

The Emerging Markets: Regulatory issues and the impact on patients' access to medicines

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CMR International Institute Workshop

THE EMERGING MARKETS: REGULATORY ISSUES AND THE IMPACT ON PATIENTS' ACCESS TO MEDICINES

SECTION 1: SUMMARY OF THE RECOMMENDATIONS

Introduction

Convened in Geneva, close to the headquarters of the World Health Organization and other major United Nations Institutions, this Workshop brought together senior regulators from government agencies and regulatory experts from industry to discuss the factors that help or hinder patients' access to new medicine in the emerging markets of the developing countries.

Against a snowy backdrop, participants from much warmer climates discussed the policies and procedures followed by their regulatory agencies. Although the countries and regions of the world under discussion were very diverse in geography and culture, a study carried out by CMR International in 2004/2005 had demonstrated clearly that the regulatory aspirations, barriers, problems and priorities related to the review and availability of new medicines are essentially similar.

Speakers throughout the Workshop¹ discussed these issues and the Round Table discussions focussed on some of the most pressing. The recommendations are reported briefly below and described in more detail in Section 2 of this report.

Recommendations

Defining Regulatory Models

There is a need for much greater openness in recognising the extent and limits of the assessment undertaken by agencies.

It was recommended that future CMR International studies on regulatory agencies in the Emerging Markets should include a classification of type(s) of review that are carried out by the agency.

Three main types of review were identified:

- Type 1: Verification Assessment
- Type 2: Abridged Assessment
- Type 3: Full Assessment

Best use of the CPP

The Workshop discussed current requirements for providing a Certificate of a Pharmaceutical Product (CPP) under the WHO Certification Scheme and concluded that a lack of flexibility in requirements and a pre-occupation with the exchange of original paper documentation, in the electronic age of the 21st century, can be a significant impediment to the efficient and timely registration of new medicines.

It was recommended that WHO should be asked to initiate a fundamental revision of guidance on the way in which the Certification Scheme is implemented, to take account of current regulatory procedures in an electronic environment.

Targets for review times

There is concern about the apparent disparity in the time taken to approve products for the Emerging Markets, especially where registration in a major market is a pre-requisite for submitting the application and therefore delays the start of the review process.

It was recommended that all regulatory agencies should be encouraged to set realistic targets for review times for NASs and that CMR International should collect further information to benchmark review and approval processes for NASs in Emerging Markets

Scientific Assessments

The importance of sharing limited resources, avoiding unnecessary duplication and benefiting from the scientific assessment of other agencies was stressed throughout the discussions.

The development of regional consortiums was recommended in order to share expertise and spread the workload for the assessment of NASs. This would allow issues such as stability requirements for the local environment and use of the product within the medical culture and infrastructure of the region to be taken into account.

¹ See page 11 for the programme of the meeting

Exchange of Scientific Evaluation Reports

It was recommended that agencies in the Emerging Markets should be encouraged to enter into formal agreements with their 'reference' agencies for the exchange of scientific evaluation reports, under suitable confidentiality agreements.

Whilst it was acknowledged that the European Pharmaceutical Evaluation Reports (EPARs) and FDA Summary Reviews for new medicines are publicly available on the Internet, it was felt that these do not provide sufficient insight into the scientific assessment to meet the requirements of other agencies that are evaluating the products.

Transparency and Partnership

It was recommended that there are substantial benefits for all parties in establishing an open and transparent relationship in which agencies and companies act in partnership to ensure that new medicines are made available to patients in a timely manner.

It must, however, be recognised that transparency needs agency resources and expectations must be set at realistic levels.

Guidelines

There was concern about the tendency for guidelines to become 'directives' and not be implemented with the flexibility and degree of discretion originally intended.

It was recommended that good regulatory practices should incorporate transparent 'good guideline practices' to ensure that guidelines are not applied as if they are binding. Companies should be allowed to deviate from regulatory guidelines provided that adequate and well-reasoned justification is provided.

Analysis of Samples

It was noted that work on the analysis of samples is an integral part of the review process in some countries and can delay the final authorisation of a new product.

It was recommended that pre-launch testing of NASs is not a good use of laboratory resources but that agencies should have access to testing facilities (either national or regional) to test for counterfeit or substandard products in the market place.

Workshop Organisation

Workshop organised by: Stuart Walker, Jennifer Collins and Neil McAuslane, CMR International, Institute for Regulatory Science.

