

African Medicines Regulatory Harmonisation (AMRH)

Evaluation of Medicinal Products Technical Committee (EMP-TC)

APPLICANT'S HANDBOOK

Guidelines on Fixed Dose Combination Medicinal Products



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Abbreviations and Acronyms

AIHW - Australian Institute of Health and Welfare

API - Active pharmaceutical ingredient

BCS - Biopharmaceutics Classification Scheme

BCS #1 - Biopharmaceutics class number 1 (the most favourable)

CHMP - Committee for Medicinal Products for Human Use; see also

CPMP - Committee for Medicinal Products for Human Use (CHMP), formerly the Committee for Proprietary Medicinal Products

CPP - Certificate of pharmaceutical product

EMA - European Medicines Agency, formerly the European Medicines Evaluation Agency

EU - European Union

FDA - Food and Drug Administration of the USA

FDC - Fixed-dose combination (see Glossary)

FDC-FPP - Fixed-dose combination finished pharmaceutical product

FPP - Finished Pharmaceutical Product

GCP - Good Clinical Practice

GLP - Good Laboratory Practice

GMP - Good Manufacturing Practice

GSP - Good Storage Practice

GTDP - Good Trade and Distribution Practice

ICH - International Conference on Harmonization

IUTLD - International Union of Tuberculosis and Lung Disease

MIC - Minimum Inhibitory Concentration

PP - Per-Protocol (a form of clinical trial design and analysis)

SPC - Summary of Product Characteristics (see Glossary)

TGA - Therapeutic Goods Administration

WHO - World Health Organization

1. Scope

- 1.1 The scope of these guidelines covers FDCs medicinal products eligible for listing through EMP-TC. FDCs are getting highly popular in the pharmaceutical markets of developing countries and have been particularly flourishing in the last few years. Unfortunately, scientific literature has provided evidence that many FDCs being introduced in certain countries are irrational.
- 1.2 The principles in these guidelines would also apply to chemical combinations and complexes that comprise more than one active.
- 1.3 The scientific principles applicable to FDC products can also be applied in the assessment of co-packaged medicines.

2. General considerations

- 2.1 These guidelines are intended to be used in conjunction with the EMP-TC guidelines on submission of documentation for listing of human medicinal products.
- 2.2 It is important that access to useful, new FDCs should not be delayed by unnecessary constraints. These guidelines are not intended to define the only means of demonstrating the advantages and disadvantages of a new FDC. In some cases, an alternative approach may be appropriate, for example when:
 - 2.2.1 Scientific developments allow alternative means of achieving the same goals.
 - 2.2.2 A circumstance unique to the product in question can be demonstrated.
 - 2.2.3 An original but acceptable approach is devised.
 - 2.2.4 Sufficient alternative studies have been conducted which, although not exactly what the guidelines seek, nevertheless satisfy the criteria of quality, safety and efficacy.

When these guidelines (or others referred to herein) describe evidence that is required, applicants may either: provide the requested evidence, or provide an alternative form of evidence that addresses the same issues. In this case, the application should include an explanation and justification of the approach taken.

- 2.3 It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality. Principles for determining whether data from the scientific literature are acceptable should be considered.

An application for Listing may comprise:

- 2.3.1 Entirely original data.
- 2.3.2 Entirely data from the literature.
- 2.3.3 Both original data and data from the literature (a “generic” submission).

For FDC-FPPs, it is likely that generic submissions will be the most common type.

The scientific literature rarely contains enough adequately validated information on quality to allow the full quality data set to be based solely on data from the literature. In particular, the complete formulation and method of manufacture are rarely specified. Consequently, the quality data set is almost always either totally original or generic.

- 2.4 When these guidelines request that an applicant explain and/or justify non-conformity with requirements, a suitable argument should be included in the section that discusses the advantages and disadvantages of the combination (see below), together with cross-references to data elsewhere in the submission.

- 2.5 When an applicant is unsure of listing requirements or wishes to deviate from these guidelines, prior consultation with the EMP TC may be advantageous. However, applicants should not request advice until they have read all relevant guidelines and WHO's Listing of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority (1999) or updates thereof. Not all of the guidelines in Tables 1–5 are necessarily relevant to a particular enquiry; the particulars of each case should be considered.
- 2.6 Risk–benefit assessments for FDCs should take into consideration any differences in anticipated patient populations. Consequently, decisions on the same data set may vary.

3. Definitions

The definitions given below apply solely to the terms as used in these guidelines. They may have different meanings in other contexts.

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form. When so used the API becomes the active moiety as defined below, often termed simply the active. The API may be a salt, hydrate or other form of the active moiety, or may be the active moiety itself. Active moieties are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Active moiety

The term used for the therapeutically active entity in the final formulation of therapeutic goods, irrespective of the form of the API. The active is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (the active) is propranolol.

