INNOVATIVE APPROACHES AND REGULATORY PATHWAYS TO ACCELERATE APPROVAL OF CRITICAL MEDICINES IN MALAYSIA

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responsible for the pharmaceutical regulatory control in Malaysia

**VISION**
To be an internationally renowned regulatory authority for medicinal products and cosmetics

**MISSION**
To safeguard the nation’s health through scientific excellence in the regulatory control of medicinal products and cosmetics

**OBJECTIVE**
To ensure that therapeutic substances approved for the local market are safe, effective and of quality and also to ensure that cosmetic products approved are safe and of quality
Staff Strength
Total staff: 490

- Pharmacy Assistants: 81
- Pharmacists: 329
- Administrative & Support Staff: 80

ORGANISATION CHART

DIRECTOR

1. DEPUTY DIRECTOR
   Centre for Development and Strategic Planning

2. DEPUTY DIRECTOR
   Centre for Compliance and Licensing

3. DEPUTY DIRECTOR
   Centre for Product Registration

4. DEPUTY DIRECTOR
   Centre for Post Product Registration and Cosmetic Control

5. DEPUTY DIRECTOR
   Centre for Investigational New Product

6. DEPUTY DIRECTOR
   Centre for Quality Control
Regulatory Functions

Product Life cycle

Pre marketing

Post marketing

National Regulatory System
  Regulatory Inspection
  Licensing premises
Laboratory access and Testing
Clinical Trial’s Oversight
Marketing authorization
Vigilance
Market surveillance and Control
Lot Release

Drug Discovery
Preclinical
Clinical trials
Regulatory Review
Approval & Launch
Post-Marketing Surveillance
NPRA protects public health while promoting access to critical medicines

1 PROTECTING PUBLIC HEALTH
Ensures approval of medicines of acceptable quality, efficacy and safety

2 PROMOTING ACCESS
Facilitates approval of critical medicines
NPRA registers products that fulfil registration criteria

New Drug Products
Biologics
Generics

QUALITY

Veterinary
Natural/herbal
Health Supplements

EFFICACY

SAFETY
Marketing Authorisation-Registration process

**Step 1**
Acceptance of Dossier for full evaluation

**Step 2**
Screening of application received via QUEST 3+ online system

**Step 3**
TECHNICAL ASSESSMENT
- Evaluator’s review.
- Expert opinion-KOL (for NCE and Biologics only)
- Correspondence with applicant

**Step 4**
ASSESSMENT COMPLETE
Evaluation report presented at NPRA Evaluation Committee

**Step 5**
DCA MEETING
Final report presented at Drug Control Authority (DCA)

**Step 6**
FINAL DECISION
Approval (MAL no.) rejection

**Normal Timeline:**
- Generics: 210 wd
- NCEs, Biologics: 245 wd
Registration requirements for pharmaceutical products

International
WHO
ICH
EMA
US FDA

Regional
ASEAN Guidelines for:
Stability
Process validation
Variation

Local
Drug Registration Guidance Document
NPRA Guidelines
DCA Directives
Circulars
NPRA protects public health while promoting access to critical medicines

**PROTECTING PUBLIC HEALTH**
Ensures approval of medicines of acceptable quality, efficacy and safety

**PROMOTING ACCESS**
Facilitates approval of critical medicines
“RELIANCE....an act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision....”

“RISK-BASED....focuses on those areas which present the greatest risk, assist in prioritizing & determining the appropriate regulatory response...”
Facilitating Approval to new/innovative medicines—alternative pathway

**PRIORITY REVIEW**

(i) **Unmet medical needs** with no treatment options locally available

(ii) **Life-saving** with no treatment options locally available

(iii) **first *generic/biosimilar product, or first locally manufactured generic/biosimilar product**

(iv) **Treatment/prevention in pandemic/endemic situations**, for the interest of public health

(v) **Emergency supply/crucial for treatment purpose** according to the current needs in the country

**CONDITIONAL REGISTRATION**

- Products for unmet need supported by **early clinical data** such as **phase II clinical data** (based on fully validated surrogate endpoints)

- Conditionally registered for **2 years period** with specific conditions

**FACILITATED REGISTRATION PATHWAY**

- Leveraging on a **Stringent Regulatory Authority decision and information**—rely on assessment report issued by the reference agencies

- Abbreviated and Verification Review
To allow promising new medicines to reach patients with unmet need earlier based on phase II clinical data to support the efficacy and safety.