Report prepared by Margaret Cone

Background Documents

Assessing the regulatory environment and its impact on patients' access to new medicines:

- **R&D 47:** South East Asia and the Western Pacific
- **R&D 48:** Middle East and Africa
- **R&D 49:** Latin America
- **R&D 50:** ***A cross-regional comparison of the regulatory environment in emerging markets***

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CMR International Institute Workshop

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SECTION 2: SUMMARY REPORT

OVERVIEW

The opening Session of the Workshop (see programme on page 11) provided an opportunity to review some of the underlying factors that have an impact on the timely registration and availability of medicines in the regions of the world outside the major pharmaceutical markets of the USA, European Union, Japan, Canada and Australia.

Professor Trevor Jones, in his keynote presentation, looked beyond the newly 'emerging markets' on which the workshop was focused and discussed access to medicines in all the so-called 'developing countries' of the world. The challenge, he noted, was not only availability of medicines but also accessibility and affordability. The latter is a particular issue with new medicines, but even for the established products that are included on the WHO list of Essential Medicines it has been estimated that 30% of the world's population lacks regular access.

A WHO perspective was provided by **Precious Matsoso** who described way that WHO is assessing national regulatory agencies (NRAs), and classifying them according to their capacity to control the medicinal products on their markets as well as helping them to progress up the regulatory 'scale'. Of a total of 192 WHO member states, about 20% have a developed capacity to carry out reviews and regulate medicines and 30% have limited or no capacity to regulate their markets. The remaining 50% are at varying stages of development ranging from a basic capacity to register medicines to a better established review and authorisation process.

Mrs Matsoso emphasised that one of the most worrying consequences of the lack of effective regulatory control was the circulation of substandard and counterfeit medicines. Later in the meeting by **Dr Harvey Bale**, IFPMA, took up this theme in his presentation on the role of

intellectual property, in relation to the development and availability of new, innovative medicines. Dr Bale also looked at the problem of medicines that are outside the control of regulation and may be substandard, non-GMP, diverted, poorly handled, expired or deliberately counterfeited.

One of the important 'emerging markets' in Latin America is Mexico and **Dr Alberto Carlo Frati Munari**, discussed recent changes proposed by the regulatory authority in order to implement the Mexican National Drug Policy agreed in September 2005. An extensive consultation had been carried out to involve all interested parties in discussions of the changes. Views were collected from the pharmaceutical industry, pharmacists, distributors, and national insurance institutes. Dr Frati's presentation reminded participants that, although the review of new active substances (NASs) is important, the major workload for agencies in the emerging markets is on the control of traditional and herbal products and OTC medicines and the need to ensure that generics are of good quality and interchangeable, with respect to bioavailability.

The issues related specifically to NASs were, however, the focus of the presentation by **Dr Paul Huckle**, GlaxoSmithKline, who gave an industry viewpoint of the factors that encourage and deter companies when planning the development and registration of new products outside the core 'ICH regions'. Dr Huckle stressed the importance of transparency and predictability in procedures for clinical trial and marketing authorisations. He also emphasised the importance of an environment with a post-authorisation framework that enables the company to maintain the safety, efficacy and availability of medicines through efficient processing of variation applications (e.g. manufacturing changes), a 'fast track' for urgent safety changes and an effective pharmacovigilance system.

THE ISSUES: RECOMMENDATIONS AND DISCUSSION

The main regulatory issues that have an impact on the registration and availability of NASs were addressed in the individual presentations and panel discussions in Sessions 2 and 3 of the Workshop (see page 11) before being debated in the Round Table Discussions at the end of the meeting. The main recommendations from these discussions are summarised in Section 1 of this report and described in greater detail below, with highlights from the relevant presentations to the Workshop.

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1. DEFINING REGULATORY MODELS

1A Round Table discussions

The Workshop discussed whether regulatory agencies could be characterised by the type of regulatory review that they carried out. It was agreed that all parties would benefit from a much greater openness in accepting that most agencies do not have the resources and skills to carry out a full review of new active substance (NAS) applications and that there should be greater clarity in defining the review process that is actually followed. This would help to justify and establish realistic timelines for the review and assist companies to plan their regulatory strategy for making important new therapeutic agents available to patients.

It was recommended that future CMR International studies on regulatory agencies in the Emerging Markets should include a classification of the review models that are used.

Three different models were identified. It was acknowledged that individual agencies might follow more than one model according to the type and status of the product under review and also that an agency, as part of its development plan, might move from one type of review to another.

Type 1: Verification Assessment

In this model the local agency recognises the scientific review and authorisation decision made by one or more reference agencies in which it has confidence. Evidence of the review and its outcome is provided by the Certificate of a Pharmaceutical Product (CPP) or its equivalent (see 2 below). The extent of the technical supporting information required in the submission (for example pharmaceutical quality/CMC data) is determined by the individual agency.

