use of the respective ICRS. Directions for use of ICRS are given in the leaflet enclosed with the substance when distributed.

ICRS are suitable for the analytical purpose described in The International Pharmacopoeia or other WHO quality assurance documents adopted by the Expert Committee on Specifications for Pharmaceutical Preparations. When used for other purposes the responsibility for assessing the suitability rests with the user or the other authority that prescribes or authorizes this use. If reference standards other than ICRS are used for purposes described in The International Pharmacopoeia or in other WHO quality assurance documents adopted by the Expert Committee on Specifications for Pharmaceutical Preparations the suitability of these substances has to be demonstrated by the user.

ICRS are supplied in adequate quantities for immediate use after opening of the container. Users should purchase only sufficient amount for short-term use.

It is generally recommended to store ICRS protected from light and moisture and preferably at a temperature of about 5 ± 3 °C. When special storage conditions are required, this is stated on the label or in the accompanying leaflet.

If an unopened container is stored under the recommended conditions it remains suitable for use as long as the respective batch is valid. Information on current batch numbers is provided on the web site of the WHO Custodian Centre for ICRS (see under ordering information).

Reference standards that are normally stored at 5 ± 3 °C are dispatched at ambient temperature since short-term excursions from the storage recommendations are considered not deleterious to the reference standard. Reference standards stored at -20 °C are packed on ice or dry ice and dispatched by courier. Reference standards stored at -80 °C or stored under liquid nitrogen are packed on dry ice and dispatched by courier.

4.1.6 Ordering information

Since April 2010 the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe is responsible for the establishment, preparation, storage and distribution of ICRS for The International Pharmacopoeia.

A list of ICRS currently available can be found on the internet site of the WHO Custodian Centre for ICRC (see <http://www.edqm.eu>).

Orders for International Chemical Reference Substances should be sent to:

European Directorate for the Quality of Medicines & HealthCare
7 allée Kastner
CS 30026
F-67081 Strasbourg
France
Fax: +33 (0)3 88 41 27 71 (For the attention of EDQM Sales Section)
E-mail: orders@edqm.eu

The current price for ICRC is 70 Euros per package. Extra charges will be added for the delivery of the reference substances. For details see the above-mentioned web site.

4.2 International Infrared Reference Spectra

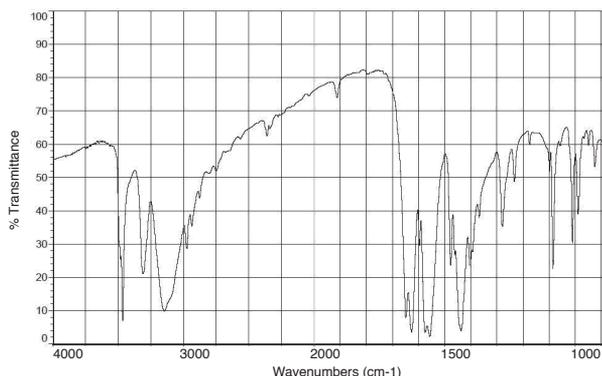
International Infrared Reference Spectra (IIRS) are provided for use in identification tests as described in monographs of The International Pharmacopoeia or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The reference spectra are produced from authenticated material using an appropriate sample preparation technique. They are recorded with a Fourier transform infrared spectrophotometer. Instructions for the preparation of spectra are given in 1.7 Spectrophotometry in the infrared region; Identification by reference spectrum.

A spectrum of the test substance is considered to be concordant with a reference spectrum if the transmission minima (absorption maxima) of the principal bands in the test spectrum correspond in position, relative intensities and shape to those in the reference spectrum.

Infrared reference spectra RS001-RS154 can be found in the first and second supplement of The International Pharmacopoeia.