To provide guidance on the application necessary for implementation of conditional registration.

To ensure that appropriate measures are in place to manage the risks inherent as additional data are still required.
REQUEST FOR A CONDITIONAL REGISTRATION AT THE POINT OF SUBMISSION

Request by PRH

• Notify NPRA about the intention to request for a conditional registration as part of the “letter of intent” with justification and supporting documents
• Appointment for pre-submission meeting

Justifications

• Provide justifications to show that the medicinal product falls within the **scope and requirements** of conditional registration
• PRH’s proposal for completion of ongoing or new studies, or the collection of pharmacovigilance data

Products that fall within the scope

• medicinal products for seriously debilitating or life threatening disease; or
• medicinal products to be used in emergency situation; or
• orphan medicinal products

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• medicinal products for seriously debilitating or life threatening disease; or
• medicinal products to be used in emergency situation; or
• orphan medicinal products
FULFILLMENT OF THE REQUIREMENTS FOR CONDITIONAL REGISTRATION

• risk benefit balance should be positive based on less than comprehensive clinical data

JUSTIFICATIONS
• there exists an unmet medical need that it is necessary to introduce new methods in therapy when no methods exist, or that it is necessary to provide a major improvement on the existing methods
• should quantify the unmet medical need based on quantifiable medical or epidemiologic data

Fulfillment of unmet medical need

Benefits of immediate availability to public health outweighs the risk

able to provide comprehensive clinical data

• PRH should commit to provide comprehensive data (phase III confirmatory trial) within an agreed timeframe.

• risk benefit balance should be positive based on less than comprehensive clinical data

JUSTIFICATIONS
• Benefits to public health in the context of immediate availability outweigh the risks
• Risks inherent in the fact that additional data are still required
NPRA ASSESSMENT OF A REQUEST FOR CONDITIONAL REGISTRATION

**Qualified for CR**
- Application received
- Scientific evaluation

**Evaluation completed**
- Decision

**Specific conditions will be clearly specified**

**Statement on Package Insert - Indication**

**CONDITIONS**
- Confirmatory trial
- Implementation of RMP including additional risk minimisation and communication activities
- PBRER
- Others

*This indication is approved under conditional registration which is based on<br>&lt;surrogate/intermediate endpoint&gt;*

*Continued approval for this indication may be based on the outcome of clinical benefit in a confirmatory trial*
GRANTING A CONDITIONAL REGISTRATION & RENEWAL

Time line

• Standard time line for NCEs and Biologics unless priority review is granted upon request

Validity

• 2 years—may be renewed with the possibility of 2 extension (2 year each)
• Additional renewal beyond 2 times will be considered on case-to-case basis based on justifications

Renewal application

• at least six months before its expiry
• Documents to be submitted via a variation app:
  i) updated Package Insert
  ii) interim/full clinical report for confirmatory trial
  iii) Latest PBRER

• NPRA will assess the renewal application on the basis of the risk-benefit balance and formulate an opinion whether the specific conditions or their timeframes need to be retained or modified

• Product will be granted full registration once the conditions have been fulfilled

• DCA may cancel the conditional registration of a product or cancel the approved indication under the conditional registration pathway if:
  - i) A trial required to verify the predicted clinical benefit of the product fails to verify such benefit.
  - ii) Other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use.
**Full Registration (Conventional Regulatory Approval) vs Conditional Registration (early access)**

**Conventional Regulatory Approval Pathway**

1. Clinical Research
2. Clinical trial (evaluating of efficacy and safety)
3. Approval
4. Marketing

**Conditional Registration Pathway**

1. Clinical Research
2. Clinical trial (prediction of efficacy and assurance of safety)
3. Conditional approval for a limited time period (2 years)
4. Marketing
5. Submission of renewal application within the limited time period
6. Full registration or Revocation of the conditional registration
7. Continued marketing (if approved)

*Faster access of patients to new product is expected*

- Based on the clinical data from limited number of patients, efficacy is predicted in a shorter time compared with the conventional process.
- Acute-phase adverse reactions etc. can be evaluated for safety in a short period of time.
Guidelines on Facilitated Registration Pathway: Abbreviated and Verification Review

1. Ensure innovative medicines addressing current unmet medical needs can be accessible to patients in need in a timely manner.