The review carried out by the local agency consists, primarily, of a 'check list' to ensure that administrative and legal requirements have been met and an assessment of the medicine in relation to, for example, risk-benefit, risk management and local medical practice and infrastructure.

The CPP would need to be available at the time of submission for a Type 1 review. Although this delays the initial submission, the time for the review should be short and patients' access to new medicines is not unduly delayed.

Type 2: Abridged Assessment

In this model the agency receives summary technical data (the equivalent of Module 2 of the ICH Common Technical Document) and may ask for additional details to be supplied in the course of the assessment.

This model normally relies on the product having been authorised by a reference regulatory agency before the authorisation is granted but the initial application need not necessarily be delayed until the formal CPP is available.

In order to carry out an abridged review, the regulatory agency needs appropriate experts to be available internally with appropriate competencies and training, which may include partnering with other agencies. The availability of evaluation reports from the reference agency (see below) is also a key factor.

Type 3: Full Assessment

Agencies that have suitable resources, including access to appropriate internal and external experts, may opt to carry out a full review of certain NASs and other new products. In these cases a full technical dossier (equivalent of the ICH CTD) is required and the timing of submission is not dependent on the product being registered elsewhere, or on the availability of a CPP.

In order to carry out a full review, agencies must have the advice of clinicians and clinical pharmacologists and be able to provide an appropriate service for pre-submission discussions with companies on scientific aspects of the application. The development of skills and resources to carry out a full review is important for countries with an indigenous research-based industry that may produce novel products and NASs for the local market.

1B Background discussion in the Workshop

The presentation by **Dr Gerard Wong**, Centre for Drug Administration, Singapore, described a regulatory system in which all three of the review models noted above are used, depending on the status of the product at the time of application. The *verification assessment* is a fast track procedure for products approved by at least two 'benchmark' agencies (US FDA, EMEA, UK MHRA, Australian TGA or Health Canada) that meet specific risk management criteria and are identical, in terms of composition, site of manufacture and product information/labeling, to products approved by a benchmark agency. The assessment, carried out by the Drug Registration Branch (DRB) is based on an evaluation report from the benchmark authority. The *abridged assessment* is the traditional route and is followed by the majority of applications. It is a pre-requisite that the product should be registered in another country and the summary data in the application is reviewed by DRB for chemical pharmaceutical products and by the Innovative Therapeutics Group (ITG) for biologic and biotech products. The agency also has the capability to carry out a *full assessment* of a complete regulatory dossier. The review is carried out by the ITG, on products that have yet to be approved by any other agency and this allows NASs to be submitted in Singapore within the same time frame as submission to a benchmark agency.

The regulatory agency operates against a background of strong Government efforts to develop Singapore as a 'biomedical hub' and the establishment of local research and clinical testing facilities is encouraged. It is the vision of the Health Sciences Authority (HSA) 'to be world class for scientific and regulatory expertise in Health Sciences'.

2. BEST USE OF THE CERTIFICATE OF A PHARMACEUTICAL PRODUCT (CPP)

2A Round Table discussions

The Workshop agreed that the principles and objectives of the *WHO Certification Scheme*, as a means of providing assurances on the regulatory status of products, remain valid but that guidance on the practical application of the Scheme needs to be updated. Lack of flexibility in requirements and a pre-occupation with the exchange of original paper documentation, in the electronic age of the 21st century, can be a significant impediment to the efficient and timely registration of new medicines.

It was recommended that WHO should be asked to initiate a fundamental revision of guidance on the way in which the Certification Scheme is implemented, to take account of current regulatory procedures in an electronic environment.

The following related recommendations for improving the use of the CPP were also made in the discussions:

- **Better use of information from official websites:** The relevance of the formal CPP should be examined by the more advanced agencies in the Emerging Markets since information on product authorisations and approved product information (labeling) is published on the official websites of the major authorities that most CPP recipients accept as reliable 'reference agencies' (e.g., US FDA, EMEA, PMDA, Health Canada, TGA, Swissmedic).
 - It was noted, however, that some of the smaller agencies do not yet have the IT infrastructure to access such sources of information
- **Greater flexibility in applying legal requirements:** It is acknowledged that a requirement for product certification is often written into national laws or regulations but agencies should explore possibilities of adopting a more flexible approach to the nature of the required documentation, provided that the necessary assurances are obtained on regulatory and GMP status and approved labeling.
 - For example companies could provide copies of authorisation documents and links to the specific information on official government agency websites.
- **Avoiding delays at the validation stage:** It was noted that some regulatory agencies use the CPP as evidence of the regulatory status of the product in order to screen applications and determine the assessment route to be followed. The application process can, however, be significantly delayed if a formal CPP is required before the dossier can be submitted. There should, therefore, be the option for companies to provide alternative evidence of regulatory status, as indicated above.
- **Encouraging direct contacts between agencies:** It was agreed that, in this electronic age, direct contact between agencies and the development of an interactive relationship is the best basis for exchanging information on the regulatory status and conditions of authorisation of new medicines:
 - The requirement for original CPPs that have been legalised by an Embassy or Consulate was considered an outmoded practice in a modern environment. The WHO Guidelines do not advocate legalisation but encourage authorities to make direct contact with the issuing agency if there are any doubts about the authenticity of the information in a CPP.

