MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

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FIXED DOSE COMBINATION PRODUCTS (FDC Products) FOR HIV/AIDS, TUBERCULOSIS, and MALARIA

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

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REGISTRAR OF MEDICINES
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MEDICINES CONTROL COUNCIL POLICY ON THE CLINICAL EVALUATION FOR REGULATORY APPROVAL OF FIXED DOSE COMBINATION PRODUCTS (FDC Products) FOR HIV/AIDS, TUBERCULOSIS, AND MALARIA

TABLE OF CONTENTS

1 INTRODUCTION

HIV/AIDS, tuberculosis, and malaria are the foremost infectious disease threats to public health. Combination therapy is considered to be essential in the treatment of these diseases and in the prevention of resistance.

From a public health perspective, an important approach to addressing the management of HIV/AIDS, tuberculosis and malaria has included the development of fixed-dose combinations (FDCs) of individual components administered together in one dosage form. Among others, FDCs simplify treatment regimens, improve convenience of use and patient adherence, facilitate the implementation of interventional programs, and potentially limit the development of resistance. The importance of combination therapy is not unique to AIDS/HIV, malaria and tuberculosis. Combination therapy is also used in the treatment of infections other than those listed above, as well as in non-infectious diseases such as hypertension, diabetes and epilepsy. However, the scope of this policy document is to concentrate only on combination therapies to be used for treating HIV/AIDS, tuberculosis and malaria.

Notwithstanding the benefits described above, there are challenges related to the development and use of FDCs such as dose-titration of the individual components, the interplay of adverse effects, allergies to one or more of the components, and complex pharmacokinetic (PK) or pharmacodynamic profiles.

It should be noted that the risk/benefit assessments for FDCs may have to take into consideration the differences in anticipated patient populations, and that decision-making may vary between the different medicine regulatory authorities. It should also be noted that this document does not relate to biological medicines.

2 PURPOSE

This policy document provides principles to be taken into account when evaluating FDC products. These principles focus on scientific aspects of efficacy and safety of FDC products intended for the treatment of HIV/AIDS, tuberculosis, and malaria.

References consulted are listed at the end of the document.

3 CONSIDERATIONS

3.1 In the evaluation of FDC products, it is necessary to take three factors into account:

3.1.1 The safety and efficacy of the individual active components;

3.1.2 The safety and efficacy of the simultaneous use of the individual active components (multi-component regimen); and

3.1.3 The possible chemical and physical interactions between active components derived from a multi-component regimen when they are formulated into an FDC product.

3.2 The following considerations generally apply when determining whether active components are suitable for a multi-component regimen and hence also for inclusion in an FDC product. The medical and scientific rationale should support the simultaneous use of more than one active component in at least one of the following ways:

3.2.1 Increased efficacy (additive or synergistic);

3.2.2 Reduced toxicity;

3 Considerations - continued

3.2.3 Limiting the development of resistant pathogens; and

3.2.4 Boosting of active moiety levels.

3.3 Additionally, FDC products have some important advantages over multi-component regimens, such as:

3.3.1 Improved adherence;

3.3.2 Convenience of use;

3.3.3 Reduced number of dosage units and/or simplified treatment regimens; and

3.3.4 Facilitating the logistics of procurement, distribution and dispensing.

3.4 In evaluating a practical FDC dosage regimen, it is necessary to ensure that constituent active components have suitable PK and physicochemical properties. Several factors need to be considered:

3.4.1 Combining active components with different pharmacokinetic characteristics may be problematic. For example, combining antimicrobials with short and long elimination half-lives may result in the emergence of resistance where a single component persists in the absence of the companion active(s) particularly in the case of long term treatment. It may be possible to address differences in pharmacokinetics by modification of FDC product formulations;

3.4.2 Conflicting effects of food on the bioavailability of the components might complicate a dosing strategy; and

3.4.3 The components used in FDC products should be chemically and physically compatible, unless formulation techniques have been demonstrated to overcome any such incompatibility.

3.5 Paediatric FDC formulations often differ from adult FDC products, and special consideration is needed concerning issues such as stability, palatability, dosing (frequency, mg/m^2, mg/kg), toxicity (e.g. excipients and degradation products) and food requirements.

