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Scientific and Technical Principles for Fixed Dose Combination Drug Products

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HIV/AIDS, tuberculosis, and malaria are the foremost infectious disease threats to public health that the world faces today and are the focus of many global initiatives. Many consider combination therapy to be essential to the treatment of these diseases and to the prevention of drug resistance.

From a public health perspective, an important approach to addressing the management of these diseases has included the development of fixed dose combinations (FDC) of individual components administered together. FDCs simplify treatment regimens, improve patient adherence, facilitate the implementation of interventional programs, and prevent the development of drug resistance. Notwithstanding these benefits, there are challenges related to the use of FDCs such as dose titration, allergies to one or more of the components, different pharmacokinetic (PK) or pharmacodynamic profiles, and pharmaceutical development.

As these diseases also affect children, paediatric formulations of FDC combinations should be considered early in development of FDCs.

The development of such FDCs may vary depending on their individual active components and on the indications that they target. Currently, there are no uniform principles, guidelines or international standards addressing the development of FDCs and their potential benefits or possible disadvantages in treating these diseases.

PURPOSE

The purpose of this document is to provide principles to be taken into account when developing, evaluating and considering FDCs. These principles focus on aspects of the efficacy, safety, and quality of FDCs.

The document is intended to provide points to consider when developing, evaluating and considering combination products for use in programs intended to address optimum drug treatment combinations as fixed drug combinations to facilitate the administration of drug regimens for the treatment of HIV/AIDS, tuberculosis, and malaria and their associated infectious diseases.

This document is not intended to be a therapeutic or regulatory guideline, and it will not address specific nonclinical, clinical, quality issues, including procurement and distribution of specific products.

CONSIDERATIONS

In developing FDCs, it is necessary to consider three factor s: the safety and efficacy of the individual active components, the simultaneous use of all the active components, and the possible interaction between active components in a single formulation by the administration of a simultaneous fixed combination.

Certain issues generally apply when determining whether components are suitable for an FDC. The medical and scientific rationale supports the combined use of the components in one or more ways:

- Increased efficacy (additive or synergistic)
- Reduced toxicity
- Prevention of antimicrobial resistance
- Boosting of drug levels

To develop a practical dosage regimen, it is necessary to choose constituent active components that have suitable PK characteristics. Several factors need to be considered:

- Combining components with different PK characteristics present problems. For example, combining antimicrobials with short and long elimination half-lives may result in the emergence of drug resistant infections where a single component persists in the absence of the companion drug.
- Conflicting effects of food on the bioavailability of the components might also complicate a dosing strategy.
- Components which do not generally require relative adjustments in dose would avoid the need for several formulations with different ratios of the same constituents, which could result in drug prescription errors.
- The chemistry of the components should be compatible with co-administration.

This document will describe the principles of FDC development in relation to these 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 components that are already well studied, and the simultaneous use of all the individual active components has been well characterized as safe and effective. The dosage regimen of the components given individually and the dosage regimen of the FDC are the same.

Scenario 3

- A new FDC product developed from individual components that are well-characterized for safety and efficacy when used as monotherapy, but the efficacy and safety of their simultaneous use is not well established, or two or more well characterized individual products are combined using a novel dosage regimen.

Scenario 4

- The FDC developed incorporating one or more new molecular entities.

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Microbiology

Microbiologic evaluations may be needed to determine the advantage of combinations of active entities over individual active entities against a given pathogen.

Such microbiologic studies may be needed to motivate the selection of appropriate entities for combined use, and evaluate the advantage of the combination over individual entities when clinical trials of monotherapy are inappropriate or unethical.

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

- Microbiologic activity in vitro against laboratory strains and clinical isolates of the targeted pathogens
- Microbiologic activity in appropriate animal models of infection with the targeted pathogens
- Microbiologic activity against resistant isolates or strains of the targeted pathogens isolated in the geographic areas where the product is intended to be used
- Characterisation of the mechanism by which the active ingredients exhibit additive or synergistic microbiologic activity against the targeted pathogens
- The potential for antagonistic effects between the active components
- The potential for development of resistance of target pathogens in vitro and in vivo.

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

Scenario 1

- Toxicology studies are generally not needed.

Scenario 2

- Toxicology studies are generally not needed, as long as internationally accepted excipients are used. In addition, certain nonclinical testing might still be warranted if the impurity profiles of the components deviate from that approved, and therefore need to be qualified in accordance with guidance documents.