EMA Certification of products for export only

It was noted that the new EU legislation includes a provision (Article 58 of Regulation (EC) No 726/2004) for the EMA to undertake a scientific assessment of new products that are not intended to be marketed within the European Community. The procedure is intended, primarily, for medicines for the diseases of developing countries where there is either no market in the EU or a different formulation is needed for the exported product. A scientific opinion is given but there is no marketing authorisation.

It was agreed that the EMA scheme served a valuable purpose but it was important that information on the procedure was made available to agencies in all parts of the world.

Article 58, paragraph 1 of Regulation (EC) No 726/2004

The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.

Note: Article 10 refers to the procedure for issuing an authorisation

CPPs issued by the US FDA

There was discussion of the new FDA policy of issuing a CPP only for products that are exported from the USA. This has resulted in a situation where a product authorised for sale in the US, but manufactured elsewhere, is not eligible for FDA certification of its regulatory and GMP status. The

FDA position is that it has no jurisdiction to provide a certificate for a product that is exported from a non-US manufacturer to another country

This has caused difficulties for companies seeking to register new products in countries where a CPP from the FDA is a pre-requisite for authorisation. Concern was expressed that the FDA policy was not well understood by agencies in importing countries and that the inability to obtain a US CPP could lead to misunderstandings about the status of a product. Information on the rationale for the policy is not readily available, e.g., from the FDA website.

It was noted that the US Industry Association, PhRMA, is taking this up with FDA.

2B Background discussion in the Workshop

The CPP was discussed at the Workshop by a panel of experts from WHO, industry and regulatory agencies. They were asked to look at 'the potential role of the CPP in facilitating the regulatory process for innovative medicines and the way that procedures could be improved through greater cooperation and flexibility among stakeholders'.

Dr Lembit Rägo, WHO, traced the background to the scheme from its original focus on the quality of pharmaceutical products to its broader current remit of exchanging information on regulatory status and authorised product information. He also described the extension of the Scheme to include international commerce in active pharmaceutical ingredients (APIs).

The WHO Certification Scheme is an international voluntary agreement, devised to enable countries with limited Drug Regulatory capacity to obtain partial assurance from exporting countries concerning QSE (Quality, Safety and Efficacy) of the products they plan to import

Essential Drugs and Medicines Policy - WHO

Fraser Stodart, Pfizer, gave an industry perspective on the way that the CPP is currently utilised and how its undoubted value could be enhanced. Of particular concern was the apparent departure from the original intention that the CPP should simplify the authorisation process by removing the need for each regulator agency to carry out an assessment. Instead, there is often a delay in making an application, while the CPP is issued, but also a lengthy review process by the national authority. Another issue was the differing interpretations of a CPP from the 'source' country or 'country of origin' and whether this was the reference agency that first authorised the product or the country from which the product is actually exported. He also questioned the value of requiring multiple CPPs and the need to have the documentation 'legalised' by an Embassy or Consulate.

Dr Lucky Slamet, NADFC Indonesia, discussed the timing of the CPP in relation to the procedures in Indonesia, which allow a degree of flexibility. The authorisation status of a new product determines the route and speed of authorisation and the stage at which the CPP is required. There is a fast track (Path 1) for life-saving and breakthrough drugs that have been approved by a reference authority. A target of 100 days is set and the CPP may be submitted after the initial application. Path 2, the most common route is used for products that are marketed in more than one country that follow 'harmonised' regulatory requirements. The CPPs must be available at the time of application and a target of 150 days is set. Path 3 is available to allow the agency to accept new drug applications 'in parallel' with their registration elsewhere. In such cases the target review time is 300 days and the CPP is needed before an authorisation can be granted.

Dr Sergio Nishioka, ANVISA, Brazil, explained that the CPP was not required in Brazil in order to initiate the review of an application, but it is a legal requirement that a new product must be approved in the country of origin before it can be registered in Brazil. This has resulted in simultaneous applications for NASs to ANVISA and agencies from more developed countries becoming 'common place'. Reviewing some of the CPP-related issues he noted the view that CPPs should be accepted from 'reference' countries that are not necessarily the source country. He questioned who should determine the status of reference authorities and, in the case of countries such as Brazil that are building up independent national expertise and resources, how a new agency could become part of the reference group and, in effect, 'join the club'.