3.6 This policy document describes the principles of FDC product clinical evaluation in relation to the following four scenarios:

3.6.1 Scenario 1

A new FDC product developed as a generic bioequivalent to an existing FDC product.

3.6.2 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 multi-component regimen has been well characterised as safe and effective. The dosage regimen of the components given individually in a multi- component regimen and the dosage regimen of the FDC product are the same.

3.6.3 Scenario 3

A new FDC product developed from individual components that have a well-characterized safety and efficacy profile on their own, but the efficacy and safety of their simultaneous use in a multi-component regimen is not well established; or an FDC product developed using two or more well-characterized individual components of an established multi-component regimen when the dosing regimen of the FDC product is novel.

3.6.4 Scenario 4

A new FDC product developed by incorporating one or more new molecular entities.

4 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

4.1 Microbiology

4.1.1 Scenarios 1 and 2

Generally, no microbiologic evaluations are needed, unless the new FDC product is intended for a different geographic area with a different pathogen and/or resistance pattern.

4.1.2 Scenarios 3 and 4

Microbiologic evaluations may be needed to determine the advantage of multi-component regimens or FDC products over individual active components against a given pathogen. Such microbiologic studies may be needed to motivate the selection of appropriate entities for combined use, and to evaluate the advantage of the multi component regimen over individual active components, when clinical trials of monotherapy are inappropriate or unethical.

The following types of data may be important and should be obtained from studies performed to accepted standards:

4.1.2.1 Characterization of microbiologic activity *in vitro* and *in vivo* against laboratory strains and clinical isolates of the targeted pathogens including those in the relevant geographic regions;

4.1.3.2 Characterization of microbiologic activity in appropriate animal models of infection with the targeted pathogens;

4.1.4.3 Characterization of the mechanism by which the active ingredients exhibit additive or synergistic microbiologic activity against the targeted pathogens;

4.1.5.4 Investigation of potential antagonistic effects between the active components;

4.1.6.5 Investigation of the potential for development of resistance of target pathogens *in vitro* and *in vivo*; and

4.1.7.6 Where there are concerns about sub-therapeutic trough levels, investigation of microbiologic activity at anticipated human C_{min} concentrations might be needed. In such cases, C_{min} should be evaluated in human steady-state PK studies.

4.2 Non-clinical Pharmacology and Toxicology Scenarios

4.2.1 Scenarios 1 and 2

Non-clinical pharmacology and toxicology studies are generally not needed, as long as internationally acceptable excipients are used, and the impurities profile does not significantly deviate from the reference product.

4.2.2 Scenario 3

4.2.2.1 For FDCs of two or more registered products, the need for non-clinical pharmacology or toxicology studies should be considered on a case-by-case basis. Generally, a bridging toxicity study should be considered if the combination is novel, or if the dose is higher than previously characterized and accepted. The design of the bridging study will depend on the individual components of the FDC. In such studies, consideration should be given to the dose ratios to be used in non-clinical studies versus the ones in clinical use and to the systemic exposure in animal versus man.

4.2.2 Scenario 3 - continued

4.2.2.2 Additional non-clinical studies may be requested if the proposed indication involves a longer treatment duration than is currently registered for one or more of the active components in the FDC.

4.2.2.3 Additional non-clinical studies may be requested based on the outcome of the bridging study or if there is potential for interactions or overlapping toxicity.

4.2.3 Scenario 4

4.2.3.1 A combination of one new molecular entity - for example, a new active component not previously registered for medicinal use in humans - with one or more registered active components requires a complete non-clinical evaluation (including genotoxicity and reproduction toxicity studies) of the new molecular entity. In addition, investigation of the toxicokinetics and a bridging toxicity study for the FDC may be needed. Alternatively, a complete non-clinical pharmacologic and toxicologic evaluation of the FDC (instead of the new molecular entity alone) may be considered as an option.

4.2.3.2 If more than one new molecular entity is included in an FDC, a complete non-clinical evaluation (including genotoxicity and reproduction toxicity studies) of each new single entity and an appropriate bridging study for the FDC are required. The design of the bridging study depends on the individual entities of the FDC and the proposed conditions of use.

