

## Annex 5

# Guidelines for registration of fixed-dose combination medicinal products

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## Abbreviations

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; <i>see also</i> CPMP
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 ( <i>see</i> Glossary)
FDC-FPP	fixed-dose combination finished pharmaceutical product ( <i>see</i> Glossary)
FPP	finished pharmaceutical product
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
GTDP	good trade and distribution practice
GSP	good storage practice
ICH	International Conference on Harmonisation
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 ( <i>see</i> Glossary)
TGA	Therapeutic Goods Administration
WHO	World Health Organization

## Introduction

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malaria and tuberculosis, which are considered to be the foremost infectious disease threats in the world today.

FDCs have advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio of doses has been shown to be safe and effective, and when

all of the actives contribute to the overall therapeutic effect. In addition there can be real clinical benefits in the form of increased efficacy and/or a reduced incidence of adverse effects, but such claims should be supported by evidence.

Additionally, in a situation of limited resources, the cost of an FDC finished pharmaceutical product (FDC-FPP) may be less than that of separate products given concurrently, and there are simpler logistics of distribution. Improved patient adherence and reduced development of resistance in the case of antimicrobials can be difficult to prove, but may be additional benefits.

Notwithstanding these potential benefits, FDCs must be shown to be safe and effective for the claimed indications. It should not be assumed that benefits outweigh risks. As for any new medicine, the risks and benefits should be defined and compared.

The World Health Organization has published a series of guidelines relating to marketing authorization of finished pharmaceutical products (FPPs) (see Table 1). Currently there are no specific international guidelines for FDCs. Some national authorities have developed their own guidelines, some for specific classes of medicines (see Table 2). These guidelines are intended to provide advice to those countries that do not, as yet, have guidelines for this type of product. They will also provide guidance to industry when developing new products and when considering the regulatory requirements that will need to be met.

In drafting these guidelines, existing international publications have been taken into account and in some cases text has been copied directly. The various scenarios considered below are essentially the same as those in the draft *Scientific and technical principles for fixed dose combination drug products* that followed a meeting of interested parties held in Botswana in April 2004.

## 1. Scope

- 1.1 The scope of these guidelines is restricted to medicines that in most jurisdictions would be available only on prescription.

Although similar principles would apply to the registration of non-prescription products, the risk–benefit considerations (and consequently data requirements) may be different.

- 1.2 The principles in these guidelines would also apply to chemical combinations and complexes that comprise more than one active.

- 1.3 Registration of co-packaged medicines is not the primary purpose of these guidelines. However, many of the same considerations apply in balancing the advantages and disadvantages of co-packaged medicines, although the quality issues are different (see Appendix 1).

## 2. **General considerations**

- 2.1 These are not intended to be stand-alone guidelines.
  - 2.1.1 Many general guidelines are also applicable to FDCs. Table 1 lists some relevant WHO publications.
  - 2.1.2 Other international guidelines that pertain to FDCs in particular are summarized in Table 2, together with brief notes as to their content. Some of these relate to particular therapeutic groups such as antihypertensives, or particular topics such as bioavailability.
  - 2.1.3 Table 3 lists other guidelines that were consulted in preparing this text.
  - 2.1.4 A number of International Conference on Harmonisation (ICH) guidelines are referred to in this text when, as at the date of writing, there was no applicable WHO guideline (see Tables 4 and 5).
  - 2.1.5 When a guideline is cited in the text or tables below, the most recent edition should normally be substituted.
  - 2.1.6 If an applicant makes reference to guidelines not cited here, this may be acceptable depending on the case in point and provided that the applicant justifies the alternative reference.
  - 2.1.7 Appendices 2, 3 and 4 provide guidance on subjects that are not exclusive to FDCs, but are nevertheless important in this context, and for which suitable guidance is not otherwise readily available.
  - 2.1.8 The guidelines in Tables 1–5 may not be a comprehensive list of all relevant guidelines.
- 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:

Table 1

**WHO guidelines relevant to marketing authorization**

Title	Date
<i>Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority.</i> A general text with relevant annexes (see below). Also known as “the Blue book”. <sup>a</sup>	1999
<i>National drug regulatory legislation: guiding principles for small drug regulatory authorities.</i> Blue book, Annex 1.	1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report</i> (WHO Technical Report Series, No. 863), Annex 10: Guidelines for Implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce and Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Blue book, Annex 2.	1996 1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report</i> (WHO Technical Report Series, No. 863), Annex 9: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability and Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Blue book, Annex 3. <sup>a</sup>	1996 1999
<i>Model guidelines on conflict of interest and model proforma for a signed statement on conflict of interest.</i> Blue book, Annex 4.	1999
<i>Model contract between a regulatory authority and an external evaluator of chemistry, pharmaceutical and bioavailability data.</i> Blue book, Annex 5.	1999
<i>Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant.</i> Blue book, Annex 6.	1999
<i>Detailed advice on evaluation of data by the drug regulatory authority.</i> Blue book, Annex 7.	1999
<i>Ethical criteria for medicinal drug promotion.</i> Blue book, Annex 8.	1999
<i>Model marketing authorization letter.</i> Blue Book, Annex 9.	1999
<i>Model list of variations (changes) to pharmaceutical aspects of registered products which may be made without prior approval.</i> Blue book, Annex 10.	1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.</i> (WHO Technical Report Series, No. 863), Annex 5: Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms and	1996