Note: The EFPIA International Regulatory Action Group (IRAG) has established a *Certification Network* and is in discussion with WHO over matters related to the CPP and with EMEA in relation to certificates issued by EU member states and the 'Article 58' provisions.

3. TARGET REVIEW TIMES

3A Round Table discussions

The discussion of review time was closely linked to the recommendations for categorising the type of review, discussed under 1A above. The time taken for a review should reflect the amount of work involved and a realistic fee should be expected provided this is reflected in the efficiency of the approval process.

It was recommended that all regulatory agencies should be encouraged to set realistic targets for review times for NASs and that CMR International should collect further information to benchmark review and approval processes for NASs in Emerging Markets

It was noted that CMR International has developed methodology for comparing review times in relation to 'modules' in the review process that are common to most review procedures, for example validation, administrative work, scientific evaluation etc. It was also noted that CMR International could adapt the quality studies currently being carried out on regulatory agencies in industrialised countries in order to monitor the implementation of quality management among agencies in the emerging markets.

The following additional recommendations on review times were made:

- **Targets for Review:** These must be realistic according to the type of review that the agency undertakes. Where the assessment is dependent on an authorisation having been given elsewhere, particularly where a formal CPP must be available before the application is accepted, the review target time should be short to reduce the delay before innovative NASs can be made available to patients.
- **Company response time:** Further studies should take account of the time taken for companies to respond to questions and requests for additional information as this is often overlooked when quoting approval times in emerging markets;

3B Background discussion in the Workshop

A report was given by **Dr Neil McAuslane**, CMR International, on the results of the CMR International study on regulatory issues in Emerging Markets that was carried out in 2004. Among the data reported were the median approval times for 28 countries in the three regions studied. These showed a median time of 282 days for the Asia-Pacific region, 283 days for the Middle East and Africa region and 175 days for the Latin American region. Within each region, however there were outliers with much longer and shorter median times. Examples of countries taking far longer than the norm included Malaysia (889 days), South Africa (921 days) and Turkey (799 days).

Factors that speed	Factors that impede
<ul style="list-style-type: none"> • Setting target times and deadlines • Monitoring timelines and work flow • Establishing agreements with outside assessors • Facilities for discussions before and during the review • Training programmes and incentives for agency staff 	<ul style="list-style-type: none"> • Reviewing in sequence rather than in parallel • Timing of major questions • Analytical work on samples • Price negotiations as part of the regulatory review process • Inadequate resources and IT facilities

Dr McAuslane also discussed the factors in the regulatory process that can that can speed or impede the review process (see box).

A panel of discussants at the Workshop addressed the subject of Review Times and Procedures. Comments from the presentations that dealt with review times are noted below.

Dr Christophe Güetli, Novartis, also referred to data from the CMR International study and noted, in particular, that most of the regulatory agencies surveyed claimed to operate target times but that these might not always be for the whole approval cycle. Furthermore, it appears that targets are rarely met and major line extensions, which are often as important to companies as NAS applications, are often left out of the timeline targets.

The study had also indicated that companies often have a different perception of the targets set by the health authorities, which is also a reflection of the way in which a lack of transparency can be an impediment to companies when planning their registration strategies.

Dr Leonie Hunt, TGA, used the history of recent changes in Australia to illustrate, among other things, the importance of introducing target times for the review. This was triggered by 'signals' from external stakeholders (government, industry, health professionals and the general public) that the agency was not meeting their needs and by internal drivers to improve efficiency and adopt best practice initiatives. In relation to setting timelines for the review Dr Hunt pointed out the need to balance procedures that allow the early availability of a few products with timely availability of all products. The targets adopted by TGA aim to achieve timely availability of all products, with a few exceptions for fast review. NAS applications have a target of 150 days and major line extensions (e.g., extension of indications) 160 days. The time limits are imposed by legislation and TGA suffers a 25% loss of evaluation fees if the decision is not made in time.

Frank Hlangwane, South Africa, described the recent reorganisation of the Medicines Regulatory Affairs (MRA) as part of an overall restructuring and reform of regulatory procedures in South Africa that is building in-house capacity and reducing the reliance on external experts. The MRA is self-sufficient in that it carries out its own reviews and is not dependent on, for example, on a CPP or prior authorisation but this has resulted in extended authorisation times. A structured flow chart with SOPs, time limits for the scientific review and company responses to questions and with service level agreements (SLAs) for external advisors are making the procedure more efficient and predictable. Mr Hlangwane referred, in particular, to the large number of variation applications that are received and the efforts to stratify these according to importance in order to streamline the procedure and reduce the backlog.