4.2.3.3 Additional non-clinical studies may be needed based on the outcome of the bridging study or if there is potential for interactions or overlapping toxicity between the new and already registered entities of the intended FDC.

4.2.4 All scenarios

For all scenarios, additional non-clinical studies may be needed if new concerns are raised from non-clinical or clinical information.

5 CLINICAL SAFETY AND EFFICACY

5.1 Scenario 1

A properly designed study should demonstrate bioequivalence (BE) between the FDC product and an adequate reference product in line with the latest Medicines Control Council guideline on Biostudies.

5.2 Scenario 2

5.2.1 A properly designed study should demonstrate bioequivalence between the FDC product and the individual active components given together.

5.2.2 The advantage of the combination may differ depending on the individual active components and the indication for use as described previously. The rationale for the simultaneous use of the individual active components in a multi-component regimen (and therefore in the proposed FDC product) must be justified. Each active component must be shown to contribute an advantage, when incorporated into the multi-component regimen or FDC product at the relevant doses. This may generally be demonstrated by means of a systematic review of the literature and/or other already existing data from clinical studies.

5.3 Scenario 3

5.3.1 The potential for favourable or unfavourable interactions between the components should have been investigated in appropriate PK and pharmacodynamic studies.

5.3.2 For a novel FDC (where a corresponding multi-component regimen has not already been established), the rationale for the simultaneous use of the individual active components generally needs to be justified by means of adequate comparative clinical studies. Such clinical studies should convincingly demonstrate the contribution to the efficacy and/or safety of each active component incorporated into the combination at the proposed doses.

5.3.3 When a novel FDC involves a change in the dose regimen of a previously characterised multi-component regimen or FDC product, comparative clinical studies should be performed, demonstrating at least equal efficacy and safety of the new dosing regimen compared to the previously used regimen.

5.3.4 In situations where comparative clinical trials are not feasible, for example when monotherapy is not acceptable, and aggregate of clinical and non-clinical data may be substituted. Such data may include:

5.3.4.1 historical clinical data on the components used alone at comparable doses / at comparable exposure as in the proposed FDC;

5.3.4.2 bridging pharmacokinetic data, where applicable;

3.2.4.3 non-clinical pharmacology and/or toxicology data; and

5.3.4.4 *in vitro* microbiologic data.

5.3.5 Clinical trials should demonstrate that the proposed FDC is statistically either non-inferior, equivalent, or superior compared to recognised treatment for the proposed indication. The reason for the choice of statistical hypothesis needs to be specified in the study protocol and the chosen option should be appropriate to the nature of the comparator and the scientific objective. For example, if a novel three-component FDC is compared to an existing FDC containing two of the active components, superiority should be shown. If an FDC is compared to a recognised treatment containing different active components, at least non-inferiority should be shown.

5.3.6 Combining the components of the proposed multi-component regimen into one product should not compromise the overall risk-benefit profile.

5.3.7 When there is potential for interaction or overlapping toxicity, preclinical toxicity studies, clinical safety studies and dose ranging studies may be needed before embarking on clinical efficacy studies.

5.4 Scenario 4

A comprehensive clinical development program is needed.

6 GENERAL CONSIDERATIONS FOR CLINICAL STUDIES *(SCENARIOS 3 and 4)*

6.1 In clinical safety and efficacy studies, comparators or comparator regimens should represent the recognised treatment for the indication in question. Because reliable performance of the comparator pharmaceutical product is crucial in determining the safety and efficacy of new FDC products or combination regimens, these comparators should be registered products, preferably innovator products or registered products whose safety, efficacy, and quality parameters have been well established and independently vetted by the Medicines Control Council *(Refer Pharmaceutical and Analytical guideline - Reference products).*

6 General Considerations - continued

6.2 Unapproved or novel combinations should be avoided as comparators, as they may introduce new toxicities and complicate the evaluation of safety and efficacy.

6.3 Individual components that are being considered for inclusion in an FDC should have a well-established risk-benefit profile in the target population when used according to the recommended dosing regimens. Consideration should be given to ethnic, environmental, co-morbid, and nutritional variations between populations, when scientifically appropriate.

6.4 The protocols should clearly state whether non-inferiority, equivalence or superiority is the objective of the studies.