Applicant

The person or company who submits an application for Listing of a new pharmaceutical product, an update to an existing Listing or a variation to an existing market authorization.

Certificate of pharmaceutical product

A WHO-type certificate of the form described in Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Geneva, World Health Organization, 1998.

Comparator

The finished pharmaceutical product with which an FDC-FPP is to be compared. The comparison may be by means of bioequivalence studies or clinical studies of safety and/or effectiveness. A single study may use more than one comparator, for example several single entity FPPs. A comparator may be a placebo.

Co-packaged product

A product consisting of two or more separate pharmaceutical products in their final dosage forms that are packaged together for distribution to patients in the co-packaging.

Drug

Any substance or product for human or veterinary use that is intended to modify or explore physiological states for the benefit of the recipient.

Finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more actives.

Fixed-dose combination (FDC)

A combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

Fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more actives.

Generic products

The term generic product has somewhat different meanings in different jurisdictions. Use of this term has therefore been avoided as far as possible, and the term multisource pharmaceutical product is used instead (see the definition below). Multisource products may be marketed either under the approved non-proprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different to those of the innovator products.

Where the term generic product is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

Microbiology

A branch of science that refers to microbes of all types, including bacteria, viruses, rickettsia, protozoa, fungi and prions. Derived words (such as microbiological) have a similar meaning.

Multisource (generic) pharmaceutical product

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

New chemical (or biological) entities

Actives that have not previously been authorised for marketing as a drug for use in humans in the country in question.

Pharmaceutical equivalents

Products are pharmaceutical equivalents if they contain the same amount of the same actives in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or manufacturing process and some other variables can lead to differences in product performance.

Pivotal clinical trials

Those clinical studies that provide the significant evidence that is the basis for the decision as to the risk–benefit assessment for a particular FDC.

Product information

The information provided by the supplier of an FPP that allows prescribers and consumers to ensure the safe and effective use of drugs. If it is written especially for prescribers, it may be termed prescribing information.

Reference product

A pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product that is the market leader may be used as a reference product, provided that it has been authorised for marketing and its efficacy, safety and quality have been established and documented.

Summary of product characteristics (SPC)

A term used in the European Union. Product information or data sheets in the European Union should be based on the approved SPC.

Well-established drugs

Actives that:-

- have been marketed for at least 5 years in countries that undertake active post marketing monitoring;
- have been widely used in a sufficiently large number of subjects to permit the assumption that safety and efficacy are well known; and
- Have the same route of administration and strength and the same or similar indications as in those countries.

4. Scenarios

An application to register List an FDC-FPP may fall into any one of the following four scenarios. These guidelines are intended to address the different requirements for each scenario.

4.1 Scenario 1

The new FDC-FPP contains the same actives in the same doses as an existing FDC-FPP; that is it is a “generic” of the existing FDC-FPP; they are “multisource” products. The quality, safety and efficacy of the existing product have been established.

4.2 Scenario 2

The new FDC-FPP contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same. Alternatively, the established regime may involve combinations of single entities and FDCs, for example, a single entity FPP combined with an FDC-FPP that contains two actives. In all cases, the established regime has a well-characterised safety and efficacy profile, and all of the FPPs used in obtaining clinical evidence have been shown to be of good quality.

4.3 Scenario 3

- The new FDC-FPP combines actives that are of established safety and efficacy but have not previously been used in combination for this indication.
- The new FDC-FPP comprises a combination for which safety and efficacy have been established, but that will be used in a different dosage regimen.

4.4 Scenario 4

The new FDC-FPP contains one or more new chemical entities.

5. Balancing the advantages and disadvantages of a new fixed-dose combination

5.1 In determining whether it is rational to combine actives into a single product, there are medical, quality and bioavailability considerations.

5.1.1 Quality issues may be addressed by much the same criteria that apply to single-component products and it is difficult to imagine a case in which essentially the same standards would not apply.

5.1.2 Medical considerations are more complex and sometimes contradictory, for example, when increased efficacy is accompanied by increased toxicity. The decision as to whether to give marketing approval for a new FDC-FPP in scenarios 3 and 4 is often based on a consideration of the balance of advantages and disadvantages from the medical perspective.

5.1.3 Interpretation of the results of bioavailability and bioequivalence tests involves both quality and medical considerations. For example, it is not acceptable that bioavailability 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.

Balancing the advantages and disadvantages of a new FDC-FPP should form a major component of submissions pursuant to this guideline.

5.2 Submissions for marketing approval of a new FDC in scenarios 2, 3 and 4 should include a section in which the advantages of the new combination are weighed against the disadvantages. All the possible advantages and disadvantages of the combination should be listed and discussed. The discussion should be based on the available data and on scientific and medical principles. In less well-developed nations, and particularly where there are difficulties with transport and the logistics of distribution, other matters may need to be taken into account, such as:

- 5.2.1 The cost of the combination as compared with the cost of individual components.
- 5.2.2 Evidence as to whether the new FDC will improve the reliability of supply as a result of simplified distribution procedures. Improved patient adherence may result from more reliable (continuing) availability of the FDC-FPP than of all of the components as loose combinations of single entity products.