4. SCIENTIFIC ASSESSMENTS AND ACCESS TO SCIENTIFIC EVALUATION REPORTS

4A Round Table discussions

The importance of making the best use of limited resources and avoiding duplication of effort was the central theme when discussing the scientific assessment of applications, particularly for NASs

The development of regional consortiums was recommended in order to share expertise and spread the workload for the assessment of NASs. This would allow issues such as stability requirements for the local environment and use of the product within the medical culture and infrastructure of the region to be taken into account.

The initiatives of the ASEAN countries and the Gulf Cooperation Council were noted and the way in which resources are shared by the new Trans-Tasman Therapeutic Products Agency.

Scientific Evaluation Reports

The Workshop also discussed ways to ensure that regulatory agencies in the Emerging Markets have access to sufficiently detailed information on the scientific assessment of NASs, carried out by other authorities,

It was recommended that agencies in the Emerging Markets should be encouraged to enter into formal agreements with their 'reference' agencies for the exchange of scientific evaluation reports, under suitable confidentiality agreements.

Reference was made to Pharmaceutical Evaluation Report (PER) scheme formerly run by EFTA¹, under which participating authorities exchanged confidential reports, with the agreement of the Sponsor. This is no longer operational but it was suggested that a similar scheme with much broader participation (see footnote) and a less formal structure would provide a valuable additional

¹ European Free Trade Area (EFTA) operated the PER Scheme which, at the time it was discontinued in 2001 had the following members: Germany, the United Kingdom, Italy, Canada, the Netherlands, Australia, Hungary, South Africa, Ireland, New Zealand and the Czech Republic

resource for agencies that are required to carry out an abridged or full scientific assessment of NASs.

During the discussion, the question was raised of whether the European Pharmaceutical Evaluation Reports (EPARs) or FDA Summary Reviews, which are published as publicly available documents,² would fulfil this function but it was felt that these did not provide the level of detail that would be required. It was agreed, however, that the evaluation report would not be expected to include details of, for example, the questions put to the company during the review process.

It was suggested that, where a decision is based on the review and assessment of other agencies it would always be more secure to seek details of more than one review.

Background discussion in the Workshop

Dr Eisha Rahman, Malaysia, was a member of the panel on Review Times and Procedures. Her presentation focused on the role of harmonisation and she described the progress towards ASEAN³ pharmaceutical harmonisation that was first proposed by Malaysia in 1999. The strategies for ASEAN harmonisation include the development of common technical requirements, through the development and adoption of guidelines and agreement on a common format for applications – the A-CTD, with the ultimate objective of mutual recognition agreements (MRA) and the implementation of harmonised pharmaceutical product information.

Discussing the challenges to establishing intra-ASEAN MRAs, Dr Rahman referred to the need to strengthen GMP and quality control in the region and intensify post-marketing surveillance. Enhancing technical capacity in drug evaluation is also a challenge and the whole undertaking requires the shared commitment of industry and regulators.

Dr Hajed Hashan's presentation discussed the work of the Gulf Cooperation Council⁴ (GCC) as a model based on sharing resources and expertise. Dr Hashan, from the Kingdom of Saudi Arabia Health Authority, provided a description of the work of the Gulf Central Committee for Drug Registration (GCC DR) in setting up a system for the central registration of pharmaceutical products, as well as its responsibilities for registering companies, inspecting for GMP compliance and approval of quality control laboratories.

The importance of building quality assurance into the network of agencies that make up the GCC was stressed and parallels were drawn with the EMEA procedures for benchmarking the progress of member states joining the centralised procedure.

Dr Hern Der Chern, Taiwan, also took up the theme of 'quality' in referring to the importance of adopting 'Good Review Practices' (GRP). He described the system in Taiwan which is in a state of change from one which was dependent on reviews carried out elsewhere to an agency with the capability of carrying out new drug assessments, in house. A team of physicians, clinical pharmacologists and biostatisticians is being built up to address the task and requirements for CPPs from other countries may be expected to be relaxed to accommodate the changes.

In moving away from the CPP, however, Dr Der Chern emphasised the importance of other resources that were becoming increasingly important in the partnership between agencies, in particular the exchange of scientific assessment reports. He referred to the PER Scheme that had not only provided a platform for the exchange of review information but had also set guidelines for evaluation reports and provided training. Dr Der Chern noted that obtaining review reports would provide assurances that the application data presented nationally were the same as that assessed by a reference authority and he also noted the value, in terms of saving duplication, of being able to study more than one evaluation report.