Pyrimethamine (RS155)



Instrument: Fourier Transform
Phase: Potassium bromide disc

Revision of monograph on capsules

Final text for addition to *The International Pharmacopoeia* (July 2012).
Please address any comments to Quality Assurance and Safety: Medicines,
World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22
791 4730 or e-mail to schmidh@who.int. Working documents are available
for comment at <http://www.who.int/medicines>.

The requirements of this monograph do not necessarily apply to preparations that are intended for use other than by oral administration, such as vaginal or rectal capsules, etc. Such preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use. Starch capsules (often known as cachets) are not included in this monograph.

Definition

Capsules are solid dosage forms with hard or soft shells. They are of various shapes and sizes, and contain a single dose of one or more active ingredients. They are intended for oral administration.

Capsule surfaces may bear symbols or other markings.

Capsule shells are made of gelatin or other substances, the consistency of which may be modified by the addition of substances such as glycerol or sorbitol. The shell should disintegrate in the presence of digestive fluids so that the contents are released. The contents of capsules may be solid, liquid, or of a paste-like consistency. Capsule shells and contents may contain excipients such as diluents, solvents, surface-active substances, opaque fillers, antimicrobial agents, sweeteners, colouring matter authorized by the appropriate national or regional authority, flavouring substances, disintegrating agents, glidants, lubricants, and substances capable of modifying the behaviour of the active ingredient(s) in the gastrointestinal tract. The contents should not cause deterioration of the shell.

When excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

The different categories of capsule include:

- hard capsules;
- soft capsules;
- modified-release capsules [including delayed-release capsules (gastro-resistant/enteric capsules) and sustained-release capsules (extended-/prolonged-release capsules)].

Manufacture

The manufacturing and filling processes for capsules should meet the requirements of good manufacturing practices (GMP).

Very broad guidelines concerning the main critical steps to be followed during production of capsules, indicating those that are the most important, are provided below.

Additional guidelines specific for hard or soft capsules are provided in the respective subsections below.

In the manufacture of capsules, measures are taken to:

- ensure that the active ingredient(s) when present in solid state form have appropriate solid-state properties such as particle-size distribution and polymorphic form;
- ensure that mixing with excipients is carried out in a manner that ensures homogeneity;
- minimize the degradation of the active ingredient(s);
- minimize the risk of microbial contamination;
- minimize the risk of cross contamination.

The particle size of the active ingredient(s) may be of primary significance in determining the rate and extent of dissolution and the bioavailability of the drug product, especially for substances of low solubility in aqueous media. The uniformity of the final drug product is affected by the particle size of the active ingredient(s) as well as the excipients.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.

Packaging is required to be adequate to protect capsules from light when required, and from moisture and damage during transportation.

Visual inspection

Unpack and inspect at least 20 capsules. They should be smooth and undamaged. Evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking, swelling, mottling, or discoloration of the shell.

Uniformity of mass

Capsules comply with the test for 5.2 Uniformity of mass for single-dose preparations, unless otherwise specified in the individual monograph.

Uniformity of content

Where a requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in an individual capsule monograph the test for 5.2 Uniformity of mass for single-dose preparations is not required.

Dissolution/disintegration

Where a choice of test is given ("Either test A or test B may be applied"), follow the instructions in the monograph. Where a requirement for compliance with a dissolution test is specified in the individual monograph, the requirement for disintegration stated in the sections below do not apply.

When justified and authorized the specified disintegration and dissolution media may contain enzymes to overcome failure in the tests caused by cross-linking of the gelatin.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

- (1) the name of the pharmaceutical product;
- (2) the name(s) of the active ingredient(s). International Nonproprietary Names (INNs) should be used wherever possible;
- (3) the amount of the active ingredient(s) in each capsule and the number of capsules in the container;
- (4) the batch (lot) number assigned by the manufacturer;
- (5) the expiry date and, when required, the date of manufacture;
- (6) any special storage conditions or handling precautions that may be necessary;
- (7) directions for use, warnings, and precautions that may be necessary;
- (8) the name and address of the manufacturer or the person responsible for placing the product on the market.

