EVALUATION OF THE IMPACT OF RELIANCE ON THE REGULATORY PERFORMANCE IN THE SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

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BACKGROUND

- The World Health Organization (WHO) advocates the use of reliance practices to enable National Regulatory Authorities (NRAs) to improve patients' access to medicines.
- Reliance could be a lever to clearing and preventing the backlogs faced by lower-to-middle income (LMIC) NRAs.
- When the South African Health Products Regulatory Authority (SAHPRA) was established in February 2018, it inherited a backlog of approximately **16,000** marketing authorization and variation applications from its predecessor, the Medicines Control Council (MCC).
- This application backlog was to be cleared within 2 years; hence a Backlog Clearance Project (BCP) was set up.

AIM

- To establish whether reliance practice implementation within SAHPRA's BCP was successful in expediting medicines authorizations and therefore enhancing patient access to medicine in LMIC countries, in accordance with the WHO predictions.

METHODS

BACKLOG CLEARANCE PROJECT – DATA COLLECTION

- This study provides a comparison between full and abridged review timelines for New Chemical Entity (NCE) and generic product applications in SAHPRA's BCP between August 2019 to December 2022.
- Unredacted assessment reports were received from:

FDA · European Medicines Agency (Science Medicines Health) · TGA Health Safety Regulation · Health Canada · MHRA · swissmedic

- The effectiveness of the implementation of reliance review was assessed across the following parameters:
  - **Chemistry, Manufacturing and Control (CMC)**
  - **Clinical**
  - **Good Manufacturing Practice (GMP) Compliance**
  - **Manufacturing Authorization (MA)**
- Effectiveness of reliance implementation was also assessed in terms of alignment between SAHPRA-approved labelling and the RRA labelling that was relied upon.

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RESULTS

NEW CHEMICAL ENTITY (NCE) MARKETING AUTHORIZATIONS

CMC Review — Abridged: n=43, Full: n=29

- Median of 91 (abridged) vs 179 (full) calendar days for SAHPRA scientific review (p<0.001)
- Median of 34 (abridged) vs 105 (full) calendar days for applicant response (p<0.001)
- Median of 125 (abridged) vs 284 (full) calendar days for total CMC review (p<0.001)

↓56%

Clinical Review — Abridged: n=50, Full: n=27

- Median of 176 (abridged) vs 258 (full) calendar days for SAHPRA scientific review (p<0.05)
- Median of 55 (abridged) vs 71 (full) calendar days for applicant response (p=0.93)
- Median of 230 (abridged) vs 329 (full) calendar days for total clinical review (p=0.027)

↓30%

Market Auth. — Abridged: n=39, Full: n=18

- Median of 619 calendar days where both CMC and clinical underwent full review

versus

- Median of 446 calendar days where both CMC and clinical underwent abridged review (p=0.0005)

↓28%

GENERIC PRODUCT CMC ASSESMENT

CMC Review — Abridged: n=81, Full: n=72

- Median of 97 (abridged) vs 191 (full) calendar days for SAHPRA scientific review (p<0.001)
- Median of 26 (abridged) vs 81 (full) calendar days for applicant response (p<0.001)
- Median of 122 (abridged) vs 272 (full) calendar days for total CMC review

↓55%

World Health Organization

Abridged Regulatory Pathways: Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance. It is expected that use of reliance will save resources and time as compared with standard pathways, while ensuring that the standards of regulatory oversight are maintained.

CMC RELIANCE – NCE VS GENERIC PRODUCTS

There was similarity between the time taken for CMC evaluation of NCE and generic products when comparing abridged and full review.

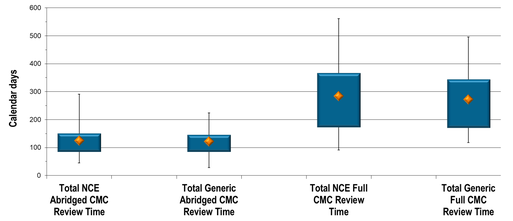

Figure 1: Comparison between the abridged and full CMC evaluation timelines for New Chemical Entity and generic product applications, respectively

CLINICAL RELIANCE (NCEs) – LABELLING ALIGNMENT

Clinical reliance was less successful in SAHPRA's BCP, as is evidenced by the high-level of misalignment between the RRA- and SAHPRA-approved labelling.

Labelling Section	Level of Alignment
4.1 Therapeutic Indications	40% non-alignment (20/50)
4.2 Posology and Method of Administration	44% non-alignment (22/50)
4.3 Contraindications	74% non-alignment (37/50)
4.4 Special Warnings and Precautions for Use	60% non-alignment (30/50)
4.6 Fertility, Pregnancy & Lactation	84% non-alignment (42/50)

GOOD MANUFACTURING PRACTICE (GMP) RELIANCE

- The SAHPRA is a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S).
- Reliance on GMP assessments performed by RRAs was also instituted.
- Full GMP review generally takes SAHPRA between 6 – 18 months.
- Reliance review in the BCP took between 2 – 3 hours.
- Minimal physical inspections done in SAHPRA's BCP.

PIC/S

DISCUSSION & RECOMMENDATIONS

- There was a time-reduction associated with abridged review across all measured timeframes.
- Reliance review of CMC aspects was successfully implemented for both NCE and generic product applications.
- Implementation of clinical reliance was less effective, as assessment timelines were longer and numerous changes were made by SAHPRA to the labelling of NCE products.
- Only 20-30% of the marketing authorization applications received in the BCP qualified for abridged review, where unredacted RRA assessment reports were obtained and submitted by the applicant.
- However, still a resource-saving review mechanism, thereby confirming the WHO's predictions.

RECOMMENDATIONS	
CULTURAL TRANSFORMATION	Ensure abridged reviewers have subscribed to the concept of reliance
OPERATIONAL EFFICIENCY	Create a dedicated priority evaluation stream with its own reviewers for reliance applications, segregated from those allocated for full review.
MINIMIZATION OF POST-REGISTRATION BURDEN	In the absence of RRA variation approvals, review additional variations declared by the applicant. This will reduce the subsequent burden on the post-registration units.
RRA COLLABORATION	Continued liaison with RRAs, keeping communication channels open and advancing sharing of unredacted RRA assessment reports via an NRA repository.

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