² EPAR: European Pharmaceutical Assessment Report. Summary of the evaluation and outcome of an application for a new medicinal product under the EU Centralised procedure. Available on the EMEA website www.emea.eu.int

"Drugs@FDA": Drug approval letters, label and review packages. Available from the CDER website: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

³ The Association of South East Asian Nations (ASEAN) has ten members: Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar (Burma), Philippines, Singapore, Thailand, Vietnam

⁴ Members of the GCC are: Bahrain, Kuwait, Qatar, Oman, Saudi Arabia, and the United Arab Emirates (UAE)

5 TRANSPARENCY AND PARTNERSHIP

5A Round Table discussions

The Workshop discussed the undisputed benefits of transparency in regulatory processes and noted that this cannot be separated from the underlying belief that the majority of regulatory agencies regard patient access to new medicines to be one of their priorities.

Referring to patient access, however, it was recognised that most agencies in the Emerging Markets are part of the Ministry of Health and their wish to make a new medicine available can be influenced by policy and political issues related to budget and the perceived medical and social needs of the population.

Furthermore, providing transparency in the regulatory process and encouraging interaction with companies has resource implications for agencies that cannot be overlooked. For the smaller agencies with scarce resources and a heavy workload, 'transparency' might be regarded as an extravagance that they can ill afford. There are, however, simple procedures that improve transparency and are of obvious benefit to both the agency and applicant. An example is a tracking system that allows files to be located and the progress of applications to be tracked. The larger agencies that provide opportunities to discuss applications with applicants can benefit from the educational value of scientific discourse with company experts.

It was recommended that there are substantial benefits for all parties in establishing an open and transparent relationship in which agencies and companies act in partnership to ensure that new medicines are made available to patient in a timely manner. It must, however, be recognised that transparency needs agency resources and expectations must be set at realistic levels.

Guidelines

The discussion of transparency covered the use of guidelines as part of the regulatory process. Concerns were raised about the tendency for guidelines to become 'directives' and not be implemented with the flexibility and degree of discretion originally intended. There may be a tendency, on the part of companies, to follow the guideline without engaging in debate in order to avoid delaying an application. This can, however, build up problems for the future as guidelines can become increasingly difficult to change the longer they remain unchallenged. Reference was made to the implications for developing relevant, dynamic guidelines for validating biomarkers and to the difficulty of removing redundant requirements as science progresses.

It was recommended that good regulatory practices should incorporate transparent 'good guideline practices' to ensure that guidelines are not applied as if they are binding. Companies should be allowed to deviate from regulatory guidelines provided that adequate and well-reasoned justification is provided.

5B Background discussion in the Workshop

Alison Harrison, AstraZeneca, gave her views, from an industry perspective on the role of partnership in making progress towards the common goals of protection of public health, timely access to new medical advances, efficient use of regulatory resources and best practices. In working towards these goals, it was important that industry and regulatory agencies actively seek solutions that represent a 'win-win' situation for all parties, within their own priorities.

Ms Harrison emphasised the importance of regional and international meetings that provide opportunities to discuss these priorities and, in addition to the current example of the CMR International Workshop, referred to the IFPMA Asian Regulatory Conferences and the meeting organised by the Drug Information Association (DIA), particularly the Middle East Regulatory Committee (MERC) conferences. An essential factor in developing and sharing industry priorities and resources is adequate and appropriate utilisation of local regional and international industry associations.

Professor Sir Alasdair Breckenridge, MHRA, UK, gave a presentation on the criteria for decision-making in the regulatory process and looked, in particular at the consideration of pharmacoeconomics and cost benefit into the assessment of clinical effectiveness. He suggested that, a few years ago, the regulators role might have been described as ensuring that only medicines with a satisfactory risk benefit profile are marketed but that the role has now extended to providing information on the safe and effective use of medicines and the need to ensure that regulatory hurdles do not impede the development of innovative products.

On the latter point he referred to the importance of the EU Roadmap⁵ and the FDA Critical Path Initiative⁶ as examples of the way in which regulatory authorities recognise the need to work with industry to ensure that pharmaceutical innovation is protected. He also highlighted the problems of the ease with which new testing requirements are added to regulatory guidelines but the difficulty and slowness in removing old and outdated procedures.

6 ANALYSIS OF SAMPLES

6A Round Table discussions

Many of the agencies outside the ICH regions ask for samples to be provided with the application and, in some cases, the completion of the analytical work can be a rate-limiting step in the overall approval process. The workshop considered the rationale for carrying out analytical work as part of the review process, especially as this is not required by agencies in the US, EU or other industrialised countries.

It was recommended that pre-launch testing of NASSs is not a good use of laboratory resources but that agencies should have access to testing facilities (either national or regional) to test for counterfeit or substandard products in the market place.