Scenario 3

- For FDCs of two or more licensed products, the need for nonclinical pharmacology or toxicology studies should be considered on a case-by-case basis. Generally, a bridging toxicity study should be performed. The design of the bridging study will depend on the individual components of the FDC and could be decided on an as-needed basis. Particular consideration should be given in the bridging studies to the dose ratios to be used in nonclinical studies vs. the ones in clinical use and into the systemic exposure in animal vs. man.
- Additional nonclinical studies can be requested if the proposed indication involves either a higher dose level or longer treatment duration than is currently licensed for one or more of the active components in the fixed dose combination.
- Additional nonclinical studies can be requested based on the outcome of the bridging study or if there is potential for drug interactions or overlapping toxicity.

Scenario 4

- A combination of one new molecular entity—for example, a new active component not previously licensed for medicinal use in humans—with one or more licensed active components requires a complete nonclinical evaluation (including genotoxicity and reprotoxicity studies) of the new molecular entity. In addition, investigation of the toxicokinetics and a bridging toxicity study with the FDC regimen may be needed. Nonclinical pharmacologic and toxicologic evaluation of the FDC (instead of the new molecular entity alone) may be considered as an option.
- If more than one new molecular entity is included in an FDC, a complete nonclinical evaluation (including genotoxicity and reprotoxicity studies) of each 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.
- Additional nonclinical studies may be needed based on the outcome of the bridging study or if there is potential for drug interactions or overlapping toxicity between the new and already licensed entities of the intended FDC.

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

CLINICAL SAFETY AND EFFICACY

Scenario 1

- Bioequivalence (BE) studies are generally sufficient.

Scenario 2

- Justification supported by data or literature is needed to support the advantage of the combination over monotherapy with each of the individual entities. This advantage may differ depending on the components and the indication for their use. These can include:
  - Increasing efficacy (additive or synergistic)
  - Reducing toxicity
  - Preventing antimicrobial resistance
  - Boosting drug levels
- BE studies are needed.
- Data or literature in support of the safety and efficacy of the combination at the relevant doses are needed per general considerations outlined above.

Scenario 3

- Advantages of the FDC may differ depending on the entities and the indication for their use. These can include:
  - Increasing efficacy (additive or synergistic)
  - Reducing toxicity
  - Preventing antimicrobial resistance
  - Boosting drug levels
- The contribution of each additional component in the FDC must be shown. Each additional component should have an advantage over the entities given as monotherapy (in the case of FDCs containing two entities) or an advantage over the remaining constituent entities (in the case of FDCs containing more than two components). This advantage should be shown in clinical trials.
- In situations where such comparative clinical trials are not feasible because, for example monotherapy is not the recognised treatment, an aggregate of clinical and nonclinical data (e.g., historical clinical data on the components used alone, PK data, animal data, or in vitro microbiologic data) supporting the combination are needed.
- Clinical trials should demonstrate that the FDC has superiority or inferiority as compared to the recognised treatment for the proposed indication. Combining the components of the regimen into one product should not compromise efficacy or safety.
- Potential for favourable or unfavourable interactions between the components should be investigated in appropriate PK and pharmacodynamic studies.
- When there is potential for a drug interaction or overlapping toxicity, toxicity studies and dose ranging studies may be needed before embarking on clinical efficacy studies.

Scenario 4

- A comprehensive clinical development program is needed.

Considerations for Clinical Studies for Scenarios 3 and 4

- 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 drugs is crucial in determining the safety and efficacy of new FDCs or combination regimens, these comparators should be licensed products with well-established safety and efficacy profiles.
- Unapproved or novel combinations should be avoided as comparators, as they may introduce new toxicities and complicate the evaluation of safety and efficacy.
- Individual components that are being considered for inclusion in an FDC should have a well-established risk-benefit profile in the target population at the recommend dosing regimens. Consideration should be given to ethnic, environmental, co-morbid, and nutritional variations between populations.
- The protocols should clearly state whether inferiority or superiority is the objective of the studies.

Selection of Endpoints in Clinical Trials

- Clinical and microbiological endpoints should be selected that are relevant for the indication. For example, where a combination is designed to reduce the development of antimalarial drug resistance, endpoints might be the frequency of new drug resistance, as well as the overall clinical outcome following the use of the drug. Guidance on endpoints and statistical design are provided in the reference section, Page 14.

Followup in Clinical Trials

- The followup period should be sufficiently long enough to allow assessment of the risk of relapse after cessation of therapy, and to allow assessments of the risk of late-appearing (two months or longer) adverse events.

