

SECRETARIAT ADDENDUM TO DISCUSSION PAPER ON FIXED DOSE COMBINATIONS

The WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series 929, 2005) has addressed issues relevant for the registration of fixed-dose combination medicinal products.

Annex 5 to the Technical Report summarizes the considerations from the regulatory point of view. It notes (page 111) that from a scientific and medical perspective, FDCs are more likely to be useful when several of the following factors apply:

1. There is a medical rationale for combining the actives.
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.
3. The combination has a greater efficacy than any of the component actives given alone at the same dose.
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. For antimicrobials, the combination results in a reduced incidence of resistance.
6. One drug acts as a booster for another (for example in the case of some antiviral drugs).
7. The component actives have compatible pharmacokinetics and/or pharmacodynamics.
8. Therapy is simplified, particularly when the existing therapy is complex or onerous (e.g. because of a "high tablet load").
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).
10. The active pharmaceutical ingredients are chemically and physicochemically compatible, or special formulation techniques have been used that adequately address any incompatibility.
11. Other potential advantages of FDCs over single entity products given concurrently in the same dose may include:
 - a. Convenience for prescribers and patients
 - b. Better patient adherence
 - c. Simplified logistics of procurement and distribution
 - d. 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.

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

1. The component actives are normally separately titrated to meet the patients' needs. Consequently:
 - a. Either of the doses of the components, and/or the ratio of doses, typically differ from patient to patient, and/or
 - b. Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment).

From the perspective of the Expert Committee on Selection and Use of Essential Medicines, the issues most likely to be important in making decisions about FDCs are:

There is an identifiable patient group for which this combination of actives and doses is suitable therapy.

There are potential advantages of FDCs over single entity products given concurrently in the same dose because of convenience for prescribers and patients, better patient adherence, simplified logistics of procurement and distribution, and lower cost.

Annex 5 also summarizes the requirements for marketing authorization of FDCs as finished pharmaceutical products (FDC-FPP). The requirements are summarized according to 4 possible scenarios (page 109).

Scenario 1: The new FDC-FPP contains the same actives in the same doses as the existing FDC-FPP; that 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.

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

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.

Scenario 4: The new FDC-FPP contains one or more new chemical entities.

Most of the FDCs to be considered by the Expert Committee will be covered in Scenario 2, i.e. the FDC contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same.

The requirements to support applications for marketing authorization for each scenario are summarized in the following table:

Summary of requirements for the various scenarios

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

Source: Annex 5, Table 6, page 114

The important points to note are that clinical safety and efficacy data are generally not required for products satisfying the conditions of Scenario 2. Point 6.1.8 of the Annex notes that:

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.

In summary, the key criteria that need to be considered by the Expert Committee in relation to FDCs would appear to be:

1. There is an identifiable patient group for which this combination of actives and doses is suitable therapy. In the context of determining which FDCs might be "essential medicines", the more patient groups that can be treated with the combination, the closer it comes to meeting the usual criterion for listing, i.e. meeting a public health need.
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.
3. There are potential advantages of FDCs over single entity products given concurrently in the same dose because of convenience for prescribers and patients, better patient adherence, simplified logistics of procurement and distribution, and lower cost.

A key decision point for the Committee is whether or not a decision to list a FDC requires the existence of a prequalified product or whether on balance the Committee wishes to identify FDCs that are clinically desirable, to list them and use this mechanism to encourage reputable manufacturers to produce quality products to recognized specifications.

Reference

World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report Series 929, 2005. Geneva, Switzerland.