7 SELECTION OF ENDPOINTS IN CLINICAL TRIALS *(SCENARIOS 3 and 4)*

7.1 Clinical and microbiological endpoints including treatment duration should be selected that are relevant for the indication. Accepted guidelines, where available, should be consulted.

7.2 The follow-up period in clinical trials should be appropriate to allow:

7.2.1 scientifically acceptable assessment of efficacy;

7.2.2 where applicable, an assessment of the risk of relapse after cessation of therapy; and

7.2.3 an adequate assessment of late-appearing adverse events.

8 REFERENCES

The reference documents listed below are intended to provide additional information. However, it should be noted that documents identified do not represent a comprehensive list of all reference documents and may be further supplemented:

1. "Note for Guidance on Repeated Dose Toxicity," July, 2000. Committee for Proprietary Medicinal Products, *www.emea.eu.int/pdfs/human/swp/104299en.pdf*
2. "Note for Guidance on Fixed-Dose Combination Medicinal Products," April 1996, Committee for Proprietary Medicinal Products/Efficacy Working Party/240/95.
3. "Note for Guidance ~~for~~ on the Clinical Development of Medicinal Products for Treatment of HIV Infection." March, 2003, Committee for Proprietary Medicinal Products, *www.emea.eu.int/pdfs/human/ewp/063302en.pdf*
4. "Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products," July, 2000. Committee for Proprietary Medicinal Products/Efficacy Working Party/2655/99. *www.isap.org/1999/Uppsala/265599en.pdf*
5. "Note for Guidance on Duration of Chronic Toxicity Testing in Animals," Nov. 1999. International Conference on Harmonization. *www.ich.org*
6. "Dose-Response Information to Support Drug Registration," March 1994. International Conference on Harmonization. *www.ich.org*
7. "Pharmacovigilance Planning, E2E," Nov. 11, 2003. International Conference on Harmonization. *www.ich.org*
8. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products", 1996, World Health Organization, Technical Report Series No. 850, 1995, Annex 3, *www.who.int/medicines/library/par/ggcp/GCPGuidePharmatrials.pdf*
9. Guidance for Industry, "E6 Good Clinical Practice: Consolidated Guidance," April 1996. International Conference on Harmonization. *www.fda.gov/cder/guidance/959fnl.pdf*
10. Guidelines for registration of fixed-dose combination medicinal products, 2005, World Health Organization, Technical Report Series No. 929, Annex 5, http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf#page=103

9 GLOSSARY OF TERMS

9.1 Active Moiety

Defined in the Biostudies guideline.

9.2 AUC

The area under the curve for the parent active or metabolite concentration in plasma, serum, or whole blood against time.

9.3 Bioavailability

Defined in the Biostudies guideline.

9.4 Bioequivalence (BE)

Defined in the Biostudies guideline.

9.5 Bioequivalent FDC product

An FDC product that can be substituted in patient care for an innovator product. It has demonstrated bioequivalence to a referenced innovator product and completed manufacturing processes and controls.

By following the innovator's administration instructions, the bioequivalent FDC product can be expected to have the same clinical safety and efficacy profile in patients as the innovator product. The bioequivalent FDC product can rely on the innovator product's clinical and preclinical safety and efficacy data and forgo a formal clinical safety and efficacy clinical testing program.

These products, often produced by many different manufacturers, are sometimes referred to as multisource interchangeable products. In some jurisdictions these products are called generic products. However, because in other jurisdictions, the term generic does not include the critical concept of BE, the use of the term generic product in international documents is not recommended.

9.6 Bridging Toxicity Study

A limited non-clinical study that allows the assessment of the overall toxicity of a multi-component regimen or an FDC product consisting of individual active components for which the toxicity is already well characterized at the dose level of interest.

The design of such a study will depend on the existing knowledge of the toxicity and toxicokinetics of the individual components.

9.7 Cmax

The observed maximum or peak concentration of a parent active moeity or metabolite in plasma, serum, or whole blood.

9.8 Cmin

The minimum concentration of a parent active moeity or metabolite measured between one dose and the next.

9.9 Efficacy

The desired effect of a medicine on a disease condition.