Other points and recommendations made in the discussions were:

- **Rational for testing samples:** Testing whether the samples submitted with an application are of substandard quality is considered to be a waste of valuable resources. It would be 'an egregiously foolish' company that would submit anything other than a good quality sample with a marketing application. The development of appropriate tests for sampling marketed products is a justifiable use of laboratory time but this should be separate from the review and approval process.
- **Company responsibility:** The application must provide sufficient detail of the analytical specifications, testing methods and validation to enable the national laboratories to implement appropriate methods for testing the product in the market place. Companies have a responsibility to cooperate with agencies in the case of suspected counterfeit products although it was acknowledged that independent testing would be required to establish the 'chain of evidence' for a prosecution.

Note: Section 3 of this report (to follow) will include summaries of the individual presentations to the Workshop (see Programme on page 11).

⁵ *The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future*, published by the EMEA, March 2004, available from the EMEA website: <http://www.emea.eu.int>

⁶ *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* published by the US Department of Health and Human Services and the FDA, March 2004, www.fda.gov

WORKSHOP PROGRAMME

SESSION 1: REGULATING NEW MEDICINES: A COMMON PURPOSE IN A DIVERSE GLOBAL ENVIRONMENT

Chairman

KEYNOTE PRESENTATION: Global Access to New Therapies: What are the limiting factors?

Learning from shared experience when setting out to upgrade regulatory procedures

Entering the Global Market: An Industry Viewpoint

Patient access as a priority: A View from WHO

Different Global Regions: Many Common Issues

Dr Murray Lumpkin, *Deputy Commissioner, International and Special Programs, US Food and Drug Administration*

Professor Trevor Jones CBE, *Member of the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPRIH)*

Dr Alberto Carlo Frati Munari, *General Secretary to the Scientific Committee, for the Protection against Sanitary Risks, National Institute of Public Health, Mexico*

Dr Paul Huckle *Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, USA*

Mrs Malebona Precious Matsoso, *Director, Department of Technical Cooperation for Essential Drugs and Traditional Medicines, WHO*

Dr Neil McAuslane, *Chief Scientific Officer, CMR International Institute for Regulatory Science*

SESSION 2: CROSS-REGIONAL REGULATORY ISSUES

Chairman

Panel discussion on: The promise and the potential of the CPP: Are these being realised?

- WHO's Role and Perspective
- The CPP from an Industry Viewpoint
- Flexibility in the timing of the CPP
- Regulatory Agency concerns

Professor Robert Peterson, *Professor of Paediatrics, University of British Columbia, Canada*

Dr Lembit Rago, *Quality and Safety of Medicines (QSM), WHO*

Fraser Stodart, *Head, Africa and the Middle East Region, Pfizer Ltd, UK*

Dr Lucky Slamet, *Directorate General of Health Services, National Agency of Drug and Food Control, Indonesia*

Dr. Sergio Nishioka, *Manager of the Office of New Drugs, Research and Clinical Trials, ANVISA, Brazil*

Panel discussion: Review times and procedures

- Setting priorities: The Australian experience
- Targets, transparency and delivery
- Industry perspective
- The role of harmonisation

Dr Leonie Hunt, *Director, Drug Safety and Evaluation Branch, TGA, Australia*

Mr Frank Hlangwane, *Director Medicines Evaluation and Research, Department of Health, South Africa*

Mr Christoph Gueetli, *Global Head Regional Regulatory Affairs, Novartis Pharma AG, Switzerland*

Eishah A. Rahman, *Deputy Director of Drug Evaluation and Safety Division, National Pharmaceutical Control Bureau, Malaysia*

Intellectual Property and global access to innovative new medicines

Dr Harvey Bale, Jr, *Director General, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)*

SESSION 3: REGULATORY MODELS: MAKING THE BEST USE OF LIMITED RESOURCES

Chairman

A model based on risk management and the local context

A model based on partial recognition of the assessment of others

The Gulf Cooperation Council: A model based on sharing resources and expertise

Progress through Partnership: An industry view

Decision-making criteria for the approval of new medicines

Professor Trevor Jones

Dr Gerard Wong, *Deputy Director, Centre for Drug Administration, Health Sciences Authority, Singapore*

Dr Heng-Der Chern, *Executive Director, Centre for Drug Evaluation, Taiwan*

Dr Haged Hashan, *Ministry of Health, Kingdom of Saudi Arabia*

Alison Harrison, *Vice President, International Regulatory Affairs, Astra Zeneca, UK*

Professor Sir Alasdair Breckenridge, *Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK*

Prof. Alasdair Breckenridge, Dr Murray Lumpkin, Dr Robert Peterson, Prof. Stuart Walker

ROUND TABLE DISCUSSION *Chairs*