Risk-Based Regulatory Assessments, The Role of SRA in the Proposed Review Process, International Relationships: Advancing the Mandate of the Regulator. The focus being on : What does Industry need to know?

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SAAPI CONFERENCE
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Bytes Conference Centre, Midrand

OUTLINE

1. Background.

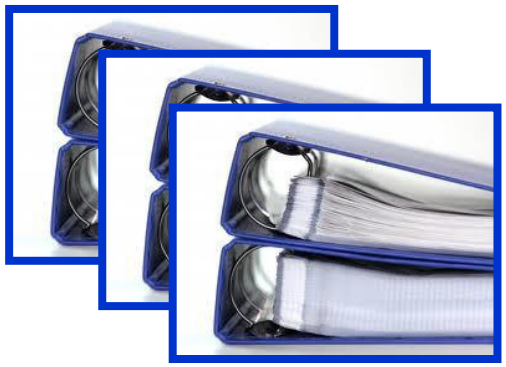
2. Risk Based Approaches: Recognition, Reliance & Work sharing.

3. Types of Reviews: Full, Abbreviated, Verification

4. Advantages of Risk Based Approaches

5. Conclusion

OVERVIEW OF REGULATORY PROCESSES FOR A NEW DRUG APPLICATION



Evaluation

Submission

Registration (or maybe not)

Post-market variations and pharmacovigilance

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OVERVIEW OF REGULATORY PROCESSES FOR A NEW DRUG APPLICATION

- Clinical Evaluation
- Non-clinical Evaluation
- Quality Evaluation

→

- Decision on benefit-risk balance

→

- Regulatory Decision – Registration and post-market commitments

↑

- Evaluator's recommendation
- Peer review
- Expert opinions/ Consultations
- Medical / Scientific Advisory
- Dialogues with applicants

↔ **Benefit-risk assessment**

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EXPECTATIONS ON REGULATORY AUTHORITIES

The Stakeholders

Within agency

Applicant/ Industry

HTAs/ Payors

The regulatory authority

Healthcare professionals

Other agencies

Patients/ Consumers

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...AND ENDLESS CHALLENGES

- **Long queue / backlog of applications, particularly new products that need a long time for evaluation**
- **Resource limitations**
- **Questions raised by industry for an explanation of different decisions following drug registration applications**
- **Obligation to scientific evidence, yet required to meet social demands**
- **Wide scope of expectations**
- **Harmonising requirements in the background of changing standards**

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PROPOSED SOLUTIONS…RECOMMENDATIONS MADE IN GENEVA

Ten years ago a group of Regulators & Industry made Five Recommendations

1. Types of assessments

2. Clinical assessment template

3. Reference agency reports

4. Project Management

5. Business best practice

RECOMMENDATIONS FROM THE 17TH INTERNATIONAL CONFERENCE OF DRUG REGULATORY AUTHORITIES: CAPE TOWN 2016

- Underlined the Importance of reliance, transparency, trust and good regulatory practices
- Emphasised that account should be taken of one another's work with a view to improving the efficiency of the global regulatory system
- Indicated the importance of utilising resources to form cooperative networks based on uniform standards
- Agencies should engage with regional and international initiatives to promote harmonization, information sharing to improve patients' timely access to medicines.

THE REALITY…

National Regulatory Authorities (NRAs) are under mounting pressure to improve performance and facilitate timely access to safe, effective and quality medicines as well as other health technologies

This task has become more challenging due to globalization, increasingly complex technologies and growing public expectations