Efficacy must be established by substantial evidence, such as independently corroborated evidence, usually from appropriately blinded well-controlled clinical trials, which demonstrate that the product will have the effect claimed in the intended population according to predetermined statistical and clinical criteria.

9 Glossary of Terms - continued

9.10 Fixed-dose combination (FDC) product

A single product created by the combination of two or more active pharmaceutical ingredients (APIs) in a single formulation, and in which each API contributes to the benefit of the new product. FDC products are not simply two single, distinct products packaged together. APIs can be pharmaceutical (i.e. chemical) or biologic in origin.

9.11 Innovator FDC product

The first registered formulation of a new FDC product, generally as a patented medicine on the basis of original scientific documentation of safety, efficacy, and pharmaceutical quality.

9.12 Innovator product

The first registered formulation of a new product, generally as a patented medicine on the basis of original scientific documentation of safety, efficacy, and pharmaceutical quality.

9.13 Microbiology

Includes bacteria, viruses, and parasites.

9.14 Monotherapy

Using one active component for the treatment of a condition.

9.15 Multi-component Regimen

Using more than one active component simultaneously for the same condition.

9.16 Multisource Product

Defined in the Biostudies guideline.

9.17 New Molecular Entity

An active pharmaceutical ingredient that has never been used in a marketed finished dosage form.

9.18 Pharmaceutical Equivalence

Defined in the Biostudies guideline.

9.19 Post-marketing Active Surveillance

Active surveillance seeks to ascertain completely the number of adverse events via a continuous pre-organised process.

9.20 Post-Marketing Surveillance

Procedures implemented after registration of a medicine for a given indication that is designed to provide information on the actual use of the medicine for that indication and on the occurrence of related side effects.
The surveillance usually involves survey techniques rather than controlled trials.

9.21 Registered FDC product

An FDC product for human use which has underlying clinical, preclinical, and manufacturing data, that has been evaluated and approved for registration by the Medicines Control Council and meets required scientific and legal standards for authorized marketing in the Republic of South Africa.

9 Glossary of Terms - continued

9.22 Safety

A measure of the product's ability to cause the desired effect without harming the patient. As no medicine is completely safe, a positive risk-benefit ratio needs to be established for the intended patient population based on non-clinical and clinical data (i.e. that the established benefits of the product outweigh the known risks of the product when used as directed in the intended population).

9.23 Surveillance

Spontaneous reports voluntarily reported either to pharmaceutical manufacturers, to national or regional pharmacovigilance centres, or to national regulatory authorities by healthcare professionals, other professionals, or consumers.

9.24 Stability

Refer to the Stability guideline.

9.25 Statistical Equivalence

When the efficacy/evaluated effect of the investigational product does not differ substantially in either direction from the comparator. If two treatments are to be declared equivalent, then the two-sided (1-α) x 100 percent confidence interval should lie entirely within a pre-specified interval (α is defined as the type I error of the test).

9.26 Statistical Non-inferiority

The efficacy / evaluated effect of the investigational product is not substantially inferior to that of the comparator. The lower bound of the (1-α) x 100 percent confidence interval around the observed efficacy / effect of the investigational product minus the observed efficacy / effect of the comparator product is greater than the pre-specified limit (α is defined as the type I error of the test).

9.27 Statistical Superiority

When the efficacy / evaluated effect of an investigational product is better than that of the comparator. The lower bound of the (1-α) x 100 percent confidence interval around the observed efficacy / effect of the investigational product minus that of the comparator product is greater than zero (α is defined as the type I error of the test).

9.28 Systematic Review

An analysis of an existing body of evidence that addresses clearly formulated questions and uses systemic and explicit methods to identify, select and critically appraise relevant research using statistical or non-statistical methods.

9.29 Therapeutic Equivalence

Defined in the Biostudies guideline.

9.30 T_{max}

The time point after administration of the medicine at which C_{max} is observed.

10 LIST OF ACRONYMS

API	active pharmaceutical ingredient
AUC	area under the curve
BE	bioequivalence
CDER	Center for Drug Evaluation and Research
EWP	Efficacy Working Party
FDC	fixed-dose combination
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
PK	pharmacokinetic
WHO	World Health Organization

UPDATE HISTORY

Date	Reason for update	Version & publication
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