FDCs AND POSTLICENSING RESPONSIBILITIES

Following licensure, postmarketing surveillance and postmarketing studies to detect and evaluate new patient safety and efficacy data are a necessary part of product development, distribution, and utilisation. All FDC product manufacturers should have in place the capacity and standard operating procedures to assess the ongoing safety, efficacy, and utility of their products after licensure.

Regulatory capacity may be needed for postmarketing surveillance in countries where the FDCs would be used. In addition to the postmarketing safety and efficacy concerns, which are typical of all medicinal products, FDC products used in the treatment of HIV/AIDS, tuberculosis, and malaria have specific postmarketing issues that should be investigated. These include:

- Adverse events caused by one of the components that change the risk-benefit profile of the combination
- Change in the resistance profile of pathogens or the relative prevalence of different organisms
- Additive or synergistic toxicities.

BIOEQUIVALENT FDC PRODUCTS

Bioequivalence studies are performed to show that a multisource drug product is interchangeable with the innovator's version, and that it can be administered with the expectation that it will be therapeutically equivalent. In a BE study, PK endpoints are used for systemically active oral dosage forms. To be interchangeable, safety has to be guaranteed, and that depends not only on BE but also on the inactive ingredients.

This section of the document is confined to FDC products and should be considered in conjunction with existing national and international BE guidelines.

It is understood that the principles of Good Clinical Practise should be used when carrying out any BE study, and appropriate guidelines should be consulted.

Study Design

- For an FDC product from Scenario 1 the reference products should be either the originator substances or be chosen from a preset list of licensed products whose safety, efficacy, and quality parameters have been well-established and independently vetted by a recognised drug regulatory authority.
- For a new fixed-dose combination product from Scenario 2 containing active substances administered in free combination and used in clinical practise under the same conditions of use, an appropriate study design would be a randomised two-way crossover in which one arm receives the fixed-dose combination, and the other arm receives the same dose of the active ingredients, each provided as a separate licensed drug product. For long half-life drugs, where the washout exceeds four weeks, a parallel study design may be used.
- Crossover studies are conducted with a washout period (generally at least five half-lives in duration) between each treatment to ensure that the effects of the treatment are entirely eliminated before administration of the next treatment. For an FDC product, the half-life chosen to determine the washout period between treatments should be the one for the active pharmaceutical ingredient (API) with the longest half-life.

Subjects

The number of subjects is determined by the error variance associated with the drug product to be studied, estimated either from a pilot experiment, previous studies, or published data. The error variance chosen should be the one for the most variable API in the FDC product.

The number of subjects should not be less than 12; in most cases, 24 to 36 subjects will be adequate. Including both male and female subjects may increase variability and the number of subjects required.

Relevant PK Parameters

The PK parameters to be reported and assessed are those which would normally be reported and assessed in a BE study, and are those which would normally be required of each API if it were in the formulation as a single entity.

- Bioequivalence of two products in a study with PK endpoints is determined by measuring blood or plasma drug concentrations over time to calculate the parameters characterising rate and extent of drug absorption.
- Sampling times should be chosen such that the concentration profile is adequately defined to allow calculation of the relevant PK parameters for all APIs in the FDC product.
- For drugs with a long half-life (>24 hours) the sampling should cover a minimum of 72 hours unless 80% is recovered before 72 hours.

Bioanalytical Method Validation

- All bioanalytical methods should be well characterised, fully validated, and documented. The method validation should be stated in the protocol.
- The following guidelines should be consulted for more detail and adhered to:
  - The World Health Organization's "Essential Drugs and Medicines Policy," Annex 3: Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements for Interchangeability.
  - Guidance for Industry: "Bioanalytical Method Validation," May 2001. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.

Study Reporting

- "Guidelines of Medicine Registration" from the Medicines Control Council of South Africa is posted at *www.mccza.com* and should be consulted for further details when designing study report presentations.

Statistical Analysis

- The BE criteria should be met on each API in the FDC product.
- The AUC and C_{max} data are log-transformed prior to statistical testing. The statistical tests are implemented using the analysis of variance procedure and appropriate nonparametric test, if applicable. A 90% confidence interval is calculated for AUC and C_{max}. Alpha is set at 5% for each of the one-tailed tests.
- For AUC, the 90% confidence interval for the test to reference ratio of each drug of the test to reference formulation should lie within the acceptance interval of 80% to 125%.
- The acceptance criteria for C_{max} must meet the criteria in existing national and international BE guidelines, as set out by the drug regulatory authority where the application for approval is made.
- Evaluation of T_{max} data should be performed as per the existing national and international BE guidelines, as set out by the drug regulatory authority where the application for approval is made.