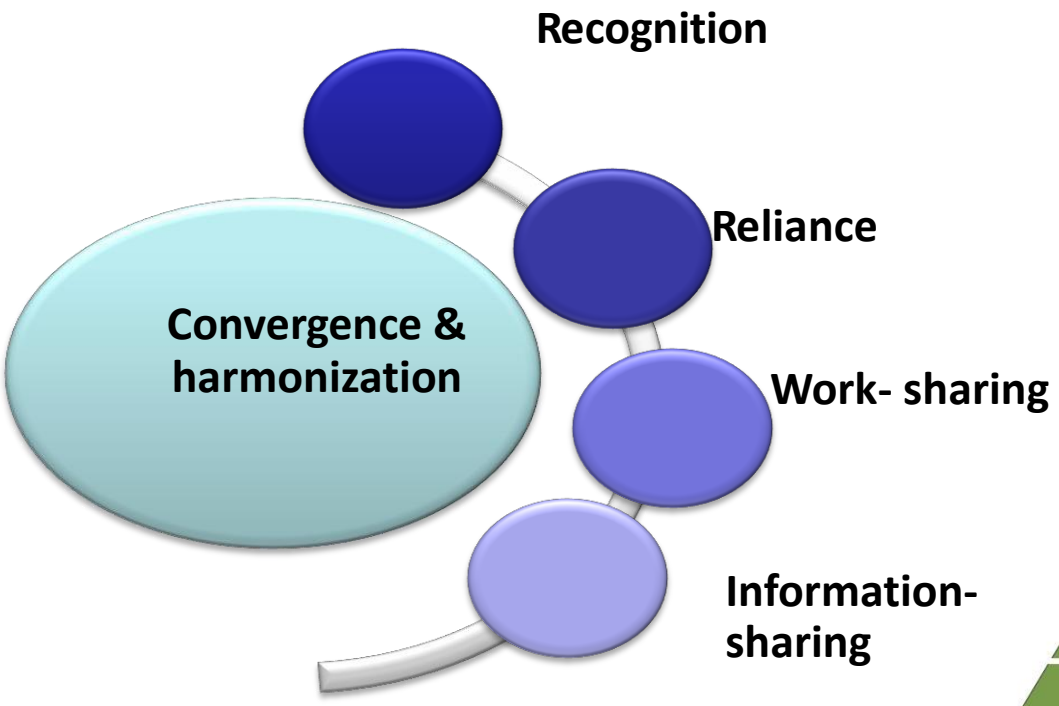
"Mike Ward WHO"

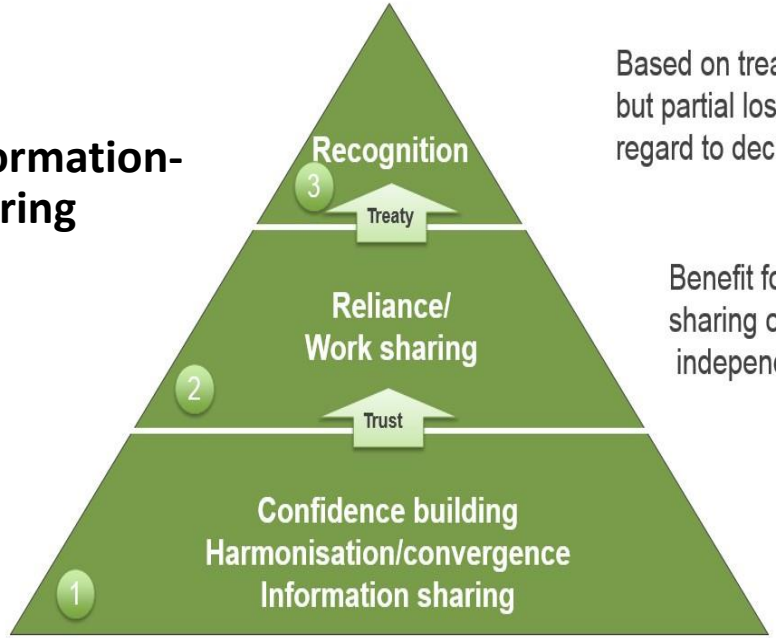
NRAs must consider more modern and appropriate models for the regulatory review that consider resource constraints, increasingly complex technologies, globalization and public expectations

Risk Based Approach Definition…

"A Risk Based Approach can be defined as referring to the overarching utilisation of reliance, recognition or prequalification approaches as well as the specific review processes such as Verification, Abridged & Full review with or without the requirement for a reference or comparable agency approval"

Different Risk Based approach Models





Based on treaties; «maximal benefit» but partial loss of sovereignty with regard to decision-making

