



# PmRN Newsletter

## No.2

June 2011

## *Interview with the Singapore medicines regulatory agency*

### 1. What is the structure and function of the Singapore medicines regulatory agency?

The regulation of medicines in Singapore is administered by the Health Products Regulation Group (HPRG) of the Health Sciences Authority (HSA), which is a statutory board of the Ministry of Health. The organization of the HPRG comprises a Group Director's Office and four Divisions, they are:

- **Pre-market Division which consists of five branches overseeing various categories of health products:**
  - Pharmaceuticals & Biologics Branch
  - Generics & Biosimilars Branch
  - Medical Device Branch
  - Complementary Health Products Branch

- Clinical Trials Branch

- **Vigilance, Compliance & Enforcement Division**
- **Audit & Licensing Division**
- **Tobacco Regulatory Division**

In the regulation of medicinal products, the HPRG implements the following controls to ensure that medicinal products in Singapore meet the required standards of safety, quality and efficacy. The key activities carried out include:

- **Pre-market evaluation and approval**
- **Post-market surveillance, compliance and enforcement**
- **Auditing and licensing of manufacturers, importers and wholesalers**
- **Clinical trials approval**
- **Medical advertisement control**

The evaluation and regulatory approval for medicinal products are performed by the Pharmaceuticals & Biologics Branch and the Generics & Biosimilars Branch. The regulatory approval process is also supported by the Audit & Licensing Division on GMP inspection and the Vigilance Branch on development of risk management plan, as well as an advisory committee comprising clinicians from practice and academia which provides scientific and clinical advice on drug applications.

Post-market regulatory functions are performed by various Divisions comprising a multitude of activities covering pharmacovigilance, post-approval variations, product quality surveillance and other compliance checks, product recalls as well as enforcement actions.

Apart from safeguarding national medicinal products' safety, quality and efficacy, the Authority participates actively in regional and international harmonization initiatives and regulatory development efforts on pharmaceutical products, such as the ASEAN Pharmaceutical Products Working Group, Pharmaceutical Inspection Cooperation

Scheme (PIC/S), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), International Conference of Drug Regulatory Authorities (ICDRA) etc. It also collaborates with the WHO on a number of programmes including pharmacovigilance, evaluation for pre-qualified medicines, counterfeit medicines and other networks.

### **New recommendations made by the 14th International Conference of Drug Regulatory Authorities related to paediatric medicines**

WHO should:

- Enhance and foster collaboration and communication between MRAs (through the Paediatric Medicines Regulators Network (PmRN) and other mechanisms), especially on:
  - common standards for clinical trials in children.
  - capacity to assess clinical trials in children.
  - development of innovative pharmacovigilance methods to enhance reporting of adverse reactions related to use of medicines in children.
- Support countries to evaluate and adopt appropriate incentives and legislative structures to encourage development of optimal medicines for children.
- Work with countries to foster effective interaction between regulators and paediatricians to promote development and licensing of better medicines for children.
- Work with countries and regulators as well as industry to define efficient regulatory pathways for medicines for children.

**For further information about ICDRA:**

[http://www.who.int/medicines/areas/quality\\_safety/regulation\\_legislation/icdra/en/index.html](http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/index.html)

## **2. Please describe the regulatory environment [for medicines] in Singapore**

The HSA applies a risk-based approach in the regulation of medicinal products. The drug registration framework employs a 3-route evaluation system which was introduced at different times as the regulatory system in Singapore evolves. The abridged route was

[http://www.who.int/childmedicines/paediatric\\_regulators/en/](http://www.who.int/childmedicines/paediatric_regulators/en/)

implemented in 1987 when the drug registration system was first established in Singapore. Under this route, medicinal products would have approval from at least one competent regulatory agency. The full route began in 1998 to perform evaluation of innovative products where there are no prior approvals from any drug regulatory agency. In 2003, the verification route was introduced for medicinal products already approved by HSA's reference agencies. Currently there are five reference agencies, namely, US FDA, EMA, UK MHRA, Australia TGA, and Health Canada.

The 3-route system enables efficiency through minimizing duplication of effort yet ensuring robustness of evaluation through leveraging on work that has already been performed by competent regulatory agencies, and at the same time evaluation capability is in place to take on "first in the world" drug applications. The 3-route also allows flexibility for drug companies to choose the evaluation route that best fit their products based on pre-requisite criteria.