Table 1 (continued)

Title	Date
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908) and Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. Blue book, Annex 11. <sup>a</sup>	2003  1999 (and 2001 rev)
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908), Annex 4: Good manufacturing practices for pharmaceutical products and inspection: main principles and <i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report</i> (WHO Technical Report Series, No. 929, Annex 2) and Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 2, updated edition.	2003     2005   2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report</i> (WHO Technical Report Series, No. 917), Annex 2: Good trade and distribution practices for pharmaceutical starting materials.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report</i> (WHO Technical Report Series, No. 917), Annex 3: WHO pharmaceutical starting materials certification scheme (SMACS): Guidelines on implementation.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908), Annex 9: Guide to good storage practices for pharmaceuticals	2003
<i>The importance of pharmacovigilance: safety monitoring of medicinal products<sup>a</sup></i>	2002
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report</i> (WHO Technical Report Series, No. 902), Annex 11: Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (under revision).	2002
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report</i> (WHO Technical Report Series, No. 902), Annex 3: Good practices for national pharmaceutical control laboratories.	2002
<i>Handbook: good laboratory practice: quality practices for regulated non-clinical research and development</i> (WHO document TDR/PRD/GLP/O1.2,WHO-TDR) in collaboration with the United Nations and World Bank.	2001
<i>Establishing the bioequivalence of rifampicin in fixed-dose formulations containing isoniazid with or without pyrazinamide and/or ethambutol compared to the single drug reference preparations administered in loose combination: model protocol.</i>	1999

Table 1 (continued)

Title	Date
Quality assurance: protocol for assessing the rifampicin bioavailability of combined formulations in healthy volunteers: WHO/IUTLD joint statement. <i>International Journal of Tuberculosis and Lung Disease</i> , <b>3</b> , S284–S285.	1999
Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: <i>The use of essential drugs</i> . WHO Technical Report Series, No. 850.	1995

<sup>a</sup> These publications are being further updated.

Table 2

**International guidelines that relate directly to fixed-dose combination finished pharmaceutical products**

Title, publisher and date	Notes
<i>Fixed dose combination and co-packaged drug products for treatment of HIV</i> . Washington, DC, Food and Drug Administration, May 2004, DRAFT	21 pages
<i>Scientific and technical principles for fixed dose combination drug products</i> . Botswana, 22 April 2004, DRAFT	21 pages
<i>Part 7. Report on bioavailability of oral dosage formulations of drugs used for systemic effects. Report C. Report on bioavailability of oral dosage formulations, not in modified release form, of drugs used for systemic effects, having complicated or variable pharmacokinetics</i> . Canada, Health Protection Branch, December 1992.	Approximately 400 words. Discusses the reporting, statistical analysis and decision criteria for bioequivalence studies on combination drug products. A notice to industry in June 2004 confirmed the decision criteria.
<i>Fixed-combination prescription drugs for humans FDA, 2003</i> 21CFR300.50	Approximately 250 words. In terms of safety and efficacy, describes the circumstances in which actives may be combined in an FDC.
<i>Estrogen estrogen/progestin drug products to treat vasomotor symptoms and vulvar vaginal atrophy symptoms recommendations for clinical evaluation</i> . FDA, Jan 2003 DRAFT	Ten pages. This guideline is <i>not</i> restricted to estrogens from a biological source. Approval will be based on two criteria: <ul style="list-style-type: none"> <li>• that each component contributes to safety and efficacy as defined in 21CFR300.50 and</li> <li>• the FDC contains the lowest effective dose of each of the actives for their respective labelled indication.</li> </ul>
Conjugated estrogens, USP-LC-MS method for both qualitative chemical characterization	Seven pages. This guideline relates only to conjugated estrogens from a

Table 2 (continued)