However, issues of cost and procurement alone are not sufficient reasons to approve an FDC if it has not been justified by appropriate data and on scientific and medical principles.

- 5.3 From a scientific or medical perspective, FDCs are more likely to be useful when several of the following factors apply:

- 5.3.1 There is a medical rationale for combining the actives.
- 5.3.2 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.
- 5.3.3 The combination has a greater efficacy than any of the component actives given alone at the same dose.
- 5.3.4 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.
- 5.3.5 For antimicrobials, the combination results in a reduced incidence of resistance.
- 5.3.6 One drug acts as a booster for another (for example in the case of some antiviral drugs).
- 5.3.7 The component actives have compatible pharmacokinetics and/or pharmacodynamics. See comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2 revise sections).
- 5.3.8 Therapy is simplified, particularly when the existing therapy is complex or onerous (e.g., because of a "high tablet load").
- 5.3.9 One of the ingredients is intended to minimise abuse of the other ingredient (e.g., the combination of diphenoxylate with atropine, or buprenorphine with naloxone).
- 5.3.10 The active pharmaceutical ingredients are chemically and physicochemically compatible or special formulation techniques have been used that adequately address any incompatibility.
- 5.3.11 Other potential advantages of FDCs over single entity products given concurrently in the same dose may include:
 - 5.3.11.1 Convenience for prescribers and patients.
 - 5.3.11.2 Better patient adherence.
 - 5.3.11.3 Simplified logistics of procurement and distribution.
 - 5.3.11.4 Lower cost.

These factors are important, but there may not necessarily be evidence to support them; they may be more significant when there is specific evidence available to support a particular case.

- 5.4 From a scientific or medical perspective, FDCs are less likely to be useful when one or more of the following factors apply:
- 5.4.1 The component actives are normally separately titrated to meet the patient's needs. Consequently:
- 5.4.1.1 Either the doses of the components, and/or the ratio of doses, typically differ from patient to patient, and/or
- 5.4.1.2 Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment).
- These two factors are particularly significant when one or more of the actives has a narrow therapeutic index and/or a steep dose– response curve in the therapeutic range.
- 5.4.2 There is a higher incidence or greater severity of adverse reactions to the combination than with any of the ingredients given alone, or there are adverse reactions not seen in response to treatment with any of the individual ingredients.
- 5.4.3 There are unfavourable pharmacokinetic interactions between the ingredients, for example when one drug alters the metabolism, absorption or excretion of another. However, see comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2) concerning circumstances in which such interaction is intended.
- 5.4.4 Dose adjustment is necessary in special populations, such as in people with renal or hepatic impairment.
- 5.4.5 The product (tablets or capsules), is so large that patients find it difficult to swallow.

6. Data requirements for Listing of fixed-dose combination finished pharmaceutical products

6.1 General

6.1.1 The framework for issuing a Listing for an FDC-FPP is the same as that for single entity FPPs and is stipulated in the EMP-TC guidelines on submission of documentation for listing of human pharmaceutical products.

6.1.2 Data requirements for Listing of FDC-FPPs depend broadly on the scenario into which the application falls (see sections 4.1–4.4 above). Table 1 summarises these differences.

However, each application should be considered on its own merits using scientific judgement and logical argument.

6.1.3 All applications to register an FDC-FPP should include a draft “product information” or “summary of product characteristics” for indicated diseases, and any package information leaflet or patient information. See the more detailed discussion below (section 7).

Summary of requirements for the various scenarios

This table is a list of the most likely set of requirements for Listing of an FDC-FPP in each scenario. However, each application should be considered on its own merits in relation to data requirements, using scientific judgement and logical argument. Some of the data may be provided in the form of literature studies.

Table 1: Requirements for Listing of an FDC-FPP in each scenario

| Requirement | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|---|---|---|------------|------------|
| Rationale for the combination | Not usually | Not usually | √ | √ |
| Balancing advantages and disadvantages of the combination | Not usually | Not usually | √ | √ |
| Marketing status in other countries | √ | √ | √ | √ |
| Analysis of literature data in the submission | Possibly for pharmaceutical development | Possibly for pharmaceutical development | √ | √ |
| Pharmaceutical development studies | √ | √ | √ | √ |
| GMP certification of sites of manufacture | √ | √ | √ | √ |
| A full quality data set | √ | √ | √ | √ |
| Bioavailability data | Not usually | Not usually | Sometimes | √ |
| Bioequivalence data | √ | √ | Sometimes | Sometimes |
| Preclinical pharmacology and safety | Not usually | Not usually | Sometimes | √ |
| Clinical safety and efficacy | Not usually | Not usually | √ | √ |
| Product information | √ | √ | √ | √ |
| Plan for passive post- marketing surveillance | √ | √ | √ | √ |
| Plan for active post- marketing surveillance | Not usually | Not usually | √ | √ |

- 6.1.4 A full quality data set is required in all scenarios (see 6.3 below).
- 6.1.5 In general, preclinical or clinical safety and efficacy data are not required in scenario 1. If the risk–benefit assessment has been found to be acceptable for an FDC, then new brands may be approved on the basis of bioequivalence with the brand(s) used in pivotal clinical trials.