Fasting and Fed Bioequivalence Studies

- The requirement for fasting and fed BE studies for an FDC product should be based on the known s and product labelling of all the API present in the FDC product. A waiver for either a fasting or fed study should be based on a sound scientific rationale.

Waivers of In Vivo Testing

In some circumstances, in vivo BE studies can be waived:

- When the drug product is the same dosage form but different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BE testing has been conducted, an in vivo BE study of one or more strengths can be waived based on dissolution tests and an in vivo study on one strength, generally the highest strength.

- If the drug product is in solution and the formulation is pharmaceutically equivalent to the reference product formulation. However, bioavailability studies of liquid dosage forms may have to be demonstrated depending on the formulation proposed.
- When the drug substance has been categorised under the Biopharmaceutics Classification system as Class I (highly soluble, highly permeable). In this case, the waiver will be based on demonstration of acceptable dissolution testing in multiple media. For further guidance consult Guidance for Industry: "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System," August, 2000. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, posted at *www.fda.gov/cder/ guidance/3618fnl.htm*.

Dissolution Testing

A discriminating dissolution method should be developed for each active pharmaceutical ingredient in a drug product. The dissolution method should be incorporated into the stability and quality control programs.

- Dissolution testing must ensure that the presence of two or more drugs does not affect the dissolution performance testing.
- For scenarios 1 and 2, multipoint dissolution profiles for both the test and reference products should be compared. Only the new FDC product is evaluated for scenarios 3 and 4.

QUALITY ASSURANCE

This section of the document outlines quality controls for FDC products and should be considered in conjunction with existing national and international quality and GMP guidelines. The quality principles below are equally applicable in all four scenarios described in this document.

Active Pharmaceutical Ingredients

- To ensure consistent quality in FDC finished products, APIs should be controlled for impurities, particle size distribution, polymorphs, and partition coefficient.
- Manufacturers should use APIs from certified suppliers per regulatory authorities or pharmacopeias.
- APIs not subject to pharmacopoeial monographs should follow ICH quality guidelines, especially for stability, impurities and residual solvents.
- APIs with pharmacopoeial monographs may still need additional information because of different physiochemical properties, impurity profiles and use of organic solvents in their synthesis, as outlined in the ICH quality guidelines.

Finished Product

- When considering FDC products, attention should be given to pharmaceutical development and manufacture, with an outline of the process-development principles of the formulation, as these products are technically more demanding than single component products.
- As part of pharmaceutical development it should be demonstrated that the individual ingredients are compatible with each other as well as the excipients in the intended dosage form and primary packaging material.
- Drug content uniformity is considered essential for FDC finished products and should be addressed in the drug development process and the final process validation. This test should be designed to demonstrate the uniformity of dose consistent with the overall performance of the product.
- Analytical methods that can distinguish each active component in presences of other APIs in the FDC should be developed and validated.
- Methods should also be developed to detect actual and potential degradation products. These methods should be appropriately validated in accordance with national and international guidelines.
- To confirm consistency and uniformity in the FDC products, in-process controls are required to ensure that the formulations are mixed properly throughout the manufacturing process.
- Uniformity of the finished dosage form should be demonstrated by assaying for each active component in the final product.
- Dissolution testing specifications should include all active components of the finished dosage form and utilise relevant media. (See Bioequivalent FDC Products, Page 9.)

Stability

- Stability studies should be designed with the geographic climate of the target market in mind.
- National or international guidelines should be used as applicable.
- Repackaging effects on the stability of FDC products must be considered.
- Methods that measure and indicate product stability should also be developed.
- Instructions concerning storage conditions should be labelled and clearly visible to minimise the effects of temperature fluctuations during product transportation.

Packaging

It should be determined whether the FDCs are moisture and light sensitive, and if so, they should be packaged with adequate protection. Repackaging of FDCs is discouraged. However, if repackaging is necessary, it should be in line with GMP principles as well as subject to appropriate release and control testing.

Inspections to Assure Compliance with GMPs

All manufacturing processes should be clearly defined and in accordance with national and international guidelines.

GMPs ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and legal requirements.

GMPs centre on both production and quality control measures and are part of the overall quality assurance of the company.

GMP specifics for FDCs:

- Manufacturers of APIs should follow ICH Q7A guidelines.
- Ideally, drug regulatory authorities should inspect API manufacturing sites.
- Manufacture and environmental controls for FDC products that include new APIs should be monitored carefully due to the complex nature of these products.

