National Department of Health

Presentation to the Portfolio Committee on Health

Criteria for registering medicines, current backlog and challenges

01 September 2010

OUTLINE

- Mandate
- Policy & legislative mandates
- How medicines are registered
- Backlog
- Challenges

NATIONAL DRUG POLICY, LEGISLATION & REGULATIONS

- NDP Aim –Ensure medicines reaching patients are safe, effective and meet approved standards and specifications
- Through strengthening the MCC, rationalising drug registration, controlling the registration of practitioners and licensing of premises, enhancing the inspectorate and laboratory functions and promoting other quality measures e.g. GCP, GMP, GWP, GLP, GDP
- Mainly Act 101 of 1965 as amended
- Provision for fast track licensing of EDL medicines & NCEs with demonstrable advantages e.g safety profile, efficacy/effectiveness

REGISTRATION

- Premised on safety, efficacy and quality of the product
- Benefit /risk ratio for the particular population
- **New Chemical entities (NCEs)**

➢ Preclinical stage the (NCE) is tested in animals to assess its pharmacodynamic, pharmacokinetic and toxicological profile

➢ Phase I study – **Toxicity**- unexpected undesirable reactions, bioavailability, pharmacokinetics –on a small group of healthy volunteers

REGISTRATION cont.

- Phase II study – **Efficacy** - pharmacokinetics, pharmacodynamics of the investigational drug on a few volunteers
- Phase III study – On a large number of participants over a period of time to determine safety and efficacy, dosing for specific indications, age group appropriateness, drug interactions, side effects etc.
- Phase III studies require a comparator - either placebo, where ethically correct, or active substance to establish efficacy (non-inferiority or superiority principles)

REGISTRATION cont.

- **Generic products**
- Knowledge of the innovative product being copied
- knowledge of formulation
- Confirmation of chemical equivalence (API) with innovator drug
- Proportional similarity of different strengths with innovator comparator
- Pharmacokinetic properties
- Bioequivalence (small study required, 12-18 participants)
- Bioavailability

REGISTRATION cont.

- **Quality** – applies to all evaluations
  - ➢ Active pharmaceutical ingredient , excipients, impurities
  - ➢ Manufacturing method
  - ➢ Good Manufacturing Practice standards
  - ➢ Specifications for the final product
  - ➢ Container suitability
  - ➢ Stability

FIXED DOSE COMBINATIONS

- A product with two or more components combined into one to reduce pill burden and improve adherence
- Usually TB medicines, ARVs, hypertension
- Four scenarios
  - ➢ Two or more innovators agree to work together on the FDC
  - ➢ A generic applicant submits a (novel) combination of registered products
  - ➢ A generic applicant submits a copy of aknown registered combination
  - ➢ An innovator has granted a license to a generic applicant for a registered FDC

FIXED DOSE COMBINATIONS

- Registration guided by a number of factors for each scenario
- Is there enough data on each molecule to support efficacy, safety and quality
- Is there sufficient data to show that when combined the efficacy is improved and there are no safety & quality concerns
- Will each component (molecule) be released in a therapeutically efficacious manner

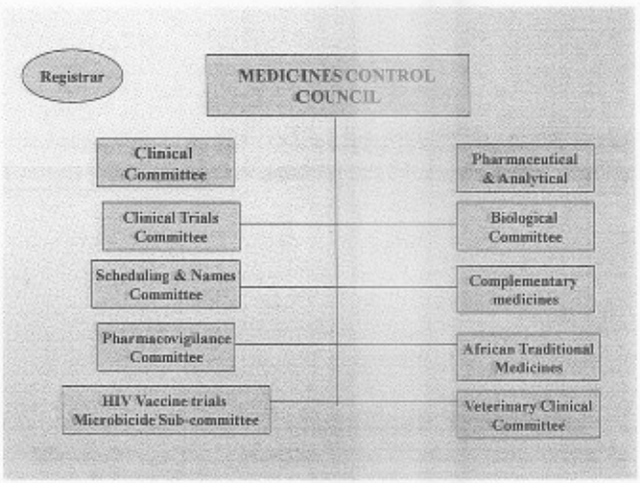
FIXED DOSE COMBINATIONS

- Is there data that demonstrates the real time stability of the FDC product
- Have formulation aspects been adequately addressed (interactions between APIs, dissolution, stability, impurities, manufacturing processes, data supporting safety of excipients etc.)
- Additional studies may be required pre- and post registration