The applicant may, however, be asked to establish that a risk–benefit assessment has been conducted and found acceptable if the EMP-TC is not convinced with the submitted data or does not have access to the data.

- 6.1.6 If the FDC directly substitutes for an established regimen of single entity products, in relation to both actives and doses and for the same indication(s), a bioequivalence study may provide adequate evidence of safety and efficacy. This is scenario 2. The established regimen should have well-characterised safety and efficacy.

6.2 **Good manufacturing practice**

Evidence of GMP compliance for all the API and FPP sites should be provided in Module 1 of the PD.

6.3 **Quality**

- 6.3.1 In relation to quality, very similar principles apply to FDC-FPPs as apply to single entity products. However, there are additional complexities arising from the need to consider two or more actives instead of one. These complexities are principally, but not exclusively, related to assay, stability, physicochemical properties (for example dissolution rate) and bioavailability/ bioequivalence. Consequently, the following considerations (and others) may be pertinent.

- 6.3.2 Pharmaceutical development studies are especially important for FDC-FPPs because they are technically more demanding than single-component products. Issues that are specific to the development of FDC-FPPs include:

- 6.3.2.1 Chemical and physicochemical compatibility of the APIs in an FDC with one another as well as with possible excipients.

- 6.3.2.2 The degradability of each API under stress conditions in the presence of the others.

- 6.3.2.3 Uniformity of content of each active prior to compression (tablets) or filling (for instance capsules, sachets and suspension dosage forms). This study determines whether mixing during manufacture is adequate.

- 6.3.2.4 Analytical procedures. These should be validated for each active in the presence of the others during development of analytical methods for quality control of the finished product, stability testing and dissolution testing.

Validation should be conducted for each active in the presence of the others and in the presence of related synthesis (process) impurities and potential degradation products. In the case of high-performance liquid chromatography (HPLC) (a common analytical technique), possible interference by degradation products in the assay of the active can usually be controlled by peak purity testing.

- 6.3.2.5 The dissolution rate of each active in pilot formulations. Multipoint limits should normally be established for routine quality control of each active. For some FDC-FPPs, different dissolution media may be acceptable for the different actives.

- 6.3.2.6 Different assay procedures may be necessary for the different actives in the finished product, and for different purposes (e.g. dissolution testing may be needed rather than stability testing).

- 6.3.3 For solid dosage forms a test and limit for content uniformity should be applied to any active that is present at a weight of ≤ 25 mg or when the API comprises 25% or less of a dosage unit.

Typically, when any one API is present at less than 25 mg or less than 25% of the weight of a dosage unit, all of the actives are subjected to content uniformity testing.

If a solid dosage form is not subject to content uniformity testing, for example because all of the actives are present at a weight of greater than 25 mg and greater than 25% of the weight of a dosage unit, there should be a test and limit for mass variation.

- 6.3.4 Acceptance criteria for impurities in FDC-FPPs should be expressed with reference to the parent API (and not with reference to the total content of APIs). If an impurity results from a reaction between two APIs, its acceptance limits should be expressed in terms of the API that represents the worst case. If available, a reference standard should be used to quantify the degradation product in percentage mass/mass with respect to the parent API. Alternatively, and if justified, other quantitative techniques that are described in Impurities in new drug products (revised) ICH-Q3B(R) (2003), may be applied.

Note: there should be an approximate mass balance. Together with the remaining active, degradants expressed with reference to the parent compound should sum to approximately 100% of initial strength.

- 6.3.5 The specifications and defining characteristics of the product should be based on the most vulnerable active. For example, expiry dates should be based on the stability of the least stable active.
- 6.3.6 In setting specifications, relevant pharmacopoeial monographs, WHO guidelines, ICH guidelines and EMP-TC guidelines should be taken into account.
- 6.3.7 Specifications in addition to those in pharmacopoeias may be necessary for APIs in some cases, for example for particle size, residual solvents and synthesis-related impurities that are not covered by relevant monographs.

6.4 **Bioavailability and bioequivalence**

Data on bioequivalence provide a bridge between two pharmaceutical equivalents (see Glossary) when safety and efficacy data are available for one of the FPPs, but not for the other. By demonstrating that the two products lead to the same profile for plasma concentration over time, available safety and efficacy data for one of the products can be extrapolated to the other. The two products being compared may be different brands, or different batches of the same brand, for example when manufactured by different methods, at different sites or according to different formulations.