Storage

Capsules should be kept in well-closed containers. They should be protected from light when required, and from excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C. Additional special packaging, storage, and transportation recommendations are provided, where necessary, in the individual monograph.

Requirements for specific types of capsules**Hard capsules****Definition**

Hard capsules have shells consisting of two prefabricated cylindrical sections that fit together. One end of each section is rounded and closed, and the other is open. The contents of hard capsules are usually in solid form (powder or granules).

Manufacture

Sometimes, the physical characteristics of the mixture of the active ingredient(s) and excipients allow it to be directly filled into the shell, but it may occasionally be necessary to granulate before filling. Normally the granulate needs to be mixed with lubricants and/or disintegrating agents. The use of excessive amounts of lubricants should be avoided since these may deleteriously affect the capsules.

In-process controls during hard capsule production should include the moisture content of the mixture and/or granulate (as well as of the shells), the size of granules, the flow of the final mixture, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

Disintegration test

Hard capsules comply with 5.3 Disintegration test for tablets and capsules. Use water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS or other medium is specified in the individual monograph. Operate the apparatus for 30 minutes, unless otherwise justified and authorized and examine the state of the capsules.

If capsules float, use a disc as described under 5.3 Disintegration test for suppositories.

Soft capsules

Definition

Soft capsules have thicker shells than hard capsules, and antimicrobial preservatives are usually added. The shells are of one piece and various shapes. The contents of soft capsules are usually solutions or suspensions of the active ingredient(s) in non-aqueous liquids. Partial migration of the contents into the shell may occur (and vice versa) depending on the nature of the materials used and the product in question.

Manufacture

Soft capsules are usually formed, filled, and sealed in one operation. However, shells for extemporaneous use are sometimes prefabricated. Liquids may be incorporated directly. Solids are usually dissolved or dispersed in a suitable excipient(s) to give a solution, suspension or dispersion of paste-like consistency.

In-process controls during soft capsule production should include the viscosity of the contents, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

Disintegration test

Soft capsules comply with 5.3 Disintegration test for tablets and capsules, using water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS or other medium is specified in the individual monograph. Add a disc to each tube. Liquid active substances dispensed in soft capsules may attack the disc; in such circumstances and where authorized, the disc may be omitted. Operate the apparatus for 30 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

Modified-release capsules

Definition

Modified-release capsules are hard or soft capsules in which the contents or the shell or both contain excipients or are prepared by special procedures such as micro-encapsulation which, separately or together, are designed to modify the rate, place or time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release capsules (Extended- or Prolonged-release capsules)

Definition

Sustained-release capsules are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

All requirements for these specialized dosage forms are given in the individual monographs.

Delayed-release capsules (gastro-resistant/enteric capsules)

Definition

Delayed-release capsules are hard or soft capsules prepared in such a manner that either the shell or the contents resist the action of gastric fluid but release the active ingredient(s) in the presence of intestinal fluid.

Manufacture

The additional statements given under either hard or soft capsules apply, as appropriate to delayed-release capsules.

Disintegration test

Delayed-release capsules with a gastro-resistant shell comply with 5.3 Disintegration test for tablets and capsules, using hydrochloric acid (0.1 mol/l) VS as the immersion fluid. Operate the apparatus without the discs for 2 hours, unless otherwise specified in the individual monograph (but in any case for not less than 1 hour), and examine the state of the capsules. No capsule should show signs of disintegration or rupture permitting the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS with added pancreatin R where specified in the individual monograph. Add a disc to each tube. Operate the apparatus for 60 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

For capsules in which the contents, rather than the shell, resist the action of gastric fluid, carry out a suitable dissolution test to demonstrate the appropriate release of the active substance(s).

Abacavir oral solution
Abacaviri solutionum peroralum**Revision of pH test**

Draft proposal for *The International Pharmacopoeia* (July 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidh@who.int. Working documents are available for comment at <http://www.who.int/medicines>.