Title, publisher and date	Notes
and documentation of qualitative pharmaceutical equivalence. FDA June 2000 DRAFT	biological source, normally urine from gestating mares, which contains multiple estrogens. There have been difficulties in preparing generic equivalents of this type of product. The guideline specifies how chemical equivalence can be demonstrated.
<i>Fixed-combination medicinal products.</i> CPMP Apr 1996 — CPMP/EWP/240/95, III/5773/94 (formerly known as <i>Testing and licensing criteria for fixed combination medicinal products</i> )	Four pages that: <ul style="list-style-type: none"> <li>• require justification of the particular combination;</li> <li>• give examples of circumstances (safety and efficacy) in which FDCs may be acceptable;</li> <li>• describe principles that define acceptable indications;</li> <li>• require consideration of possible pharmacokinetic and pharmacodynamic interactions;</li> <li>• require evidence as to safety and efficacy (allowing bibliographical data as supportive evidence in certain circumstances); and</li> <li>• require evidence as to safety and efficacy of the doses selected.</li> </ul> <p>“This guideline is also applicable to a new chemical substance which dissociates in vivo into two well known active substances.”</p> <p>“Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.”</p>
<i>Part 7. Fixed combinations in Note for guidance on clinical investigation of medicinal products in the treatment of hypertension.</i> CPMP Nov 1997 — CPMP/EWP/238/96 Rev1	Three pages that: <ul style="list-style-type: none"> <li>• describe the circumstances (in terms of safety and efficacy) in which FDCs may be acceptable in the therapy of hypertension; and</li> <li>• provide advice on their clinical development as first- or second-line therapy.</li> </ul>
IV.3. The ratio and/or fixed content of one component of a combination drug product. In: <i>Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products.</i> CPMP Jul 2000 — CPMP/EWP/2655/99	Seven pages. This guideline discusses the relationship between plasma concentration/time profiles and clinical efficacy. Selection of a suitable ratio of doses for FDCs is discussed in Part IV.3 (approx. 100 words).



Table 2 (continued)

Title, publisher and date	Notes
5.1.5 Fixed combination products. In <i>Note for guidance on the investigation of bioavailability bioequivalence</i> CPMP July 2001 — CPMP/EWP/QWP/1401/98	Approximately 50 words. States that FDCs should in general be assessed as to the bioavailability and bioequivalence of the individual actives administered either as single entity products given concurrently (in the case of a new combination) or as an existing combination. Studies should be designed to detect any pharmacokinetic drug–drug interaction.
<i>Part 6. Fixed combination products in ICH principles document for clinical evaluation of new antihypertensive drugs.</i> ICH/CPMP/541/00, DRAFT Also issued by CPMP as CPMP/ICH/541/00, DRAFT	Approximately 250 words. Describes two experimental designs for safety and efficacy studies on FDCs of antihypertensives, namely: <ul style="list-style-type: none"> <li>• factorial studies; and</li> <li>• studies in patients who have failed to respond adequately to each of the drugs given alone.</li> </ul>
5.2.1 Fixed-combination products in <i>Australian Guidelines for the Registration of Drugs</i> , Volume 1. Australia, TGA, July 1994.	Approximately 250 words. Discusses justification of the combination in terms of either pharmacodynamics or demonstrated therapeutic effect.

- 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 (see Appendix 2 entitled *Principles for determining whether data from the scientific literature are acceptable*).

Table 3

**Other guidelines consulted in preparing these guidelines**

Title	Publisher	Date
<i>Consort E-checklist</i> . Available at: <a href="http://www.consort-statement.org">www.consort-statement.org</a>		2004
<i>The Cochrane Collaboration</i> . Available at: <a href="http://www.cochrane.org/index0.htm">http://www.cochrane.org/index0.htm</a>		2004
<i>Literature-based submissions: points to consider</i> . Available at: <a href="http://www.tga.gov.au/docs/html/litbsubs.htm">http://www.tga.gov.au/docs/html/litbsubs.htm</a>	TGA, Australia	2003
<i>Bioanalytical method validation</i> . Available at: <a href="http://www.fda.gov/cder/guidance/index.htm">http://www.fda.gov/cder/guidance/index.htm</a>	FDA	2001
<i>Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system</i> . Washington, DC, US Food and Drug Administration. Available at: <a href="http://www.fda.gov/cder/guidance/index.htm">http://www.fda.gov/cder/guidance/index.htm</a>	FDA	2000
<i>Specifications: test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances</i> . Available at: <a href="http://www.ich.org/UrlGrpServer.jsr?@_ID=276&amp;@_TEMPLATE=254">http://www.ich.org/UrlGrpServer.jsr?@_ID=276&amp;@_TEMPLATE=254</a>	ICH	1999
<i>Points to consider on switching between superiority and non-inferiority</i> . CPMP/EWP/482/99	CPMP	1999
<i>Points to consider on the choice of non-inferiority margins</i> . EMEA, CPMP/EWP/2158/99, DRAFT	CPMP	1999
<i>Statistical principles for clinical trials</i> . EMEA, CPMP/ICH/363/99, DRAFT	CPMP	1998
<i>Development pharmaceuticals and process validation</i> , Eudralex 3AQ1a, <a href="http://pharmacos.eudra.org/">http://pharmacos.eudra.org/</a>	CPMP	1988
<i>Impurities in new drug products (revised)</i> . Q3B(R)	ICH	2003

An application for a marketing authorization 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 “hybrid” submission).