- 6.4.2 Data on bioequivalence may also be important when the same FPP is administered under different circumstances, for example before or after food, in different patient populations (such as children versus adults), or by different routes of administration (such as subcutaneous versus intramuscular injection).
- 6.4.3 In the context of these guidelines, an additional application of bioequivalence studies is in scenario 2 in which safety and efficacy data on single entity products given concurrently may be extrapolated to an FDC-FPP, provided that all of the conditions described elsewhere in these guidelines are met.
- 6.4.4 Evidence as to bioequivalence is required for scenarios 1 and 2, and sometimes for scenarios 3 and 4, for example when there are major differences between the formulation and/or method of manufacture of the product to be registered and that used in pivotal clinical trials.

- 6.4.5 If a study of bioequivalence finds that the two treatments are bioequivalent, it may be assumed that any pharmacokinetic interactions between the actives were the same, even if one treatment comprised an FDC-FPP and the other comprised separate products.
- 6.4.6 Data on absolute bioavailability are usually required in scenario 4, i.e., comparison of the area under the curve for plasma concentration over time after an intravenous injection with that after administration of the dosage form to be marketed, for example a tablet given orally.
- 6.4.7 A decision as to whether it is necessary to conduct a study of the effect of food on the bioavailability of an FDC-FPP should be based on what is known of the effect of food on the individual actives, and any relevant recommendations in the product information for the single entity products.

The effect of food should normally be studied in scenario 4.

- 6.4.8 Recommendations as to the conduct and analysis of bioequivalence studies are provided in the EMP TC guidelines on submission of documentation for listing of human medicinal products.

6.5 Preclinical pharmacology and safety

- 6.5.1 Preclinical data are not normally required in scenarios 1 and 2. Data may, however, be required in some circumstances, for example if an unusual excipient is included in the formulation or if the impurity profile differs significantly from that of reference products.
- 6.5.2 Preclinical data will be required in scenario 4 as for any new chemical entity. The standard of evidence should be the same as for any new chemical entity.
- 6.5.3 In scenario 3, preclinical studies may not be required if all the actives have been extensively used in humans in the same combination for a long period and the safety of the combination has been well demonstrated. Bridging studies may be appropriate in some cases, for example for a new ratio of doses.
- 6.5.4 If the safety of the combination in humans has not already been demonstrated (i.e., in scenarios 3 and 4), preclinical studies should be conducted on the actives administered in combination in order to investigate possible additive or synergistic toxicological effects.

The preclinical data that are required in scenarios 3 and 4 will vary according to the data that are already available. For example, by definition in scenario 3, the safety and efficacy of each active will have already been established, but that of the combination will not. In scenario 4, the safety and efficacy of one or more of the actives may already have been established, but not those of all the actives or of the combination.

- 6.5.5 When preclinical data are required, the studies should aim to determine both the pharmacological and the adverse effects that may be expected from the combination of actives during clinical use.
- 6.5.6 6.5.6 As a general rule, preclinical studies on the combination should be performed with the actives in the same ratio as in the FDC-FPP in question. If this is not the case, the applicant should explain and justify the proportions used. A comparison of the systemic exposures in animals and humans will be relevant.
- 6.5.7 6.5.7 In the absence of relevant EMP-TC guidelines, WHO, EMA or the ICH preclinical guidelines may be used as a source of guidance.
- 6.5.8 6.5.8 Preclinical studies should comply with a suitable code of good laboratory practice (GLP); see, for example Handbook: Good laboratory practice: Quality practices for regulated non-clinical research and development. World Health Organization (2001)

6.5.9 Microbiological preclinical studies

In general, this section is applicable to scenarios 3 and 4, but not to scenarios 1 and 2. There may be some exceptions, for example microbiological data may be appropriate in scenarios 1 and 2 if a different pathogen or resistance pattern is encountered.

- 6.5.9.1 In scenarios 3 and 4, when a new combination is proposed for an antimicrobial indication, microbiological studies may be needed to determine the advantage of the FDC over the individual active moieties against relevant pathogen(s), and especially when clinical trials of monotherapy are inappropriate or unethical.
- 6.5.9.2 Data from microbiological preclinical studies of FDCs are particularly useful when clinical trials of monotherapy are inappropriate or unethical.
- 6.5.9.3 Data from the following types of studies should normally be available for the combination:
 - 6.5.9.3.1 Characterization of microbiological activity in vitro and in vivo against laboratory strains and clinical isolates of the targeted pathogen(s), including those strains in the relevant geographical regions.
 - 6.5.9.3.2 Characterization of microbiological activity in appropriate animal models of infection with the targeted pathogen(s).
 - 6.5.9.3.3 If possible, characterization of the mechanism by which the actives exhibit additive or synergistic microbiological activity against the targeted pathogen(s).
 - 6.5.9.3.4 The potential for antagonistic effects between the actives.
 - 6.5.9.3.5 The potential for development of resistance by target pathogens.