Category. Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor)

Storage. Abacavir oral solution should be kept in a well-closed container.

Labelling. The designation of the container of Abacavir oral solution should state that the active ingredient is in the sulfate form and the quantity should be indicated in terms of the equivalent amount of abacavir.

Additional information. Strength in the current WHO Model list of Essential Medicines: 100 mg of abacavir per 5ml (20 mg per ml). Strength in the current WHO Model list of Essential Medicines for Children: 100 mg of abacavir per 5ml (20 mg per ml).

Requirements

Complies with the monograph for "Liquid preparations for oral use".

Definition. Abacavir oral solution is a solution of Abacavir sulfate in a suitable vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of abacavir (C₁₄H₁₈N₆O) stated on the label.

Identity tests

Either tests A, C and D or tests B, C and D may be applied.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica R6 as the coating substance and a mixture of 8 volumes of dichloromethane R, 2 volumes of 2-propanol R as the mobile phase. Apply separately to the plate 5 µl of each of the following 2 solutions. For solution (A) dilute a volume of the oral solution with methanol R to give a solution containing the equivalent of 5 mg of abacavir per ml. For solution (B) use 6 mg of abacavir sulfate RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B. See the test described under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

C. To a volume of oral solution containing the equivalent of 15 mg of abacavir add 100 ml of water R and shake; dilute 5 ml of this solution to 50 ml with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 220 nm and 320 nm, exhibits a maximum at about 291 nm.

D. To a volume of the oral solution containing the equivalent of about 20 mg of abacavir add 5 ml of water R and shake. The resulting solution yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

pH value (1.13). pH of the oral solution, 3.8–4.5.

[Note from the Secretariat: Based on updated information received from manufacturers and assessment specialists a revision of the limits is consider to read:

pH value (1.13). pH of the oral solution, 3.8–5.0.]

Related substances

Apply criteria A in all cases and criteria B, whenever possible.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the same chromatographic conditions as described under Assay.

Prepare the following solutions in the dissolution solvent prepared by diluting 1 ml of phosphoric acid (~ 1440 g/l) TS in 1 litre of water R.

For solution (1) transfer a volume of the oral solution containing the equivalent of 10 mg of abacavir in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (2) dilute 5.0 ml of solution (1) to 50.0 ml with the dissolution solvent; dilute 5.0 ml of this solution to 50.0 ml with the same solvent. For solution (3) dissolve 5 mg of abacavir sulfate for system suitability RS (containing abacavir sulfate and impurities B to F) in the dissolution solvent and dilute to 25 ml with the same solvent. For solution (4) dissolve a suitable amount of each of the excipients stated on the label in 10 ml of a suitable solvent and dilute to 100 ml with the dissolution solvent. Inject separately 20 µl each of solutions (1), (2), (3) and (4) and of dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the impurity peaks are eluted at the following relative retention with reference to abacavir (retention time about 19 minutes): impurity C about 0.7; impurity D about 1.05; impurity E about 1.10; impurity B about 1.3; impurity F about 1.7. The test is not valid unless the resolution between the peaks due to abacavir and impurity D is at least 1.5.

If information concerning the excipients used in manufacturing the oral solution is not available or, if any of the peaks in the chromatogram obtained with solution (4) corresponds to any of the peaks in the chromatogram obtained with solution (3) or, if interference by excipients has been demonstrated by any other means, apply only criteria A.

A. In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%); the area of any peak with a relative retention greater than 0.5 but less than that of impurity C is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (impurity G, 0.5%).

B. In the chromatogram obtained with solution (1), the area of any other peak, apart from the principal peak, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%). The sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with the same retention time as that of any of the peaks in the chromatogram obtained with solution (4) and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm), packed with octadecylsilyl silica gel for chromatography (5 µm).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 0.05% solution of trifluoroacetic acid R in water R.