For FDC-FPPs, it is likely that hybrid 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

Table 4

**Preclinical guidelines from the International Conference on Harmonisation that may be a source of guidance**Available at: [www.ich.org](http://www.ich.org) (last accessed 03/09/04)**Carcinogenicity studies**

- S1A* Guideline on the need for carcinogenicity studies of pharmaceuticals
- S1B* Testing for carcinogenicity of pharmaceuticals
- S1C* Dose selection for carcinogenicity studies of pharmaceuticals
- S1C(R)* Addendum to S1C: addition of a limit dose and related notes

**Genotoxicity studies**

- S2A* Guidance on specific aspects of regulatory tests for pharmaceuticals
- S2B* A standard battery for genotoxicity testing for pharmaceuticals

**Toxicokinetics and pharmacokinetics**

- S3A* Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies
- S3B* Pharmacokinetics: guidance for repeated dose tissue distribution studies

**Toxicity testing**

- S4* **Single dose toxicity tests**  
Agreement was reached, at the time of ICH 1, in 1991, that the determination of the median lethal dose (LD<sub>50</sub>) should be abandoned for pharmaceuticals. The recommendation was published in the *Proceedings of the First International Conference on Harmonisation*, p. 184.
- S4A* Duration of chronic toxicity testing in animals (rodent and non-rodent)

**Reproductive toxicology**

- S5A* Detection of toxicity to reproduction for medicinal products
- S5B(M)* An addendum on toxicity to male fertility (amended guideline)

**Pharmacology studies**

- S7A* Safety pharmacology studies for human pharmaceuticals
- S7B* Safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals

**Joint safety/efficacy (multidisciplinary) topic**

- M3(M)* Maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals

specified. Consequently the quality data set is almost always either totally original or hybrid.

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 registration requirements or wishes to deviate from these guidelines, prior consultation with the relevant regulatory authority may be advantageous. How-

Table 5

**Clinical guidelines from the International Conference on Harmonisation that may be a source of guidance**Available at: [www.ich.org](http://www.ich.org) (last accessed: 03/09/04)**Clinical safety**

- E1* The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions
- E2A* Clinical safety data management: definitions and standards for expedited reporting
- E2B/M2* Maintenance of the clinical safety data management including the maintenance of the electronic transmission of individual case safety reports message specification
- E2C* Clinical safety data management: periodic safety update reports for marketed drugs
- E2CA* Addendum to E2C: periodic safety update reports for marketed drugs
- E2D* Post-approval safety data management: definitions and standards for expedited reporting
- E2E* Pharmacovigilance planning

**Clinical study reports**

- E3* Structure and content of clinical study reports

**Dose–response studies**

- E4* Dose–response information to support drug registration

**Ethnic factors**

- E5* Ethnic factors in the acceptability of foreign clinical data

**Good clinical practice**

- E6* Good clinical practice: consolidated guideline

**Clinical trials**

- E7* Studies in support of special populations: geriatrics
- E8* General considerations for clinical trials
- E9* Statistical principles for clinical trials
- E10* Choice of control group and related issues in clinical trials
- E11* Clinical investigation of medicinal products in the paediatric population

**Guidelines for clinical evaluation by therapeutic category**

- E12A* Principles for clinical evaluation of new antihypertensive drugs (consensus draft principle)

**Clinical evaluation**

- E14* The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

ever, applicants should not request advice until they have read all relevant guidelines and WHO's *Marketing authorization 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 between different national drug regulatory authorities.

### 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 marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization 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 form 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 nonproprietary 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 of 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 authorized 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 authorized 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 postmarket 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 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-characterized 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 reason 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).

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 minimize 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 (but the evidence for this is largely anecdotal) (*I*, and Haynes, RB, personal communication, 2003).

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 marketing authorization of fixed-dose combination finished pharmaceutical products**

### 6.1 **General**

6.1.1 The framework for issuing a marketing authorization for an FDC-FPP is the same as that for single entity FPPs and is summarized in WHO's *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (1999) — the “Blue book”, or updates thereof. Information on the pharmaceutical development of a new product is planned for inclusion in the next edition of the Blue book and is summarized in Appendix 3.

6.1.2 Data requirements for marketing authorization of FDC-FPPs depend broadly on the scenario into which the application falls (see sections 4.1–4.4 above). Table 6 summarizes these differences. However, each application should be considered on its own merits using scientific judgement and logical argument.

6.1.3 Data requirements for marketing authorization do not differ when the combination is in the *WHO Model list of essential medicines*, i.e. data requirements are the same whether or not the combination or its components are in the *Model list of essential medicines*.

6.1.4 Submissions should include a statement of the marketing status of the FDC-FPP in other countries.

6.1.5 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).

6.1.6 A full quality data set is required in all scenarios (see 6.3 below).

6.1.7 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

Table 6

**Summary of requirements for the various scenarios**

This table is a list of the most likely set of requirements for marketing authorization 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, subject to the guidance given in the main text and Appendix 2.