Benefit for regulators; sharing of workload, but independent decisions

«Foundation», Equivalence of requirements

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DEFINITIONS…

Recognition*: the* ***routine acceptance of the regulatory decision of another regulator or other trusted institution****. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.*

Reliance*: 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.*

Work sharing: *If two regulators receive the same application, share workload by evaluating different parts of the dossier (e.g. clinical, quality, toxicology….)*

Definitions …. Review processes

Verification Review: *Recognition of an authorisation by a "reference' or 'benchmark agency'. The process is to validate the status of the product and ensure that the product for local marketing conforms to the authorised product*

Abridged Review: *The pre-requisite here is that the product has been registered by a 'reference' agency & the Assessment is carried out in relation to its use under local conditions & Regulatory requirements*

Full Review: *The agency is capable (has the resources & expertise) to carry out a full assessment of quality, pre-clinical & clinical (safety & efficacy) data Information on a prior registration elsewhere may still be a pre-requisite before final authorisation or the review may be self standing*

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TYPES OF REVIEW PROCESSES

Emerging Markets	Scientific Assessment Model			
	V	A	F(3A)	F(3B)
Argentina				
Brazil				
Colombia				
Mexico				
Algeria				
Egypt				
Israel				
Saudi Arabia				
South Africa				
Russia				
Turkey				
China				
India				
Indonesia				
Malaysia				
Singapore				
South Korea				
Taiwan				

DATA ASSESSMENT TYPE 1 (Verification Review)

- **Recognition of an authorisation by a 'reference' or 'benchmark agency**
- **Verification process to validate the status of the product and ensure that the product for local marketing conforms to the authorised product**

DATA ASSESSMENT TYPE 2 (Abridged review)

- **Pre-requisite that the product has been registered by a 'reference' agency**
- **Abridged assessment carried out in relation to the use of the product under local conditions**

DATA ASSESSMENT TYPE 3 (Full review)

The agency is capable of carrying out a full assessment of quality, pre-clinical (safety) and clinical (efficacy) data. Information on prior registration elsewhere may still be a pre-requisite to final authorisation (Model 3A) or the review may be "self standing" (model 3B)

RISK-BASED REFERENCING…SINGAPORE

Figure 3 is a schematic diagram illustrating the evaluation routes for NDAs:

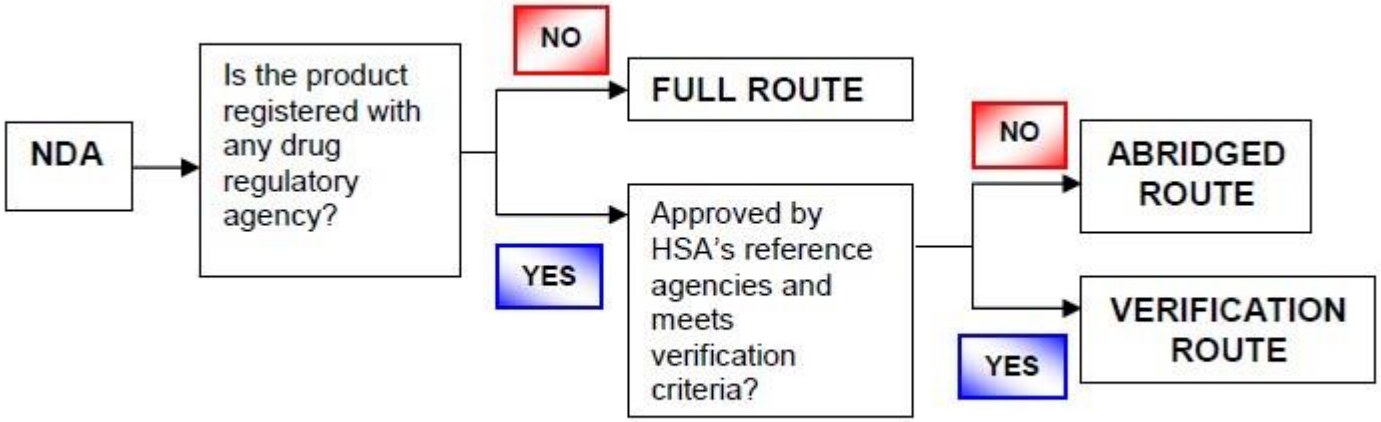

Figure 3 Schematic Diagram of Evaluation Routes for NDAs

- **Full**
  - product that has not been approved by *any* drug regulatory agency at the time of submission
    - Full documentary requirements applied
    - Entire review procedures will be applied