Mobile phase B: 85 volumes of methanol R and 15 volumes of water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 20	95 to 70	5 to 30	Linear gradient
20 – 35	70 to 10	30 to 90	Linear gradient
35 – 40	10	90	Isocratic
40 – 41	10 to 0	90 to 100	Linear gradient
41 – 50	0	100	Isocratic
50 – 51	0 to 95	100 to 5	Return to initial composition
51 – 55	95	5	Re-equilibration

Operate with a flow rate of 0.8 ml per minute and the column oven temperature at 30 °C. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Prepare the following solutions in the dissolution solvent prepared by diluting 1 ml of phosphoric acid (~ 1440 g/l) TS in 1 litre of water R.

For solution (1) transfer an accurately weighed quantity of the oral solution containing the equivalent of about 10 mg of abacavir into a 50 ml volumetric flask. Add about 40 ml of dissolution solvent, shake mechanically for about 10 minutes and make up to volume using the same solvent. For solution (2) use 0.23 mg of abacavir sulfate RS per ml of dissolution solvent. For solution (3) dissolve 5 mg of abacavir sulfate for system suitability RS (containing abacavir sulfate and impurities B to F) in the dissolution solvent and dilute to 25 ml with the same solvent. For solution (4) dissolve a suitable amount of each of the excipients stated on the label in 10 ml of a suitable solvent and dilute to 100 ml with the dissolution solvent.

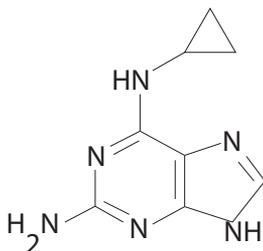
Inject separately 20 µl each of solutions (3) and (4). In the chromatogram obtained with solution (3), the impurity peaks are eluted at the following relative retention with reference to abacavir (retention time about 19 minutes): impurity C about 0.7; impurity D about 1.05; impurity E about 1.10; impurity B about 1.3; impurity F about 1.7. The assay is not valid unless the resolution between the peaks corresponding to abacavir and impurity D is at least 1.5. The assay is also not valid if any of the peaks in the chromatogram obtained with solution (4) corresponds to the peak due to abacavir in the chromatogram obtained with solution (3).

Inject alternatively 20 µl each of solution (1) and (2) and record the chromatograms. Measure the areas of the peak responses obtained in the chromatograms from solution (1).

Determine the weight per ml (1.3.1) of the oral solution and calculate the percentage content of abacavir (C₁₄H₁₈N₆O) weight in volume in the oral solution using the declared content of (C₁₄H₁₈N₆O)₂.H₂SO₄ in abacavir sulfate RS. Each mg of (C₁₄H₁₈N₆O)₂.H₂SO₄ is equivalent to 0.8537 mg of C₁₄H₁₈N₆O.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph for Abacavir sulfate and the following:



G. (*N*⁶-cyclopropyl-3*H*-purine-2,6-diamine)

Pyrantel oral suspension

Draft proposal for *The International Pharmacopoeia* (July 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidh@who.int. Working documents are available for comment at <http://www.who.int/medicines>.

Category. Anthelmintic.

Storage. Pyrantel oral suspension should be kept in a tightly-closed, container, protected from light.

Labelling. The designation on the container of Pyrantel oral suspension should state that the active ingredient is in the embonate form, and the quantity should be indicated in terms of the equivalent amount of pyrantel.

Additional information. Strength in the current WHO Model List of Essential Medicines: 50 mg of pyrantel/ml.

Requirements

Complies with the monograph for «Liquid preparations for oral use».

Definition. Pyrantel oral suspension is a suspension of pyrantel embonate in a suitable vehicle which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of pyrantel (C₁₁H₁₄N₂S) stated on the label.

Identity tests

Either tests A, or any two of tests B, C, D and E may be applied.

