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Regulatory requirement for Generic Drug Product Application of Fixed Dose Combination in ZAMBIA-A Review

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ABSTRACT:

The overview on the Regulatory Framework of Fixed Dose Combination (FDC) in Zambia with a brief view on the arguments for rational based fixed dose combination products used in Combination Therapy. The criteria of J.R. Crout have been a milestone of rational combination therapy and have been established the core objective of the most international regulations concerning FDC medicinal products. The justification of the rationale, the balancing of advantages and disadvantages and the risk benefit assessment are the basis for regulatory considerations of a fixed dose combination product discussed according to Zambia. FDC drugs tend to have a smaller effect radius in the genetic interaction networks, which is an important parameter to describe the therapeutic effect of a drug combination from the network perspective.

KEYWORDS: FDC, Fixed Dose Combination, Generic Drug Product, Generic Drug Product in Zambia, Regulatory

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INTRODUCTION:

1. Regulatory affairs[1,2]

The regulatory professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products. They also advise on the legal and scientific restraints and requirements, and collect, collate and evaluate the scientific data their research and development colleagues are generating.

They are responsible for the presentation of registration documents to regulatory agencies, and carry out all the subsequent negotiations necessary to obtain and maintain marketing authorization for the products concerned.

They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development programme and the company as a whole.

- **Helps to avoid problems**
- **Marketing and advertising**

2. Generic drugs; regulatory [3,4]

A generic medicinal product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as a reference medicinal

product which has been previously authorized. Bioequivalence between the two has also normally been demonstrated by appropriate bioavailability studies. An authorized generic medicinal product cannot be placed on the market until ten years have elapsed from the initial authorization of the reference product.

Known active substances are also utilized for new formulations; new indications or new fixed combinations which will need further development work to bridge to the original development work performed. For example new fixed combinations will require new pre-clinical tests or new clinical trials relating to that combination but it may be sufficient to refer to the original development data and provide bibliographic references relating to each individual active substance. When known active substances are successfully developed for new indications with significant pre-clinical or clinical studies, one year of data exclusivity can be granted.

❖ **Characteristics of generic product:**

- **Transparency Directive**
- **Better Patent Regulation**
- **Data exclusivity for Fixed Combinations**
- **Unexpected questions cause delays**
- **Bioequivalence**

3. Fix dose combination[5-19]

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective.

Fixed dose drug combinations (FDCs), also known as Combination products& 'combination pack & 'fixed-ratio combination product; are combinations of two or more active drugs in a single dosage form.

The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product.

Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance.

Fixed dose combination drug products contain more than one API in a fixed dose, allowing the patient to reduce the number of drug products to be taken. Improved patient compliance is the fundamental purpose of the fixed dose combination concept.

Different APIs (e.g. in the form of granules, pellets, micro pellets) can be processed into tablets, capsules, stick packs, sachets, etc.

FDCs will achieve better patient compliance than prescription of the same actives in separate products. This belief would appear to be intuitive rather than evidence-based. A recent Cochrane review examined available evidence as to the value of interventions in improving patient adherence to medication schedules

FDC has wide role in treatment of hypertension, dyslipidemia and diabetes as tuberculosis, malaria and HIV. It has also very wide role in the fields of diabetes, hypertension, dyslipidemia, internal medicine, cardiology, endocrinology, nephrology, hyperlipidemia.

❖ **Examples of some rational FDCs**

sulfamethoxazole + trimethoprim

antitubercular FDCs like rifampicin + isoniazid, isoniazid + ethambutol, etc

antiparkinsonism FDCs like levodopa + carbidopa

❖ **Characteristics of FDC;**

Patient compliance
Cost and logistics
Considerations for drug regulation
Affordability

❖ **FDCs should be based on certain aspects:**

The drugs in the combination should act by different mechanisms.

The pharmacokinetics must not be widely different.

The combination should not have supra-additive toxicity of the ingredients

❖ **Criteria for FDC**

The risk/ benefit ratio

Relevance of each API of the combination

Relevance of specific dosage regimen

Criteria for combination packs

❖ **FDCs are more likely to be useful following factors apply**:

There is a medical rationale for combining the actives.

There is an identifiable patient group for which this combination of actives and doses is suitable therapy. The larger the patient group in question, the more significant is this factor. It is not appropriate to combine actives that separately treat conditions that do not commonly coexist.

The combination has a greater efficacy than any of the component actives given alone at the same dose.