6.6 Clinical efficacy and safety

This section is in general applicable to scenarios 3 and 4 but not to scenarios 1 and 2. Bridging studies may sometimes be appropriate in scenario 3, for example for a new ratio of doses or a longer duration of treatment.

- 6.6.1 General principles
 - 6.6.1.1 The risk–benefit assessment for a new combination may be based on data generated using either the components given as single entity products concurrently or the FDC as a single FPP.
 - 6.6.1.2 Any theoretical advantages of a particular combination should be confirmed by means of efficacy studies. The risk–benefit assessment should not be based on theoretical considerations only, or on extrapolation from other data.
 - 6.6.1.3 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 symptoms in isolation should not be indications for the FDC.
 - 6.6.1.4 Clinical studies should be designed to determine whether the combination has an advantage over the component actives given alone in a substantial patient population. The data should demonstrate that each active contributes to the therapeutic effect of the combination.

It may not be essential to show that all of the components have efficacy when administered as single entities; for example, clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

- 6.6.1.5 In situations where comparative clinical trials are not feasible, for example when monotherapy is inappropriate or is unethical, an aggregate of clinical and preclinical data may be substituted. Such data may include:
- 6.6.1.5.1 Historical clinical data, preferably at an exposure comparable to that for the proposed FDC.
 - 6.6.1.5.2 Bridging pharmacokinetic data.
 - 6.6.1.5.3 Preclinical pharmacology and/or toxicology data.
 - 6.6.1.5.4 In vitro data (e.g., microbiological studies).
- 6.6.1.6 If the FDC is available in more than one strength or ratio of doses, there should be a risk–benefit assessment for each combination.
- 6.6.1.7 The choice of comparators for the purposes of safety and efficacy studies should be justified. They should normally represent the recognized treatment for the indication in question. As far as possible, comparators should be licensed products with well-established safety and efficacy profiles and of established quality. Unapproved or novel combinations should be avoided as comparators as they may introduce new efficacy or toxicity characteristics and thus complicate assessment of the combination under test.
- 6.6.1.8 If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer.
- 6.6.1.9 If one or more of the component actives has an established use and dosage regimen in indications unrelated to the indications of the FDC, existing experience as to its safety may nevertheless be taken into account, bearing in mind the relative doses for the two sets of indications.
- 6.6.1.10 End-points in clinical trials should be such as to characterise the advantages and disadvantages of the combination.
For example, for a combination designed to reduce the development of drug resistance, end-points might include the frequency of new drug resistance as well as the overall clinical outcome.
- 6.6.1.11 Parallel group comparisons are one means of demonstrating a therapeutic effect. A parallel placebo group should be included if feasible and if consistent with the indications under treatment. Multi factorial designs are another means by which it may be possible to demonstrate that a combination is superior to the individual actives.
- 6.6.1.12 In some cases, studies have to be specifically designed to confirm the minimal effective dose and the usual effective dose of the combination. Multiple dose–effect studies may be necessary.
- 6.6.1.13 The design and analysis of studies of efficacy and safety should consider (among other things) whether the combination is indicated as first- or second-line therapy.
- 6.6.1.14 In general, all of the actives in a combination should have a similar duration of action. If this is not the case, the applicant should explain and justify the combination.
- 6.6.1.15 In general, the actives in a combination should have similar pharmacokinetics. If this is not the case, the applicant should explain and justify the combination.
If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages of the combination outweigh the disadvantages. These should be included in the section of the submission entitled “Balancing the advantages and disadvantages of a new FDC”.

- 6.6.1.17 Data generated in clinical safety and efficacy studies should comply with the AVAREF current guidelines and WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995 revised to fit the current/plus updating statement).

6.6.2 Pharmacokinetics and pharmacodynamics

This section is generally applicable to scenarios 3 and 4, but not to scenarios 1 and 2. In scenarios 1 and 2, the information described below will usually already be available.

- 6.6.2.1 In general, it is desirable that there be no pharmacokinetic or pharmacodynamic interactions between the components of a combination. However, there are circumstances in which such an interaction is intentional and may even contribute to the therapeutic outcome.