To a quantity of the oral suspension containing the equivalent of about 20 mg of pyrantel add a mixture of 10 ml of dichloromethane R, 10 ml of methanol R, and about 1 ml of ammonia (~260 g/l) TS, shake and filter. Evaporate the filtrate to dryness on a water-bath, dissolve in a small volume of methanol R (about 3 ml) by heating on a water-bath and then allowing the solution to cool. Separate the crystals, dry at 80 °C for 2 hours, and use the dried crystals for «Identity tests A, C and D».

A. Carry out the examination with the dried crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from pyrantel embonate RS or with the reference spectrum of pyrantel embonate.

B. See the test described under Related substances method A. The principal spots obtained with solution (1) correspond in position, appearance, and intensity with those obtained with solution (3).

C. The absorption spectrum (1.6) of a 13 µg/ml solution of the dried crystals in methanol R, when observed between 230 nm and 360 nm, exhibits 2 maxima at about 288 nm and 300 nm. The ratio of the absorbance at 288 nm to that at 300 nm is about 1.0.

D. Dissolve about 5 mg of the dried crystals in 1 ml of hydrochloric acid (~70 g/l) TS and add 1 ml of formaldehyde/sulphuric acid TS; a violet-red colour is produced.

E. See the test described under Assay method B. The retention times of the principal peaks in the chromatogram obtained from solution (1) are similar to those obtained from solution (2).

pH value. (1.3) pH of the oral suspension, 4.5–6.0.

Related substances

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Either method A or B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 3 volumes of ethyl acetate R, 1 volume of water R, and 1 volume of glacial acetic acid R as the mobile phase.

To a quantity of the oral suspension equivalent of about 35 mg of pyrantel add a mixture of 10 ml of dichloromethane R, 10 ml of methanol R, and about 1 ml of ammonia (~260 g/l) TS, shake, and filter. Evaporate the filtrate to dryness on a water-bath, and dissolve the dried residue in 10.0 ml dimethylformamide R (1). For solution (2) dilute 1.0 ml of solution (1) to 100 ml with dimethylformamide. For solution (3) use 10 mg of pyrantel embonate RS (equivalent to about 3.5 mg of pyrantel) per ml dimethylformamide. For solution (4) expose a quantity of solution (3) under 2000 lx illumination for 24 hours.

Apply separately to the plate 5 µl of each of the solutions (1), (2), (3) and (4).

After application allow the spots to dry for 15 minutes in a current of air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber, allow it to dry in a current of air for 10 minutes. Examine the chromatogram in ultraviolet light (254 nm).

Pyrantel and related substances have the following R_f values: impurity A about 0.2; pyrantel about 0.3; embonic acid about 0.9. The test is not valid unless the chromatogram obtained with solution (4) exhibits three well separated spots.

In the chromatogram obtained with solution (1) any spot, other than the two principal spots, is not more intense than the pyrantel spot in the chromatogram obtained with solution (2) (1.0%). Disregard any spot remaining at the point of application.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay method B.

Prepare the following solutions. For solution (1) transfer a quantity of the oral suspension containing the equivalent of about 25 mg of pyrantel, into a 100 ml volumetric flask. Add 7 ml of a mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R. Shake and dilute to volume with acetonitrile R, mix and filter. For solution (2), dilute 1.0 ml of solution (1) to 100 ml with mobile phase. For solution (3) expose 10 ml of solution (1) under 2000 lx illumination for 24 hours.

Inject separately 20 µl of each of solution (1), (2) and (3) and record the chromatograms for 4 times the retention time of pyrantel.

In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention times with reference to pyrantel (retention time about 14 minutes): embonic acid about 0.5; impurity A about 1.3. The test is not valid unless the resolution factor between the pyrantel peak and the impurity A peak is at least 4.0. In the chromatograph obtained with solution (1): the area of any impurity peak is not greater than the area of the pyrantel peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.1%).

Assay

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Either method A or B may be applied.