The incidence of adverse reactions in response to treatment with the combination is lower than in that response to any of the component actives given alone, for example as a result of a lower dose of one component or a protective effect of one component, and particularly when the adverse reactions are serious.

❖ **Rationale for Fixed Dose Combination**

1. **Quality:** The same quality standards that apply to single-component products will apply to FDCs. It will be necessary to demonstrate that the quality of the combination is similar to that of the individual ingredients.

2. **Medical:**

i. There should be a medical rationale for combining the actives.

ii. If the actives in an FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptom in isolation should not be indications for the FDC.

3. **Interpretation of the results of bioavailability (BA) and bioequivalence (BE) tests** involves both quality and medical considerations. For example, it is not acceptable that bioavailability of the FDC is reduced or variable, when compared with that of single entity products, because of poor formulation, but an interaction between two actives that leads to an increased bioavailability may be one of the advantages that is taken into account when balancing advantages and disadvantages.

❖ **Broad classification**

FDCs can be broadly divided into following groups:

- FDC not marketed in India and one or more active ingredient(s) is a new drug
- FDC not marketed in India but the active ingredients are approved/marketed individually and it is likely to have significant (pharmacokinetic/pharmacodynamic) PK/PD interactions. This can be further categorized into,
- FDC marketed abroad
- FDC not marketed anywhere but individual components used concomitantly
- FDC not marketed and individual components are not used concomitantly
- FDC marketed in India but some changes are sought
- FDC - only for convenience
- Subsequent FDC approvals after the approval of primary applicant's FDC in India
- **Indian scenario**

Appendix VI of Schedule Y (Drugs & Cosmetics Rules 1945, India) provides details about the requirements for manufacture/import approval and marketing of various types of FDCs.

New fixed dose combinations (FDCs) have been granted licenses by state authorities without mandatory approval of the Drug Controller General of India and action will be taken in these cases, Government clutch of fixed-dose-combination (FDC) drugs. These FDC drugs, which had found their way into the market without the approval from the drugs controller general of India (DCGI) and under licenses issued by state drug regulators, include muscle relaxants, painkillers, anti-depressants and antispasmodics, according to official sources.

Principles of FDC development in relation to four scenarios

Scenario 1: A new FDC product developed as a generic bioequivalent to an existing FDC

Scenario 2: A new FDC product developed by combining active components that are already well studied and for which the simultaneous use of all the individual active components in a multidrug regimen has been well characterized as safe and effective.

Secondly the dosage regimen of the components given individually in a multidrug.

Regimen and the dosage regimen of the FDC are the same.

Scenario 3: A new FDC product is developed from individual components that have a well characterized safety and efficacy profile of their own, but the efficacy and safety of their simultaneous use in a multidrug regimen is not well established; or when two or more well-characterized individual components from an established multidrug regimen

are combined using a novel dosing regimen.

Scenario 4: The FDC is developed by incorporating one or more new molecular entities.

❖ **Merits of FDC**

- FDCs are potentially lower costs of manufacturing compared to the costs of producing separate products administered concurrently, simpler logistics of distribution and reduced development of resistance in the case of antimicrobials
- Drugs that are normally given in combination are more conveniently prescribed and consumed as an FDC.
- Better patient compliance is claimed
- It is cheaper to purchase an FDC product than to purchase the products separately.
- The logistics of procurement and distribution are simpler (which can be especially important in remote areas).

4. INTRODUCTION TO EAST AFRICAN NATION [20-29]

Regulatory Authorities of east African nations

Table 1.4.1 overview of regulatory guidelines of east african nation

COUNTRY	REGULATORY AUTHORITY
Angola	Ministry of health
Burundi	Ministry of health
Comoros	Ministry of health
Democratic Republic of Congo	Ministry of health
Eritrea	Ministry of health
Ethiopia	Drug Administrative Control Authority
Kenya	Pharmacy and Poisons Board.
Madagascar	Ministry of health
Malawi	Ministry of health
Mauritius	Mauritius Institute of Health
Namibia	The Namibia Medicines Regulatory Council (NMRC)
Rwanda	Ministry of health
Seychelles	Ministry of health
Swaziland	The Government of the kingdom of the Swaziland
Tanzania	Tanzania Food and Drugs Authority
Uganda	National Drug Authority
Zambia	Ministry of health
Zimbabwe	Medicines Control Authority of Zimbabwe

ZAMBIA

Pharmaceutical Regulatory Authority of Zambia (PRA)

RA approval is required before a study may commence. In practice, 'RA Approval', effectively registering the Investigational Medicinal Product (IMP) in Zambia with the PRA is required before a clinical trial may commence for any IMP. IMP is defined as any unregistered products/ registered products in a new indication, route, dosage, etc. However the PRA is becoming ever more involved in clinical trial review.