In terms of submission format and technical requirements in Singapore, drug applications can be made in either the ICH common technical dossier (CTD) or ASEAN CTD format. The technical requirements of the respective CTD apply according to the dossier format chosen by the drug company. For drug applications submitted via the verification route, there are additional pre-requisites including the full assessment report from the reference agency.

To ensure regulatory transparency, all regulatory guidelines and requirements, target processing timelines, as well as relevant legislations are published on HSA website. Information on approved medicinal products is also freely accessible by the public through an online searchable database on HSA's website.

### 3. What is the approval procedure for the conduct of Clinical Trials in Singapore?

The conduct of clinical drug trials in Singapore is regulated under Medicines (Clinical Trials) Regulations. All companies sponsoring clinical drug trials and doctors conducting them are expected to abide by the Singapore Guideline for Good Clinical Practice (GCP). This guideline is essentially based on ICH E6 guidelines, which has been adapted for Singapore's local context. The system of regulation requires that Principal Investigators conducting clinical drug trials must obtain both ethics and regulatory approval before initiating a study. The ethics approval is from the hospital's Institutional Review Board (IRB). The applicant can submit in parallel to HSA and IRB. The target timeline for completion of regulatory evaluation is 30 working days excluding any stop-clocks (which is the time taken for questions to be answered by the applicant).

The regulatory approval, in the form of a Clinical Trial Certificate (CTC), is issued to the principal investigator (PI) of each trial site. In order to receive regulatory approval from

HSA to conduct clinical drug trials here, companies must provide relevant evidence that the investigational drug is acceptably safe and the design and conduct of the trial provide adequate levels of protection for participants. As part of the evaluation and approval process, HSA may also seek advice from an expert advisory committee.

#### 4. What is the approval procedure for marketing authorization:

Various technical guidelines are used in the evaluation of drug applications in Singapore:

- **ASEAN guidelines, e.g. stability**
- **ICH guidelines, e.g. E4, E5, E6**
- **EMA guidelines, e.g. efficacy, quality etc**
- **FDA guidance documents, e.g. paediatric rules (if disease pathophysiology is the same for adults and children, it is possible to extrapolate adults efficacy data based on safety study and PK data/simulation model)**

No specific guidelines for the evaluation of paediatric drug applications have been developed in Singapore.

- **What are the different evaluation processes that are offered?**

The Authority offers three evaluation routes with varied processing timelines. The eligibility of an application for a particular evaluation route depends on whether the defined prerequisites for the chosen route can be met:

- Full: this is a default evaluation route where there is no prior approval by any drug regulatory agency and requires submission of complete pre-clinical, clinical and CMC data according to the CTD requirements. The

process is split into three parallel tracks for pre-clinical, clinical and CMC evaluations with a target processing timeline of 270 working days excluding stop-clock. This route is particularly useful for medicinal products which are developed for diseases that are prevalent in this region where the clinical development programme does not focus on major markets such as Europe and US; or where simultaneous submission to Singapore and other major markets is desirable for the drug company. An example of such products would be the vaccine for immunization against gastro-enteritis due to rotavirus infection in paediatric population.

- Abridged: this evaluation route is an option for drug applications where prior approval has been obtained from one competent drug regulatory agency. This route accepts abridged pre-clinical and early phase clinical data. However, comprehensive Phase II and III clinical data and complete CMC data are still required. The process involves two parallel tracks for pre-clinical/clinical and CMC evaluations with pre-clinical subsumed under clinical. The target processing time is 180 working days excluding stop-clock.
- Verification: this route offers a significantly reduced processing timeline of 60 working days excluding stop-clock. It is eligible for drug applications which have obtained approvals from two reference agencies and the product label sought in Singapore is identical to that approved by the reference agencies. In addition to the CTD requirements, drug companies are required to submit the full assessment of the chosen reference agency as the evaluation by the Authority will heavily leverage on the assessment by the reference agencies.

There is no separate evaluation process specifically for paediatric medicines.