2. Reduce duplication, especially for products where safety and efficacy have already been confirmed by Stringent Regulatory Authorities.

3. Drive greater focus toward risk-based evaluations, focusing on what is locally critical versus what can be leveraged/relied upon from decisions made by SRAs.
Facilitated Registration Pathway

#### Scope
a) New Drug Products
b) Biologics including Biosimilar

#### Routes
- **Abbreviated review** - approved by at least 1 reference drug regulatory agency
- **Verification Review** - Approved by 2 reference drug regulatory agencies

#### Reference Agencies
- **US FDA & EMA**
- WHO Prequalified Medicinal Products covered by the alternative listing procedure (evaluated by US FDA and EMA)

“RELIANCE...an act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision....”
Eligibility criteria

1. Submitted within **2 years** from the date of approval by the chosen primary DRA

2. Manufacturing facilities have been inspected by any PIC/S member

3. All aspects of the drug product’s quality, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications and primary packaging = approved by the chosen primary DRA

4. Drug Master File submitted to NPRA = submitted to the chosen reference DRA

5. Product designated as an ORPHAN DRUG /or approved FAST-TRACK APPROVAL/ APPROVAL UNDER EXCEPTIONAL CIRCUMSTANCES OR EQUIVALENT APPROVAL PROCESS NOT ELIGIBLE if documentation is deemed insufficient to support for abbreviated and verification review

6. Product requiring a more stringent assessment as a result of differences in local disease patterns and/or medical practices (e.g. some anti-infectives) does not qualify for the facilitated

7. The product and its intended use have not been rejected, withdrawn, suspended, approved via appeal process, or pending deferral by any reference DRA for quality, safety and/or efficacy reasons

8. The proposed PI & PIL = approved by the reference DRA (with the exception of country-specific information).

9. The proposed indication(s), dosing regimen(s), patient group(s) and/or direction(s) for use should be the most stringent among those approved by the reference DRAs
Documents required

1. FULL DOSSIER
   - Complete Common Technical Document-stability study complies with ASEAN stability guideline
   - Protocol of Analysis & analytical method validation – checklist as Appendix

2. ASSESSMENT REPORT
   Complete assessment report including assessment on the Q&A documents between the PRH and reference DRA and all annexes.
   Note: may consider accepting public assessment reports accompanied by redacted information and Q&A provided that the applicant has shown proof and effort to obtain the unredacted assessment reports

3. PROOF OF APPROVAL
   Proof of approval from the chosen reference DRA-

4. DECLARATION LETTER
   Relevant declaration letter(s) issued by the product owner/PRH- a different type of the container closure system (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements; any difference in manufacturing site of drug product will be considered if it is clearly justified.
NORMAL REGISTRATION PATHWAY vs FACILITATED REGISTRATION PATHWAY

**Normal Registration Pathway**
- Full Dossier
- Approved by at least one regulatory agency
- Full evaluation: quality, non-clinical & clinical
- Timeline: 245 wd

**Abbreviated Registration Pathway**
- Full Dossier + Ref agency assessment report
- Approved by one reference agency
- Abridged evaluation: quality and clinical
- Timeline: 120 wd

**Verification Registration Pathway**
- Full Dossier + Ref agency assessment report
- Approved by two reference agencies
- Ref agency assessment report
- Timeline: 90 wd

3 times correspondence within 60 working days in total
CONCLUSION: Striking the RIGHT BALANCE
Speed vs Q,S,E

#Post Marketing Surveillance strengthening
THANK YOU FOR YOUR ATTENTION