REGULATIONS OF ZAMBIA

Introduction

These guidelines are to assist applicants in completing application forms and preparing dossiers for submission to the Zambia they prescribe the format and content of registration dossier, number of samples, fees payable and labelling and package insert information requirements. Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the application and hence the product licensing. This will enable the prospective licence holders to market their products on time and make them available to the consumers. In view of this, applicants are advised to read these guidelines carefully and adhere in full to the prescribed instructions.

Application forms

(i) Each application for registration of a medicine must be submitted in accordance with the requirements of the Pharmaceutical PRA (PRA).

(ii) All forms are to be completed in English.

(iii) Application forms are available from the PRA secretariat and all completed applications are to be submitted to the address

(iv) An application not submitted in the appropriate format or which is incomplete will be rejected.

(v) Application for registration must be accompanied by:

(a) Two copies of a motivation letter of not more than 500 words as to why the product should be registered.

(b) Two copies of package inserts or drafts thereof and 2 labels or drafts thereof

(c) Copies of any literature in support of the application.

(d) A checklist indicating that all the sections of the application have been completed and the pages thereof.

(e) Two samples of the product in the smallest packaging.

(vi) Each section of the dossier is to be marked by use of clearly annotated tabs.

(vii) The documentation should be filed in accessible files. **Lever** arch files are not acceptable.

PART IA GENERAL INFORMATION

1 Details of Applicant	1.1 Details of responsible person. 1.2 Details of Manufacturers 1.3 Source (manufacturers) of Active Pharmaceutical Ingredient(s) (API).
2 Proprietary Name	2.1 Name(s) of active pharmaceutical ingredient(s) 2.2 Pharmacotherapeutic classification
3 Pharmaceutical dosage form	3.1 Route of administration 3.2 Container, closure and administration devices. 3.3 Package sizes 3.4 Shelf life 3.5 Storage conditions. 3.6 Categories for Distribution
4 Registration in the country of original development	
5 Registration in other countries	
6 Proposed indications	
7 Unit (Master) Formulation	
8 Declaration by an applicant	

PART IB PRODUCT PROFILE

9. Summary of product characteristics	
9.1 Proprietary name of a medicinal product	
9.2 Approved generic name(s)	
9.3 Qualitative and quantitative composition	
9.4 Dosage form	
9.5 Clinical particulars	(i) Therapeutic indication(s) (ii) Route of administration (iii) Contra-indications- (iv) Special warnings and precautions for use (v) Interactions (vi) Pregnancy and lactation (vii) Effects on the ability to drive and operate (viii) Undesirable effects
9.6 Pharmacological properties	(i) Pharmacodynamic properties (ii)Pharmacokineticproperties (iii) Preclinical safety data
9.7 Pharmaceutical particulars	i) List of excipients (ii) Incompatibilities (iii) Shelf-life (iv) Special precautions for storage (v) Nature and composition of containers (vi) Instruction for use/handling (vii) Restriction on sale /distribution

9.8 Administrative data	**(i**) Name and address of holder of a Product licence (ii) Registration number (iii) Date of first registration/renewal of a Product licence. (iv) Date of (partial) revision of the text
9.9 Registration in a SADC member state	
10 Package Insert	
11 Patient Information Leaflet (PIL)	
12 label	**12 A** Immediate Container Label 12B Outer packaging label

PART IIA BIOAVAILABILITY / BIOEQUIVALENCE DATA

Data about the biovailability must be presented concerning the medicinal products acting systemically, which are administered enterally and which have not been registered before.

PART IIB EXPERT REPORTS	(i) Chemical and pharmaceutical documentation (ii) Toxicological and pharmacological documentation (iii) Clinical documentation

PART III CHEMICAL AND PHARMACEUTICAL INFORMATION

PART IIIA COMPOSITION	
<u>1 Composition of the medicinal product</u>	
<u>2 Container /packaging</u>	(i) Nature of container materials (ii) Qualitative composition (iii) Method of closure (iv) Method of opening
<u>3 Clinical trial formula(e) for new chemical entities</u>	

PART IIIB DEVELOPMENT PHARMACEUTICS
(i) Explanation with regard to the choice of formulation, composition, ingredients and container, supported if necessary, by data on development pharmaceutics (ii) The overage, with justification thereof (iii) Tests carried out during pharmaceutical development must be described in detail e.g. in vitro dissolution studies for solid pharmaceutical forms must be stated. (iv) Reasons for the choice of the primary packaging must be given.