RISK-BASED REFERENCING

- **Abridged**
  - product that has been approved by *at least one* drug regulatory agency at the time of submission
    - Non-clinical overview is allowed in place of usual requirements
      - Leverage on existing approval(s) and risk of impact of non-clinical findings on overall benefit-risk conclusion
    - Reduction in time to review non-clinical data
    - CMC review remains unchanged
  - Many occasions the prior approving authority is a major reference agency
    - Publicly available assessment reports

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RISK-BASED REFERENCING

- **Verification**
  - products with similar indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use that have been approved by at least two of the following HSA's reference drug regulatory agencies (US FDA, Health Canada, TGA, EMA via Centralised Procedure, UK MHRA)
  - Use of assessment reports from reference agencies (a required submission for this route)
    - Leverages on converging opinions from two established sources
      - Reduce time required to review all data, allowing an expedition of market decision
      - Reduce burden on staff

SITUATION IN AUSTRALIA…

Australia is the only country where international regulatory cooperation is Government policy

" if a system, service or product has been approved under a trusted international standard or risk assessment, then our regulators should not impose any additional requirements for approval in Australia, unless it can be demonstrated that there is a good reason to do so".
Dr John Skerritt: Aust PM 14 Oct 2014

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Accepted recommendations by Australian Government to the Review of Medicines - 2016

Recommendations

Recommendation Three: The Panel recommends that there be three pathways to seek registration of a new chemical entity and its inclusion in the ARTG:

Pathway One - **Submission of a complete dossier for de novo assessment**. This assessment may be undertaken in full by the Australian National Regulatory Authority (NRA) or via a work-sharing arrangement between the Australian NRA and a comparable overseas NRA.

Pathway Two - **Submission of an un-redacted evaluation report from a comparable overseas NRA**, along with a copy of the dossier submitted to that NRA and an Australian specific Module 1, for assessment by the Australian NRA. The Australian NRA to make a recommendation regarding registration of the medicine once it has considered the data within the Australian context.

Pathway Three - **Application for expedited approval of a medicine in certain circumstances**. Any expedited approval pathway should make provision for submission of data and assessment consistent with requirements of Pathways One and Two as outlined above.

AUSTRALIAN RECOMMENDATIONS *CONT…*

Recommendation Five: The Panel recommends that the Australian Government develop and apply transparent criteria for identifying comparable overseas NRAs. Such criteria might include that a comparable overseas NRA must:

Regulate for a population demographic that is broadly representative of the Australian population and has similar health outcomes; and

1. **Adopt ICH guidelines;**
2. **Have a credible and consistent track record of approving safe and effective medicines;**
3. **Conduct de novo evaluations of data dossiers for all types of medicines, e.g. new chemical entities, generics and biosimilars;**
4. **Have processes in place that require peer review or independent assessment of the evaluations that they conduct;**
5. **Have evaluators with the necessary technical and clinical capabilities to evaluate the data provided and make an independent regulatory decision in accordance with the ICH guidelines;**
6. **Provide access to un-redacted evaluation reports and, where applicable, individual patient data;**
7. **Communicate and prepare evaluation reports in the English language**