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 <sup>a</sup>	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	√	√
Assurances <sup>b</sup>	√	√	√	√

√ This is a requirement.

<sup>a</sup> Normally absolute bioavailability for a new chemical entity, or comparative bioavailability for a new dosage form.

<sup>b</sup> The applicant should provide assurances that:

- “The Product Information will not be altered without prior approval from [name of regulatory authority], except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to [name of regulatory authority] within five days of making the change”; and
- “No changes will be made to the product without prior approval, except for changes of the type listed in [name of regulatory authority]’s policy on ‘Changes to pharmaceutical aspects which may be made without prior approval’ and subject to the conditions in that policy.”

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, for example the drug regulatory authority to which the application is submitted is not convinced that this is the case or does not have access to the data.

- 6.1.8 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-characterized safety and efficacy, and all of the FPPs should have been shown to be of good quality, including compliance with a suitable code of good manufacturing practice (GMP) during manufacture. Again the applicant may have to establish that this is the case.

## 6.2 Good manufacturing practice

- 6.2.1 Application of a suitable and relevant code of GMP is a critical element in assuring the current and continuing quality of medicines. Certification of GMP should be provided for all sites of manufacture of finished products, and preferably also for the sites of manufacture of active pharmaceutical ingredients (APIs). A suitable code of GMP would be the WHO Good manufacturing practices (GMP): main principles for pharmaceutical products, and for Inspection, both in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*, Volume 2, updated edition. Geneva, World Health Organization, 2004, and subsequent additions and revisions (e.g. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 2).

Assurance as to certification of GMP may conveniently be obtained using the WHO Certification Scheme — Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, and WHO pharmaceutical starting materials Certification Scheme (SMACS) (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 3).

6.2.2 Sites of storage and distribution, including company storage facilities, should also be subject to ongoing audits of GMP. Relevant guidelines include: Guide to good storage practices for pharmaceuticals (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 9); and Good trade and distribution practices for pharmaceutical starting materials (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 2).

### 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 Appendix 3, entitled *Development (or preformulation) studies*, makes some general points about this type of study. 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  $\leq 25$  mg or when the API comprises 25% or less of a dosage unit. Some authorities permit an exception for soft gelatin capsules that contain a solution of the API. 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 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 and ICH guidelines should be taken into account. For example in the absence of a relevant WHO guideline, the ICH guideline *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances* (1999) is a suitable source of guidance.
- 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**

- 6.4.1 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.
- 6.4.3 There are two common circumstances in which data on bioequivalence are likely to be generated for *pharmaceutical equivalents*:

- 6.4.3.1 Pivotal clinical trials were generated on one formulation and another is to be marketed by the same company (for example because the second formulation is more stable or more marketable than the first); or
- 6.4.3.2 A relevant patent has expired and a multisource pharmaceutical equivalent has been developed.
- 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.<sup>1</sup>
- 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 WHO guidelines, *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates). Other guidelines may be relevant depending on the jurisdiction in which the application is submitted.
- 6.4.9 In demonstrating bioequivalence it may not always be necessary to provide in vivo data. The nature of suitable evidence as

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<sup>1</sup> See the WHO guidelines on *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates) for options to be employed when an intravenous solution cannot be prepared or is unsafe.

to bioequivalence differs according to the type of application and the remainder of the data set.<sup>1</sup>

6.4.10 During analysis of the results of a bioavailability or bioequivalence study for an FDC-FPP, the parameters to be reported and assessed are those that would normally be required of each active if it were present as a single entity and the same statistical confidence intervals and decision criteria should be applied.

6.4.11 An additional scientific consideration that has been elaborated in recent years is the option for biowaivers based on the Biopharmaceutics Classification Scheme (BCS). This is an area in which further developments are expected. The main relevant publication to date is *Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system*. US Food and Drug Administration (2000). At present, and in the absence of clear guidance for FDCs, it is recommended that biowaivers based on the BCS classification as the sole criterion for a decision be handled cautiously because there is at present no guidance as to how to consider the possibility of a chemical or pharmacokinetic interaction between actives that may affect bioequivalence. However there are circumstances in which the BCS classification may nevertheless be relevant to FDCs. In such a case the BCS classification of all the actives in the FDC should be taken into account. For example:

6.4.11.1 For a new multisource product, if all the actives are in the most favourable biopharmaceutics classification of high solubility and high gastrointestinal permeability (i.e. BCS #1), and the criterion of dissolution of not less than 85% in 30 minutes is met for each active in the requisite media, a biowaiver may be considered.

6.4.11.2 For approval of new strengths when all actives are in BCS #1.

In addition, the BCS classification and in vitro dissolution rates may be factors in marginal cases, for example when considering whether a new study is required in support of a change in site or method of manufacture, or another change that might be considered minor.

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<sup>1</sup> See the WHO guidelines on *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates) for options to be employed when an intravenous solution cannot be prepared or is unsafe.