## 5. What is the role of Singapore in the development of paediatric medicines?

### • **How many medicines with a paediatric indication do you have registered at this time?**

A number of medicines that are used regularly in the treatment of diseases commonly seen in children are approved with a paediatric indication. Some examples are:

- Anti-viral (anti-HIV, pandemic flu) and anti-bacterials
- Anti-asthmatics
- Anti-histamines
- Vaccines & immunoglobulins
- OTC medicines in general such as anti-diarrhoeals, cold & flu etc
- Anti-rheumatics e.g. TNF-blockers for juvenile idiopathic rheumatoid arthritis
- Some oncologic drugs e.g. anti-leukaemic drugs (Glivec for AML)
- Iron-chelating agents for iron overload
- Insulin
- Growth hormones

### • **How many applications to conduct clinical trials in medicines for children were received between 2009 and 2010?**

Between 2009 and 2010 a total of 11 clinical trials involving children have been undertaken in Singapore. These trials are carried out primarily in public healthcare institutions. There is currently one specialized children's hospital in Singapore and several general public hospitals with paediatric department or specialized clinics for paediatrics.

### • **What resources and procedures are available for paediatric medicines regulation in Singapore?**

There are no specific procedures. However, consideration will be given in terms of data set requirements based on internationally accepted guidelines/practice.

### • **Do you have a designated in-house paediatric specialist?**

At the present time there is no designated in-house paediatric specialist.

### • **Do you have contact with external paediatric experts in Singapore?**

In-house evaluation is complemented by pool of external paediatricians and experts in academia. Experts are chosen based on their professional qualifications and experience and are nomination by the Chairman of Medical Board of the various hospitals in Singapore. The agency also has an advisory committee which comprises clinicians from various medical specialties including a paediatrician.

### • **Has any one received any specific training for the assessment of paediatric medicine dossiers?**

Evaluators are given on-the-job training for the evaluation of paediatric medicines.

### • **Is there a capacity development programme for paediatric medicines?**

Currently there is no specific in-house training programme for the regulatory assessment of paediatric medicines. However, evaluators are encouraged to attend relevant training programmes conducted by other regulatory agencies or international bodies if available.

### • **What areas do you believe need be further developed in the area of paediatric medicines?**

Currently not all medicines (even when used in paediatric population) carry specific dosing recommendation for children. A lot of times physicians will have to base the dosing on their clinical judgement and extrapolate from adult dose. Hence, defining appropriate dosing regimen for paediatric medicines would be an

area that could be further developed to enhance the optimal use of medicines in children.

Training in the scientific principles of pharmacokinetic modeling and interpretation of simulation results for children's medicines would be helpful for regulatory purposes.

## 6. What provision is made for pharmacovigilance of paediatric medicines/formulations?

The HSA Vigilance Branch (VB) has an active post-marketing vigilance and surveillance system for reporting, investigating and monitoring adverse reactions to medicines, including paediatric medicines.

In late 2009, HSA collaborated with Kandang Kerbau Women and Children Hospital (KKH), Singapore's national hospital for the healthcare of women and children to set up a sentinel site for the active safety surveillance of H1N1 vaccines in pregnant women and children. This surveillance has further been extended in early 2010 to cover all childhood vaccines given according the national childhood immunization schedule. The

### Second PmRN meeting

**Date:** 3-5 October 2011  
**Venue:** Dar es Salaam, Tanzania  
**Host:** WHO

Intended participants: Representatives from National Medicines Regulatory Authorities who are responsible for paediatric-related activities, such as clinical trial officers, dossier assessors and pharmacovigilance officers

For further information please contact:  
[pmr\\_network@who.int](mailto:pmr_network@who.int)

sentinel site is headed by a Principal Investigator and an assistant consultant in immunology, assisted by a research nurse. Cases which have been identified to be possibly related to recent vaccination will then be reported to the VB. The reports are captured in the Adverse Drug Reaction (ADR) database for aggregate analysis to detect potential safety signals associated with vaccines.

## 7. Please provide relevant website links and contact details for the agency, and the references/links for any paediatric guidelines that are used

HSA official website: [www.hsa.gov.sg](http://www.hsa.gov.sg)

For queries related to this interview, please contact: [agnes\\_chan@hsa.gov.sg](mailto:agnes_chan@hsa.gov.sg)

Paediatric medicines Regulators' Network  
Medicine Access and Rational Use (MAR)  
Department of Essential Medicines and  
Pharmaceutical Policies (EMP)  
Health Systems and Services (HSS)  
World Health Organization  
20 Avenue Appia  
1211 Geneva 27, Switzerland

[pmr\\_network@who.int](mailto:pmr_network@who.int)