PART IIIC CONTROL OF THE STARTING MATERIALS	
<u>1 Active pharmaceutical ingredients (API)</u> **(i) Route of synthesis including impurities**	
(a) scientific data	(1) Nomenclature; (2) International Non-proprietary Name (INN); (3) Chemical name; (4) Other names; (5) Laboratory code; (6) Description; (7) Physical form; (8) Structural formula; (9) Molecular formula; (10) Relative molecular mass;
(b) Manufacture:	(1) Name (s) and address(es) of manufacturing source (s); (2) Synthetic or manufacturing route, including flow chart for the process; (3) Description of process, including in-process control; (4) Analysts, also data about solvents, reagents, auxiliary materials; (5)Purification stages, including reprocessing criteria for purification steps
(c) Quality control during manufacture	(1) Starting materials; (2)Control tests on intermediate products.

(d) Development chemistry	(1) Evidence of chemical structure (2) Potential isomerism; (3) Physiochemical characterisation (4) Full characterisation of primary reference material; (5) Analytical validation and comments on the choice or routine tests and standards, e.g. working standard
(e) Impurities	(1) Potential impurities originating from the route of synthesis; (2) Potential arising during the production and purification (degradation products); (3) Analytical test procedures and their limits of detection;
(f) Batch analysis	(1) Date of manufacture, place of manufacture, batch size, and use of batches tested including batches used in pre clinical in pre clinical and clinical testing; (2) Results of tests; (3) Analytical results of reference material, primary and others (ii) Physical and chemical characteristics. (iii) Specifications and routine tests: (iv) Certificates of analysis of the API (v) Analytical validation for the test methods used for the analysis of the API should be submitted (vi) Stability data for the API should be generated and presented as per stability guidelines
2 Excipient(s)	
(i) Specifications and routine tests:	(1) Characteristics, (2) Identification tests; (3) Purity tests, (4) Other tests; (5) Assay(s) and/or evaluations,
(ii) Additional tests	Any additional tests done on the excipients must be indicated.
(iii) Scientific data	(a) Nomenclature (b) International non-proprietary name (INN) (c) Chemical name (d) Other names (e) Laboratory name (f) Physicochemical properties
PART IIID PACKAGING MATERIAL	
(i) Specifications and routine tests	(a) Type of material; (b) Construction; (c) Quality specifications (routine tests) and test procedures
(ii) Scientific data	(a) Development studies on packaging materials; (b) Batch analysis results
PART IIIE CONTROL TESTS ON INTERMEDIATE PRODUCTS	(i) Identification of intermediate product e.g. powder mix or granules ready for compression (ii) Specification of the intermediate product (iii) Justification for the tests and the control tests in detail
PART IIIF: CONTROL TESTS ON THE FINISHED PRODUCT	
(i) Specifications and routine tests	(a) Pharmacopoeial (include copy of the monograph; (b) In-house (supply details) (c) Quality specifications (routine tests) and test procedures. The detailed methods should be submitted to allow repetition of the tests by another laboratory
(ii) Justification for tests must be given	
(iii) Analytical validation of methods and comments on the choice routine test and standards (e.g. working standards).	

PART IIIG METHOD OF PREPARATION FOR THE FINISHED PRODUCT

(i) Batch manufacturing formula including details of batch size.	
(ii) Site of manufacture	(a) The name and business address of each manufacturing facility where any aspect of manufacture occurs including activity performed in each site