Even if one or more of the actives is not in BCS #1, if an in vitro/in vivo correlation has been established, then in vitro comparison of dissolution performance in various media may be an option.

- 6.4.12 Validation of assays of actives in biological media is crucial in order to generate a meaningful bioavailability and bioequivalence study. See, for example, the guidelines *Bioanalytical method validation*. US Food and Drug Administration (2001).
- 6.4.13 Selection of a suitable comparator for the purpose of bioequivalence is described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*. World Health Organization (2002). Some additional comments follow.
  - 6.4.13.1 The comparator should be of known quality, safety and efficacy.
  - 6.4.13.2 For applications in scenario 1, the decision as to the comparator depends on whether there is more than one existing brand of the combination whose safety and efficacy is known to be acceptable. If only one brand is known to have acceptable safety and efficacy, this should be used as comparator. In other circumstances, the decision is more difficult and should be justified by cogent argument and data. The WHO *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (2002) may be of assistance.
  - 6.4.13.3 For applications in scenario 2, single entity products will have been used in the majority of pivotal clinical trials. The same brands of those single entity FPPs should be the comparator and should be given concurrently as was the case in the pivotal clinical trials.
  - 6.4.13.4 For applications in scenarios 3 and 4 (with which evidence as to safety and efficacy will be submitted), the new product should be shown to be bioequivalent to the product(s) that was (were) used in pivotal clinical trials.
    - 6.4.13.4.1 If an FDC-FPP was used in the majority of pivotal clinical trials, then that brand should be the comparator.

- 6.4.13.4.2 If single entity products were used in the majority of pivotal clinical trials, then they should be the comparator, but should be given as (1) the same brands and (2) concurrently, as in the pivotal clinical trials.
- 6.4.13.4.3 If approximately equal numbers of pivotal clinical trials used an FDC and single entity products, then in principle either may be used as comparator. However judgement should be applied in deciding which to use, for example if one group of studies was more rigorous than another, or if the conclusions were more definitive in relation to one group.
- 6.4.13.5 If in any of the scenarios, the selection of comparator cannot be made according to the suggestions above (for example because the brand in question is no longer available), the decision is more difficult and should be justified by cogent argument and supporting data. It may be necessary to conduct bridging clinical studies. See the WHO *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (2002).

## 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 As a general rule, preclinical studies on the combination should be performed with the actives in same the 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 In the absence of relevant WHO guidelines, the ICH preclinical guidelines in Table 4 may be used as source of guidance.
- 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 study 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 characterize 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. Multifactorial 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.
- 6.6.1.16 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 WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products* (1995).

## 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 reabsorption. 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 characterized, 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 on *Paediatric dosage forms*).

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

Appendix 4 defines superiority, equivalence and non-inferiority trials and makes some general points concerning different types of study. More information can be found in the Committee for Medicinal Products for Human Use (CHMP) guidelines in Table 3.

- 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 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 the table below).

#### Paediatric populations

Neonate	Birth to under 1 month
Infant	1 month to under 2 years
Children	2 years to under 12 years
Adolescent	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**

The product information is 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. The summary of product characteristics (SPC) is a term used in the European Union (EU). Product information or data sheets in the EU should be based on the approved SPC.

This section of the guideline applies to all scenarios.

- 7.1 The product information should contain all of the information listed in the Appendix to WHO's Ethical criteria for medicinal drug promotion (see Table 1) in addition to the information mentioned below.
- 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 postmarketing 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. Postmarketing studies and variations

- 8.1 Postmarket 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 *The importance of pharmacovigilance: safety monitoring of medicinal products* (2002). Manufacturers should have (and use) written operating procedures for continuous assessment of the safety and utilization of their products following marketing authorization; 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, co-morbidity 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 draft ICH guideline *Pharmacovigilance planning* (Table 5), or later updates thereof.
- 8.3 Once the product information has been approved, any proposed changes should be validated according to principles similar to those for the initial application.

To ensure that drug regulatory authorities are aware of proposed changes to product information, it is recommended that marketing approval 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 [name of regulatory authority] within five days of making the change."

From Annex 9 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999).

- 8.4 Variations to pharmaceutical aspects of registered FDC-FPPs are subject to similar considerations to those described in Section IV and Annex 10 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999). As outlined in that text, some changes may be made without prior approval (“self-assessable” changes), and some require prior consideration by the drug regulatory authority.

To ensure that drug regulatory authorities are aware of proposed variations, it is recommended that marketing approval letters contain this statement:

“No changes may be made to the product without prior approval, except for changes of the type listed in [name of regulatory authority]’s policy on ‘Changes to pharmaceutical aspects which may be made without prior approval’. Conditions in that policy apply.”

From Annex 9 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999).

## Reference

1. Haynes RB, McDonald HP, Garg AX. *Interventions for helping patients to follow prescriptions for medications*. Cochrane Library: Update software Issue #2, 2002.