HOW DOES THE MCC WORK

- Relevant parts of the application dossier assigned to different evaluators according to expertise
- Complement of 140 experts about 30% of whom serve on two expert committees
- Reports peer reviewed by at least 4 expert committees
- Ascertain that the manufacturing sites currently meets Good Manufacturing Practice standards
- Committees meet every eight weeks
- Peer review reports submitted to MCC with a recommendation to register or reject
- MCC peer reviews and registers, recommends that committees do further work or rejects applications

HOW DOES THE MCC WORK cont.



EVALUATION PROCESS

- Evaluator analyses data supplied by applicant for safety, efficacy & quality
- Iterative process depending on the quality and completeness of data supplied and appropriateness of responses to questions raised
- Do not have a stop-clock system in place currently
- Generic applications generally take a shorter time than NCEs and biosimilars

BACKLOG

- Project team appointed a year ago
- Appointed additional technical assistants and evaluators to assist the MCC who worked with permanent staff and current evaluators
- Established off-site storage for old files
- Secured fire proof shelving for current files
- Augmented funding for implementation of Electronic Document Management System

BACKLOG

- Assisted staff with verification of pending applications with industry against the database and analysed each response
- Total outstanding was 2700
- Sytematically cleared poor quality dossiers
- Assisted with data entry to consolidate data bases to fewer sets
- Defined as all **pending** applications from 2007 backwards

BACKLOG cont.

- Pending includes applications that are not finalised at the behest of applicants & those still under evaluation
- Number of unregistered products from backlog currently standing at 1240
- Contacting applicants who have not responded to recommendations for more than a year
- Contacting applicants who have requested extension to stipulated timelines for data more than two times

REGISTRATION STATUS (example)

	RECEIVED	RECEIVED & REGISTERED THE SAME YEAR	REGISTERED TO DATE	CANCELLED TO DATE	WITHDRAWN TO DATE
2005	613 (20 NCE)	8 (Generics)	406 11 NCEs 4 of which in 2006	1 NCE	34 (2 of which are NCEs)
2006	940 (20 NCE)	14 (Generics)	589 11 NCE 1 of which in 2007	4 (Generics)	27 1 of which is an NCE

9/1/2010

17

CURRENT BACKLOG

YEAR	2003	2004	2005	2006	2007
PENDING	108	99	168	321	647

Total pending 1283

9/1/2010

18

AWAITING APPLICANT'S RESPONSE ON ARVs IN PIPELINE (example)

YEAR	READY FOR MCC OCT 2010	FOR FINAL PEER REVIEW SEPT 2010	AWAITING APPLICANT'S RESPONSE	BEING EVALUATED	TOTAL PENDING
2007	8		1 since Sept 07	2	22
56			1 since Feb 08 1 since Sept 08 4 since Sept 09 1 since Dec 09 1 since April 10 3 since July 10		
2008	2	4	3 since Dec 09	2	22
38			1 since March 10		
			4 since April 10		
			4 since July 10		
			2 oustanding BE		

AWAITING APPLICANT'S RESPONSE ON ARVs IN PIPELINE (example)

YEAR	READY FOR MCC OCT 2010	FOR FINAL PEER REVIEW SEPT 2010	AWAITING APPLICANT'S RESPONSE	BEING EVALUATED	TOTAL PENDING
2009	1	11	1 since Dec 09	3	
96			4 since Jan 10		
			1 since Feb 10		
			3 since March 10		
			2 since April 10		
			5 since May 10		
			2 Since June 10 13 since July 10 3 Rejected		

CHALLENGES

- Over reliance on external evaluators
- Volume of safety related post registration updates increased substantially
- Pro-generic medicines policies not matched to personnel needs
- Changing therapeutic landscape to biotherapies
- Reliance on general budget allocation
- Paper based system
- Poor quality of some submissions for evaluation