For example: -

- 6.6.2.1.1 Ritonavir boosts the activity of protease inhibitors.
- 6.6.2.1.2 Carbidopa and benserazide both reduce decarboxylation of levodopa in the gut wall, and consequently reduce the dose of levodopa that should be administered.
- 6.6.2.1.3 Clavulanic acid reduces bacterial hydrolysis of beta lactam antibiotics and consequently both increases the concentration and prolongs the duration of effectiveness.
- 6.6.2.2 Tests should be conducted to elucidate any pharmacokinetic or pharmacodynamic interaction between the actives in a combination. Some interactions may be predictable from pharmacokinetic and enzyme profiles, but should be confirmed by experiment. Any interaction should be quantified so that its effect on safety and efficacy is either predictable or (preferably) has been tested in a clinical study. This includes competing metabolic effects and effects on gastrointestinal efflux mechanisms or on renal excretion or re-absorption. Interactions may be additive, synergistic or antagonistic.
- 6.6.2.3 If there is an unintended pharmacokinetic interaction between the actives, it should be demonstrated that the therapeutic advantages of the combination outweigh any disadvantages resulting from the interaction. Relevant argument and cross-references to data should be included in the section that discusses the balance between the advantages and disadvantages of the combination.

6.6.3 Additional guidelines for scenario 3

- 6.6.3.1 The risk–benefit assessment for a new combination may be based (at least in part) on a demonstration of the clinical non-inferiority of the combination to another product licensed for the same indication. See Appendix 4, entitled Superiority, equivalence and non-inferiority clinical trials, for more information.
- 6.6.3.2 Pharmacodynamic studies for new combinations should normally be conducted at several dose ratios of the actives unless the applicant can provide justification for not doing so.

6.6.4 Additional guidelines for scenario 4

- 6.6.4.1 When an FDC-FPP contains an active that is a new chemical entity, data requirements are the same as for any new chemical entity. In some circumstances, some of the preclinical and clinical data on safety and/or efficacy may have been generated from studies on the combination rather than on single entities, for example when one active confers a protective effect in relation to adverse reactions or when the actives act synergistically.

6.6.4.2 Dose-finding monotherapy studies should normally be conducted for the new chemical entity before commencing studies of combination therapy, unless the new chemical entity is not intended to have activity when used alone (such as clavulanic acid). Alternative approaches may be acceptable if they can be justified.

6.6.4.3 The pharmacokinetics and enzyme profile of any new chemical entity should be fully characterised, including prediction of possible interactions and pharmacokinetics in children if the new chemical entity could be used in that population (see also section 7.6.6.6 on Paediatric dosage forms, revise section).

6.6.5 Superiority, equivalence and non-inferiority trials and fixed-dose combinations

For superiority, equivalence and non-inferiority trials; general points concerning different type of studies can be referenced from AVAREF guidelines.

More information can be found in the Committee for Medicinal Products for Human Use (CHMP) guidelines.

6.6.5.1 In the context of FDCs, equivalence trials are largely confined to bioequivalence studies.

6.6.5.2 An FDC-FPP should be shown, directly or indirectly, to be superior to the component actives given as single entity treatments.

Only a superiority trial can give the necessary statistical confidence. Submissions should discuss both the statistical significance and clinical relevance of the results. Any alternative form of evidence that purports to address the same issues, for example one that concerns a dose–response surface, must be explained and justified with appropriate statistical confidence.

6.6.5.3 In clinical trials that are intended to test for superiority and/or non-inferiority, the choice of comparator should be carefully considered and will depend in part on the medical and ethical circumstances. The comparator may be:

6.6.5.3.1 The treatment whose risk–benefit profile is best supported by evidence or is at least well established.

6.6.5.3.2 One or more of the actives in the FDC given as a single treatment.

6.6.5.3.3 A placebo.

6.6.5.4 Depending on the claim, superiority or non-inferiority should be demonstrated for each specified clinical outcome. For example, if the claim is less bone marrow depression, but similar efficacy, a non-inferiority outcome should be demonstrated for efficacy and a superiority outcome for safety.

6.6.6 Paediatric dosage forms

6.6.6.1 6.6.6.1 Different FDC-FPPs may be needed in paediatric populations from those needed in adults because of differences in pharmacokinetic and pharmacodynamic profiles of the actives, and for reasons of palatability. The doses of each active may need to be lower or higher, and the appropriate dose ratio may be different.

Scenarios 1 and 2

6.6.6.2 In scenarios 1 and 2, when the combination of actives and doses has already been shown to be safe and effective in the paediatric population, a bioequivalence study in adults may be extrapolated to the paediatric population provided that the pharmacokinetics of all actives are well-established in both populations and it is known that there are no differences that could affect the outcome of the bioequivalence study. Extrapolation of bioequivalence data between age groups should be justified in these terms.

Scenarios 3 and 4

- 6.6.6.3 If the FDC is indicated in a paediatric population, but the combination of actives and doses has not been shown to be safe and effective in this population, suitable doses of the actives given in combination should be established. In some cases, it may be necessary to do this in more than one age group (see table 2 below).

Table 2: Paediatric populations

| Paediatric populations | |
|------------------------|----------------------------|
| Neonate | Birth to under 1 month |
| Infants | 1 month to under 2 years |
| Children | 2 years to under 12 years |
| Adolescents | 12 years to under 16 years |

From the age of 16 years, individuals are considered to be adults in the context of these guidelines.