REFERENCE DOCUMENTS

Nonclinical and Clinical

"Note for Guidance on Repeated Dose Toxicity," July, 2000. Committee for Proprietary Medicinal Products. *www.emea.eu.int/pdfs/human/swp/104299en.pdf*

"Note for Guidance on Fixed-Dose Combination Medicinal Products," April 1996, CPMP/EWP/240/95.

"Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products," July, 2000. CPMP/EWP/2655/99. *www.isap.org/1999/Uppsala/265599en.pdf*

"Note for Guidance on Duration of Chronic Toxicity Testing in Animals" November 1999. International Conference on Harmonization. *www.emea.eu.int/pdfs/human/ich/030095en.pdf*

ICH Guideline on "Dose-Response Information to Support Drug Registration," March 1994. International Conference on Harmonization. *www.ich.org/MediaServer.jser?@_ID=480&@_MODE=GLB*

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Guidance for Industry: “Conduct, and Analysis of Bioavailability and Bioequivalence Studies, Part A: Oral Dosage Formulations Used for Systemic Effects,” 1996. Health Canada, Health Products and Food Branch.

“Essential Drugs and Medicines Policy,” Annex 3: Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements for Interchangeability. World Health Organization. *www.who.int/medicines/organization/par/edl/expcom13/eml13_en.pdf*

GLOSSARY OF TERMS

Bioavailability: the rate and extent to which the active ingredients or active moieties are absorbed from the drug product and become available at the site of action (the treatment site) within the body. For drug products that are not intended to be absorbed into the bloodstream, bioavailability can be assessed by measurements intended to reflect the rate and extent to which the active components or active moieties become available at the site of action.

Bioequivalence (BE): the scientific, physiopharmacologic basis on which a test and a reference drug are compared or an FDC of active ingredients and the individual active ingredients administered simultaneously are compared. To be determined bioequivalent, the bioavailability of the two products must not differ significantly when the two products are given in the same dosages under similar conditions to the same person. Substitution of one product by a bioequivalent product should result in the same clinical safety and efficacy profile in the patient. It is important that those who substitute various products based on a finding of BE understand the definition of "not differ significantly," as that is the basis of the claim of BE for the product being substituted.

Bioequivalent FDC product: an FDC product that can be substituted in patient care for an innovator product. It has demonstrated BE 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 drug product in international documents is not recommended.

Efficacy: the desired effect of a drug 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 demonstrates that the drug will have the effect claimed in the intended population according to predetermined statistical and clinical criteria.

Fixed dose combination product: a single product created by the combination of two or more active components and in which each active component contributes to the benefit of the new product. FDCs are not simply two single, distinct products packaged together. Active ingredients can be pharmaceutical (i.e., chemical) and/or biologic in origin.

Innovator FDC product: the first licensed formulation of a new FDC product (generally as a patented drug) on the basis of original scientific documentation of safety, efficacy, and pharmaceutical quality.

Licensed FDC product: an FDC for human use which has underlying clinical, preclinical, and manufacturing data that has been examined and vetted independently by government-recognised, competent drug regulatory authorities and meets required scientific and legal standards for authorized marketing in those jurisdictions (also called "approved," "registered," or "authorized" products in some jurisdictions).

Quality: the ability of a product to consistently meet established physiochemical purity and potency standards based on adherence to adequate manufacturing process controls and recognised Good Manufacturing Practise. Manufacturing quality of the product is ensured by having in place robust systems to assure that products are manufactured according to established GMPs, including recognised validation practises that establish the product can be consistently manufactured from batch to batch.

Safety: a measure of the product's ability to cause the desired effect without harming the patient. As no drug is completely safe, a positive risk-benefit ratio needs to be established for the intended patient population based on nonclinical 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).

Stability: the drug product's resistance to changes in its physical, chemical, and microbiological properties over time in the market environment.

LIST OF ACRONYMS

ANOVA	analysis of variance procedure
API	active pharmaceutical ingredient
AUC	area under the curve
BE	bioequivalence
CDER	Center for Drug Evaluation and Research
CPMP	Committee for Proprietary Medicinal Products
DHHS	United States Department of Health and Human Services
EWP	Efficacy Working Party
FDC	fixed dose combination
GMP	Good Manufacturing Practise
ICH	International Conference on Harmonization
NIH	National Institutes of Health
PK	pharmacokinetic
WHO	World Health Organization