Proposal on listing FDCs for infectious diseases

The Subcommittee is invited to comment on these criteria with respect to children:

The 'Procedure to update and disseminate the WHO Model List of Essential Medicines', Criteria for Selection was modified in 2005 to include the following statement regarding fixed-dose combination products (FDCs):

> "Most essential medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, adherence or in delaying the development of drug resistance in malaria, tuberculosis and HIV/AIDS."

Given that the agenda for this meeting required consideration of several applications for new FDCs across three infectious diseases clinical areas, the Secretariat sought clarification of the principles on which drug selection should be based before consideration of any individual application.

From a regulatory viewpoint, fixed-dose combinations would also need to demonstrate bioequivalence of the single combined dose unit with the components administered in the same doses separately but concomitantly. These requirements for efficacy of the combination beyond that of the individual drugs and for bioequivalence are relevant to all clinical areas, including infectious diseases.

The Committee noted the 2005 Expert Committee report *(1)* that described a number of different scenarios for possible registration of fixed-dose combination products. It seemed likely that most products to be considered by the Committee would be described according to 'Scenario 2' in the specifications i.e.

> "the new FDC contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same or the established regimen may involve combinations of single entities and FDCs, for example a single entity finished pharmaceutical product (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 the FPPs used in obtaining clinical evidence have been shown to be of good quality."

Accepting this, the Committee noted that it would imply that for products fitting this description, clinical trials of the FDC would not usually be required; bioequivalence between the FDC and the components could be used to infer clinical efficacy and safety of the combination.

The Committee considered the evidence available to support the proposal that FDCs improve adherence, noting the results from two recent systematic reviews *(2, 3)* that address the question of whether FDCs have a positive effect on adherence to medication regimens and also the WHO Report from a meeting in 2003. (Fixed-Dose Combinations for HIV/AIDS, Tuberculosis, and Malaria - Report of a Meeting Held 16-18 December 2003 Geneva at: http://www.who.int/medicinedocs/library.fcgi?e=d-0edmweb--00-1-0--010---4----0--0-10l--1en-5000---50-about-0---01131-0011FZeOxQNl9ee80ca700000000459a6ca2-0utfZz-8-0-0&a=d&c=edmweb&cl=CL2.1.2&d=Js6172e.

Based on the information in these reviews there are very few clinical trials that assess the relationship between FDCs and adherence to treatment, and the studies that exist have significant methodological flaws. There is therefore limited direct evidence that strongly supports the benefits of use of FDCs. However, the 2003 report noted that "FDCs/CBCs are very important tools for scaling-up treatment for HIV and AIDS, TB and malaria and remain the first choice when they are available. Fixed-dose combinations and co-blistered combinations (CBCs) must be considered as one element in an effort to ensure adherence that also includes supportive counselling, appropriate information and other measures."

One advantage of FDCs compared to loose combinations is that if one component of a loose combination is missing, resistance is more likely to develop. A disadvantage is that the optimal combinations of components may change rapidly. The Committee recognized the rapid development of science of therapeutics in the area of infectious disease and that new FDCs may be conceptually appropriate. The Committee recognized that some FDCs could encourage rational prescribing (e.g., avoid use of antagonist compounds together).

The Committee also considered 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.

On balance the Committee decided that it will consider listing some existing FDCs to be useful to countries that use the list for procurement. However, the Committee also wants to encourage the development of new FDCs and trials comparing these.

The Committee decided that co-packaged products for use in combination but not formulated as an FDC, can be assumed to be covered by listing individual components.

Overall, the Committee, having reviewed its current criteria for listing FDCs as essential medicines, decided to retain them unchanged.

REFERENCES

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

2. Connor J, Rafter N, Rodgers A. Do fixed combination pills or unit-of -use packaging improve adherence? A systematic review. *Bull World Health Organ.* 2004 Dec;82(12):935-9.

3. Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD005025. DOI: 10.1002/14651858.CD005025.pub2.