- 6.6.6.4 The pharmacokinetic profile of each active should be established in the age groups for which the FDC is indicated.
- 6.6.6.5 If it is possible to define target plasma concentrations in both adults and the paediatric population for an FDC that has established safety and efficacy in adults, then it may be possible to define suitable doses in the paediatric population on the basis of pharmacokinetics. The task is easier for actives that have the same target concentrations in adults and the paediatric population, such as antimicrobials that have established minimum inhibitory concentrations (MICs) and established safety at these concentrations.
- 6.6.6.6 When defining target plasma concentrations in the paediatric population, possible differences in the concentration–effect relationship should be taken into account.
- 6.6.6.7 If safe and effective use of the FDC has not been established in any age group, and extrapolation between groups is not possible based on pharmacokinetic data, then new clinical, and possibly also preclinical, safety and efficacy data should be obtained.

7. Product information (or summary of product characteristics) for fixed-dose combination finished pharmaceutical products

- 7.1 This section of the guideline applies to all scenarios.
- 7.2 The product information should be an integrated evaluation of the FDC, and not a summation of the product information for each of the actives.
- 7.3 The rationale for use of the product should be presented in terms of the combination rather than in terms of the individual actives.
- 7.4 Only those indications for which each active in the FDC makes a useful contribution should be included in the product information.
Each indication should be a well-recognized disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity.
- 7.5 For each indication there should be a statement as to whether the FDC is recommended for first- or second-line therapy.
- 7.6 Any pharmacokinetic and pharmacodynamic interactions between the actives should be described in qualitative and, as far as possible, in quantitative terms.
- 7.7 All clinically relevant interactions between the FDC and other drugs should be described, together with the resulting contraindications and precautions. Any deviations from expected interactions known for the single components should be highlighted.

- 7.8 When safety experience with the FDC is limited in comparison with that for the individual components, safety experience from clinical trials and post marketing experience should be presented for both the FDC and the individual components, and should be identified as such.
- 7.9 If the safety profile for the combination is different to that for the individual actives, this should be highlighted. For example a combination of a fibrate and a statin might carry a risk of more frequent or more severe rhabdomyolysis than for either individual active.

8. Post marketing studies and variations

- 8.1 Post market monitoring of safety is an important part of the role of both drug regulatory authorities and manufacturers. It is especially important when there are unresolved concerns regarding safety, and when a new product is intended for wide community use, as for example a new antimicrobial FDC-FPP for use in the treatment of tuberculosis, malaria or HIV/AIDS. See WHO's importance of pharmacovigilance: safety monitoring of medicinal products (2002 revise if current available). Manufacturers should have (and use) written operating procedures for continuous assessment of the safety and utilisation of their products following Listing; SOPs can be examined during a GMP inspection.

For antimicrobials, monitoring of patterns of resistance is an important component of pharmacovigilance. Note also that pharmacovigilance outcomes can differ with diet, ethnicity, comorbidity and other factors.

- 8.2 For scenarios 1 and 2, passive surveillance (spontaneous reporting) would usually be acceptable. For scenarios 3 and 4, additional active (prospective) surveillance should be considered, especially when there is an outstanding safety concern. For more information, see the ICH guideline Pharmacovigilance planning or later updates thereof.

To ensure that the EMP-TC is aware of the proposed changes to product information, it is recommended that positive opinion letters contain this statement:

"The product information may not be altered without prior approval, except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to the EMP TC within five days of making the change."

- 8.3 Variations to pharmaceutical aspects of listed FDC-FPPs are subject to the EMP-TC guidelines on variations .

To ensure that the EMP-TC is aware of the proposed variations, it is recommended that positive opinion letters contain this statement:

"No changes may be made to the product without prior approval, except for changes of the type listed in the EMP TC's policy on 'Changes to pharmaceutical aspects which may be made without prior approval' (confirm this statement in line with EMP-TC policy). Conditions in that policy apply."

9. Guidelines for co-packaged fixed-dose combinations

A co-packaged product consists of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

1. Co-packaged products may fall into any of scenarios 1 to 4. The data requirements for each scenario are the same as those listed above.

2. A full quality data set is required for all components of co-packaged pharmaceutical products, except for any component that already has Listing in which case more limited requirements apply (see below).

3. If one or more of the pharmaceutical products is already listed, then the additional quality information to support co-packaging of those pharmaceutical products will typically be limited to data on stability of the products in the co-packaging.

However, the manufacturer of each component pharmaceutical product should provide an assurance that the product as used in co-packaging will be identical in formulation and method of manufacture to the one that is already listed. This is especially important when the manufacturer of a component is not the manufacturer of the co-packaged product.

4. Submissions concerning co-packaged pharmaceutical products should take into account the Guidelines on packaging for pharmaceutical products. WHO Technical Report Series, No. 902, Annex 9.