## Appendix 1

### **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 in Table 6 of this Annex.
2. A full quality data set is required for all components of co-packaged pharmaceutical products, except for any component that already has marketing authorization in which case more limited requirements apply (see below).
3. If one or more of the pharmaceutical products already has marketing authorization, 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 already has marketing authorization. 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. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.

## Appendix 2

### **Principles for determining whether data from the scientific literature are acceptable**

Literature-based data concerning FDCs may be acceptable, subject to the principles below.

1. Bibliographical data should not replace the source data (i.e. original study reports) if they are available.
2. The overall strength of literature-based evidence will depend on its quality, quantity and consistency of outcomes.
3. Unless otherwise justified by the applicant, literature-based data concern actives that have an extensive marketing history.
4. All documents that are directly relevant to the application should be provided.
5. Literature-based submissions should include:
  - 5.1 Details of the search strategy, including a list of the databases searched and the service provider.
  - 5.2 The date on which the search was performed.
  - 5.3 The rationale for the search strategy, including an explanation of and reasons for the inclusion and exclusion criteria.
  - 5.4 An unedited search strategy and the outcome thereof.
  - 5.5 An analysis of the data collected, including both favourable and unfavourable results; this is a critical component of a submission that includes data from the scientific literature.
6. The applicant's analysis of literature-based data should:
  - 6.1 Include an appraisal of:
    - 6.1.1 The quality of the data.
    - 6.1.2 Relevance to the application being made (including a comparison of formulations and methods of manufacture of products used in clinical studies reported in the literature with those proposed for marketing).
    - 6.1.3 Consistency and compatibility of the data from the literature with any original data submitted.
    - 6.1.4 The impact of the literature-based data on the risk-benefit assessment for the FDC.
    - 6.1.5 Any contradictions between favourable and unfavourable results.
  - 6.2 Include cross-references to appended copies of publications and to any original data submitted.
  - 6.3 Include separate sections for clinical, preclinical and quality data.

- 6.4 Include an appraisal of the sources of information, in particular whether the data come from an independently refereed source or from other sources.
7. If a literature search and/or the analysis of data from the literature is more than 6 months old, the submission should justify using this search and analysis and should indicate why more recent publications and data have not been used. Alternatively a supplementary review of the more recent literature may be appended to the report that brings it to within 6 months of the date of submission.
  8. Copies of all documents referred to in the submission or in the data analysis should be appended to the submission. If a document is not written in a language that is acceptable in the jurisdiction, a certified translation should also be attached (in addition to the original).
  9. Review articles are acceptable in principle, but should be judged on their quality.
  10. "Consensus" publications are acceptable in principle, but should be judged on their quality and on whether the original data and documentation are attached.
  11. Searches of company or in-house databases (including post-marketing surveillance reports) are acceptable, provided that they are identified as such. If possible, these searches should be stratified according to patient groups such as age and ethnicity.
  12. The relative strength of clinical publications is generally in this order:
    - 12.1 Controlled clinical trials.
    - 12.2 Cohort/case-control studies.
    - 12.3 Uncontrolled studies.
    - 12.4 Case descriptions.
    - 12.5 Expert opinion.
  13. Clinical studies published according to accepted protocol guidelines (for example Consort, Cochrane and others) generally carry more weight than studies that fail to report all pertinent data (e.g. safety data). Although a good reporting format facilitates evaluation, it is not in itself a criterion for the quality of the data set.
  14. Papers from peer-reviewed journals carry more weight in the regulatory decision than papers from non-peer-reviewed publications.
  15. Clinical studies carry more weight if they meet current standards of design and control, including compliance with a code of good clinical practice.

16. Reports of preclinical studies carry more weight in the regulatory decision if they:
  - 16.1. Include individual animal reports.
  - 16.2. Are reported according to internationally accepted guidelines.
  - 16.3. Are in compliance with the principles of good laboratory practice (GLP). See, for example WHO's *Handbook: Good laboratory practice* (2001).

## Appendix 3

### **Pharmaceutical development (or preformulation) studies**

Pharmaceutical development studies identify, document and control those attributes of the ingredients of the formulation and critical parameters of the manufacturing process that influence final product quality. If a manufacturer fails to conduct such studies or to obtain the information from the literature, and consequently develops a poor formulation, there is a temptation to continue with that formulation and method of manufacture rather than lose time and possibly competitiveness. Consequently it is in the interests of product quality that a drug regulatory authority seek the results of preformulation studies with applications to register new products.

Consequently a section on pharmaceutical development is an integral part of an application for marketing authorization. A thorough literature search may provide some of the information and commonly this part of a submission will be a hybrid of new data and reports from the literature.