A. Transfer a quantity of the oral suspension containing the equivalent of about 35 mg pyrantel, accurately weighed, into a 100 ml volumetric flask. Add a mixture of 10 ml of dioxan R and 10 ml of ammonia (~100 g/l) TS. Shake for 10 minutes and dilute to volume with perchloric acid (~140 g/l) TS. Filter, discard the first 10 ml of the filtrate, and transfer 5.0 ml of the subsequent filtrate to a 50 ml volumetric flask. Dilute to volume with perchloric acid (~140 g/l) TS and mix. Transfer 25.0 ml to a 250 ml separatory funnel, and extract with two quantities, each of 100 ml of dichloromethane R. Combine the dichloromethane extracts into another 250 ml separatory funnel, and extract with three quantities, each of 50 ml of hydrochloric acid (0.05 mol/l) VS. Combine the aqueous phases in a 200 ml volumetric flask, rinse the separatory funnel draining into the volumetric flask, and dilute to volume with hydrochloric acid (0.05 mol/l) VS. Measure the absorbance (1.6) of a 1 cm layer at the maximum at about 311 nm against a solvent cell containing hydrochloric acid (0.05 mol/l) VS.

Determine the weight per ml (1.3.1) of the oral suspension and calculate the content of pyrantel (C₁₁H₁₄N₂S), weight in volume, in the oral suspension by comparison with pyrantel embonate RS, similarly and concurrently examined. Each mg of pyrantel embonate C₁₁H₁₄N₂S, C₂₃H₁₆O₆ is equivalent to 0.3469 mg of pyrantel C₁₁H₁₄N₂S.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm×4.6 mm) packed with high purity base particles of silica gel for chromatography R (5 µm). Shim-pack HRS-SIL column (25 cm×4.6 mm, 5 µm) has been found suitable.

As the mobile phase, use a mixture of 92.8 volumes of acetonitrile R and 7.2 volumes of a solvent mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R.

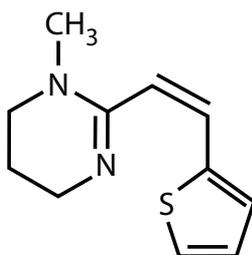
Prepare the following solutions. For solution (1), transfer a quantity of the oral suspension containing the equivalent of about 6.9 mg of pyrantel, accurately weighed, into a 50 ml volumetric flask. Add about 30 ml of mobile phase, shake for 10 minutes and dilute with mobile phase to volume, mix and filter. Transfer 2.0 ml of the clear filtrate to a 10 ml volumetric flask, dilute with mobile phase to volume and mix. For solution (2), prepare a solution of 0.40 mg of pyrantel embonate RS (equivalent to about 0.14 mg of pyrantel) per ml mobile phase. Transfer 2.0 ml of this solution to a 10 ml volumetric flask, dilute with mobile phase to volume, and mix to obtain a standard preparation having a known concentration of 80 µg of pyrantel embonate RS (equivalent to about 28 µg of pyrantel) per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 288 nm.

Inject separately 20 µl each of solution (1) and (2) and record the chromatograms. In the chromatogram obtained with solution (2), the peak due to embonic acid is eluted at a relative retention time of about 0.5 with reference to pyrantel (retention time about 14 minutes).

Measure the areas of the peak responses due to pyrantel obtained in the chromatograms from solution (1) and solution (2). Determine the weight per ml (1.3.1) of the oral suspension and calculate the content of pyrantel (C₁₁H₁₄N₂S), weight in volume, in the oral suspension. Each mg of pyrantel embonate C₁₁H₁₄N₂S, C₂₃H₁₆O₆ is equivalent to 0.3469 mg of pyrantel C₁₁H₁₄N₂S.

Impurities



A. 1-methyl-2-[(Z)-2-(thiophen-2-yl)ethenyl]-1,4,5,6-tetrahydropyrimidine.