WORK SHARING - SOME CURRENT MODELS

- **The EMA evaluation model** – not really work-sharing, but rapporteur and co-rapporteur teams from two regulators separately evaluating products
- **EU Centralised and Decentralised Procedures on evaluation of generic drug applications**
- **International Generic Drug Regulator's Programme (IGDRP)**
  - Convergence of technical requirements e.g. bioequivalence, bio-waivers, choice of foreign reference products, drug master file and report structures
  - Work-sharing trial underway
- **ACSS (Australia, Canada, Singapore, Switzerland)** and **Australia - Canada Regulatory Cooperation**
  - Australia and Canada collaborated on over a dozen generic medicine applications in 2014/15 (information sharing)
  - Risk benefit assessment methodology leading to a cooperation
- **Regional Regulatory Initiatives** –Africa – SADC: ZaZiBoNa, EAC, WAHO; Caribbean Community Regulatory Efforts

INFORMATION SHARING
(USE OF A COMPLETED EVALUATION REPORT)

Already used e.g. by Singapore, Mexico, New Zealand, Taiwan and several other small-medium regulators

But these countries **have to accept a submission lag** of a year or more

So yes, but there are challenges:

- Difficult to **obtain un-redacted evaluation reports** from some regulators
- **Some regulators do not publish** a compiled evaluation report
- **Differences between the indications approved** in reference countries
- **Cultural change** is needed if staff are not used to using external reports

Situation in SA?

- **The Medicines and Related Substances Act (Act 101 of 1965), as amended, now includes an enabling provision that provides significant opportunities for regulatory harmonisation and engagement:**
- **Section 2B (2a &b)**
  - 2. The Authority may—

a) liaise with any other regulatory authority or institution and may, without limiting the generality of this power, require the necessary information from, exchange information with and receive information from any such authority or institution in respect of—

(i) matters of common interest; or

(ii) a specific investigation; and

b) enter into agreements to cooperate with any regulatory authority in order to achieve the objects of this Act.

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South Africa

- ***SA NRA is already engaged in a number of harmonisation efforts, where local and other guidelines are being brought into alignment. These include amongst others:***
    - Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S)
    - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
    - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Veterinary Use (VICH)
    - International Medical Devices Regulators Forum (IMDRF)
    - International Generic Drug Regulators Programme (IGDRP)
    - African Vaccine Regulatory Forum (AVAREF)

RISK BASED APPROACH IN SA CONTEXT

- **The use of a staged series of call-up notices for CAMS based on risk;**
- **The staged introduction of regulation of medical devices and IVDs**
- **PIC/s inspection reports**
- **Work sharing – SADC Zazibona**
- **Verification – WHO PQ Collaborative process**
  - SA NRA member since December 2016
- **Abbreviated Medicines Review Process**

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Risk-based referencing

Pre-submission consultation

- **Product yet to be approved by any regulatory agency** → Full Evaluation → Full evaluation and Regulatory Decision
- **Product approved by one drug regulatory agency** → Abridged Evaluation → Abridged evaluation and Regulatory Decision
- **Product approved by reference regulatory agencies*** → Verification → Evaluation and Regulatory Decision based on assessment report by benchmark regulatory agency

Facilitates access

Reference regulatory agencies: US FDA, Health Canada, UK MHRA, Australian TGA, EMA, SwissMedic

Advantages of Risk-based Approach

- Large Agencies tend to be very comprehensive in their review
- Agency can review assessments by Reference Country and assess if the evaluation has significance
- Allows Agency to focus review where Country has concerns which is often influenced by local experience (CMC, clinical safety, benefit/risk)
- Avoids duplication

Steps towards Implementing a Risk-based Review Strategy

- Obtaining Management Support
  - Pilot Studies on Information Sharing (trust)
  - Data on timeline and local impact
- Policy Changes
  - Details on how to conduct review
- Cultural Changes
  - Buy-in at all levels

Conclusion…

With Risk based approaches

- ***Only the country-specific requirements would be assessed, e.g.:***
  - **Product Information, Consumer Medicine Information**
  - **National clinical guidelines/ context of use**
  - **Risk Management plans, medicines classification and local labelling requirements**
- ***Could potentially provide faster evaluation times and earlier availability if reports shared or obtained in a timely manner***
- ***There will be benefits for***
  - **industry** – faster market access, lower costs
  - **earlier patient access to medicines**
  - **regulators** – reduced workload, less duplication

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THANK YOU FOR YOUR ATTENTION.

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