Systematic studies should be conducted on APIs, on pilot formulations of the finished product and on manufacturing processes. For each API, there should be studies of:

- physicochemical properties;
- chemical and physicochemical stability, including stability under stress conditions (see below);
- impurity profile and batch-to-batch variation thereof;
- chemical and physicochemical compatibility of the API with possible excipients under stress conditions;
- the manufacturing process, and definition and control of its critical parameters;
- dissolution rate of the API in pilot formulations; and
- stability of pilot formulations under accelerated stability testing conditions and under the maximum recommended conditions of storage.

With this information there is a greater likelihood that the finished product will:

- meet specifications, including for assay, impurities and dissolution rate;
- be of consistent quality within and between batches;
- have optimum chemical and physicochemical stability;

- be manufacturable for the minimum cost that is consistent with acceptable quality; and
- be found acceptable in stability and bioequivalence studies.

### A typical set of studies of the degradation paths of an active pharmaceutical ingredient

Degradation paths for APIs are typically reactions of hydrolysis, oxidation, photolysis and/or acid–base chemistry. To force these reactions, the API is placed in solution under stress conditions such as those shown in Table A.1 below. For well-established drugs, some of this information may already be available in the literature.

The objective is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10–30% loss of active by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor.

If no degradation products are detectable after 10 days under the conditions in Table A.1, the API is considered stable. If degradation is detectable, but its extent is significantly less than 10%, then the stress factors, stress conditions or duration may need to be increased to identify and monitor degradation products.

Table A.1  
**Typical stress conditions in preformulation stability studies**

Stress factor	Conditions	Concentration of API <sup>a</sup>	Time
Heat	60°C	1:1 with diluent <sup>b</sup>	1–10 days
Humidity	75% relative humidity or greater	Solid state	1–10 days
Acid	0.1N hydrochloric acid	2:1 in 0.1N hydrochloric acid	1–10 days
Base	0.1N sodium hydroxide	2:1 in 0.1N sodium hydroxide	1–10 days
Oxidation	3% hydrogen peroxide	1:1 in 3% hydrogen peroxide	1–3 hours
Photolysis	Metal halide, mercury, xenon or ultraviolet-B fluorescent lamp	1:1 with diluent <sup>b</sup>	1–10 days
Metal ions (optional)	0.05 M Fe <sub>2+</sub> or Cu <sub>2+</sub>	1:1 with solution of metal ions	1–10 days

<sup>a</sup> When testing degradability of APIs in combination, the APIs should be in the same ratio as in the FDC-FPP.

<sup>b</sup> In each case, the diluent is either an excipient or all excipients in the formulation in the same ratios as in the formulation. Other ratios of diluent may also be appropriate, for example the approximate ratio in which the drug and excipients will be used in a formulation.

Solid-state degradation can also be considered. For APIs, exposing a solid sample to elevated temperatures such as 60–120 °C, or 5–10 °C below the melting point, can generate a different degradation profile. This approach usually generates degradation products that can be used as a worst case to assess the performance of the analytical method.

## Appendix 4

# Superiority, equivalence and non-inferiority clinical trials

### Definitions

#### ***Equivalence trial***

A trial that has the primary objective of testing whether the difference in quantitative response to two or more treatments is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

#### ***Non-inferiority trial***

A trial that has the primary objective of testing whether the response to the investigational product is clinically inferior to that of a comparator product. The comparator may be an active or a placebo control. The aim is to test whether the new product is inferior to the comparator by more than a specified small margin (the non-inferiority margin).

#### ***Superiority trial***

A trial that has the primary objective of testing whether the response to the investigational product is superior to that to a comparator. The comparator agent may be an active or a placebo control.

### Points to note

1. Protocols should clearly state whether the demonstration of non-inferiority, equivalence or superiority is the objective of the study.
2. If superiority is demonstrated in a non-inferiority trial, the results can generally be considered to show superiority, but the analysis should be based mainly on the intention-to-treat analysis.
3. If superiority cannot be demonstrated in a superiority trial, non-inferiority can generally not be claimed unless the lower margin of the confidence interval for the treatment difference is above a level that had been defined in the planning of the study. If non-inferiority is an acceptable outcome, it is, therefore, prudent to specify a non-inferiority margin in the protocol before the study is conducted. A non-inferiority margin may not be specified after the trial has commenced.



4. In a non-inferiority trial, the intention-to-treat analysis and the per-protocol analysis have equal importance for interpretation of the results.
5. In therapeutic areas where there is a problem of lack of assay sensitivity (e.g. allergy or depression), a non-inferiority trial that does not also include a placebo arm is not possible.
6. If the comparator has only modest efficacy, it may not be possible to define a non-inferiority margin. Therefore, if a placebo arm is not permissible, the only other alternative for demonstrating efficacy is a superiority trial.

## Further reading

See these CHMP guidelines.

*Points to consider on switching between superiority and non-inferiority.* CPMP/EWP/482/99.

*DRAFT Points to consider on the choice of non-inferiority margins.* EMEA, CPMP/EWP/2158/99.

*DRAFT Statistical principles for clinical trials.* EMEA, CPMP/ICH/363/99.