	(b) GMP certificate for each site and the manufacturing licence from the PRA must be submitted
(iii) For domestic companies supply the current license number issued by a regional or national PRA.	
(iv) Manufacturing process	(a) Detailed manufacturing procedure including equipment, in process controls, processing conditions and packaging procedure must be presented. (b) A flow chart of the entire manufacturing process (including packaging and labelling) must be presented (c) Validation of the process when a non-standard method of manufacture is used or it is critical for the product. Experimental data showing that the manufacturing process, using materials of the stated quality and the types of manufacturing equipment specified is a suitable one and will consistently yield a product of the desired quality, which is described in the finished product specification. (d) A copy of the Master formula should be presented (e) Copy of the batch manufacturing record including the ingredient analytical reports, in process control tests reports, intermediate product test reports, reconciliation records and a certificate of analysis for the batch must be presented
PART IIIH STABILITY TESTS ON THE FINISHED PRODUCT	(i) Quality specification for the proposed shelf-life (ii) Characteristics to be tested and the justification thereof (iii) Batches types and sizes tested (iv) Packaging material and the sizes where applicable (v) Real-time and accelerated conditions (vi) Validation of stability indicating tests (vii) Results of tests, including initial results and reference to degradation products (viii) Discussion of the results must be done (ix) Conclusion and shelf life claim is expected in relation to the results
PART IV SUMMARY OF TOXICO-PHARMACOLOGICAL DOCUMENTATION OF A MEDICINE	
PART IVA SINGLE DOSE TOXICITY	
PART IVB REPEAT DOSE TOXICITY	
PART IVC REPRODUCTION STUDIES	(i) Fertility and early embryonic development (ii) Embryo-fetal development (iii) Prenatal and post natal development, including maternal function (iv) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted
PART IVD GENOTOXICITY	(i) *in vitro* non-mammalian cell system (ii) *in vitro* mammalian cell system (iii) *in vivo* mammalian system (including supportive toxicokinetics evaluation) (iv) other systems
PART IVE CARCINOGENICITY	(i) Long-term studies (by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) (ii) Short or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) (iii) Other studies
PART IVE CARCINOGENICITY	(i) Long-term studies (by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) (ii) Short or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) (iii) Other studies
PART IVF PHARMACODYNAMICS	

PART IVG PHARMACOKINETICS	
PART IVH LOCAL TOLERANCE	
PART IVJ OTHER TOXICITY STUDIES	(i) Antigenicity (ii) Immunotoxicity (iii) Dependence (iv) Studies on metabolites (v) Studies on impurities (vi) Other studies
PART V SUMMARY OF CLINICAL STUDIES	
PART VA HUMAN PHARMACOLOGY (i) Pharmacodynamics (ii) Pharmacokinetics	
1 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES **Product Development Rationale**	(i) Identify the pharmacological class of the medicinal product (ii)Describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose. (iii) Briefly summarise the scientific background that supported the investigation of medicinal product for the indication(s). (iv) Briefly describe the clinical development programme of the medicinal product including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. (v) Briefly describe plans for the use of foreign clinical data.
2 SUMMARY OF BIOPHARMACEUTIC (BC) STUDIES AND **ASSOCIATED ANALYTICAL METHODS**	(i) Background and Overview (ii) Summary of results of Individual Studies (iii) Comparison and Analyses of Results Across Studies
3 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES	(i) Background and Overview (ii) Summary of Results of Individual Studies (iii) Comparison and Analyses of Results Across Studies (iv) Special Studies

PART VB CLINICAL DOCUMENTATION	
1 SUMMARY OF CLINICAL EFFICACY	(i) Background and Overview of Clinical Efficacy (ii) Summary of results of Individuals Studies (iii) Comparison and Analyses of Results Across Studies
2 SUMMARY OF CLINICAL SAFETY	(i) Exposure to the Medicine (ii) Adverse Events (iii) Narratives (iv) Clinical Laboratory Evaluations (v) Vital Signs, Physical Findings, and other Observations Related to Safety (vi) Safety in Special Groups and Situations

CONCLUSION

From the above article we can conclude that it facilitates regulatory reviews and communication with the applicant by a standard document of common elements. Simplifies exchange of regulatory information between Regulatory Authorities etc. Provide for a scientifically sound means of establishing the quality, safety and efficacy of therapeutic products. Improve the transparency, predictability and efficiency of the regulatory process. Contribute to reducing unnecessary regulatory burden and promoting industry compliance. Promote bilateral and multilateral regulatory communication and cooperation – common regulatory platform. Level playing field good for export market Zambia is a model of a regional integration initiative undergoing dynamic development and changes. It has become one of the most successful regional groupings of developing nations, to promote cooperation, and trade in the face of wider international competition and economic upheavals. Since its inception decades ago, it is now at a crucial stage in transforming itself from a regional Association into a dynamic, integrated economic Community.
Zambia drug regulatory authorities and industry have worked very close regionally. Largely they have been realized already, the next step will be to focus on mutual recognition of pharmaceutical registrations and implementing a harmonized placement system. There is still much work to be carried out in the implementation. The future will show if this can be achieved by the versioned end goal of economic community.

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