

Fixed dose combinations for HIV/AIDS, Tuberculosis, and Malaria

Current status and future challenges from clinical, regulatory, intellectual property, and production perspectives

Geneva, 16-18 December 2003

Observations and some ways forward

A. Overall Observations

The overall objectives of treatment for HIV/AIDS, malaria and tuberculosis

1. Safe, effective, quality treatment of three major communicable diseases, HIV/AIDS, TB, and malaria, which together claim 6 million lives each year.
2. Formulations and packaging that help to ensure effective use, contain resistance and thereby keep existing medicines available for use, for as long as possible.
3. Formulations and packaging that support massive scaling up of treatment will make the best use of limited human and financial resources. At present, very few patients who would benefit from effective treatment of AIDS, TB, and malaria actually receive optimal treatment.

Provisional observations concerning fixed-dose combinations

1. Combination therapy has become the standard for treating HIV/AIDS and TB, and is rapidly becoming the standard for malaria. Combination therapy has recognized benefits in slowing resistance, improving clinical outcomes, and facilitating logistics. In the case of ARV triple therapy, the FDC's usually offer the most affordable option.
2. The key question for the meeting was: are there additional benefits in presenting combination therapy as fixed dosage combinations (FDCs) or co-blistered combinations (CBCs), thus enhancing the likelihood that all active ingredients in the combination travel together from producer, through the supply system, to the prescriber, to the dispenser, and into the patient's hands.
3. In response to this question, the following main observations were made:
 - a. FDCs/CBCs are very important tools for scaling up treatment for HIV/AIDS, tuberculosis, and malaria. FDCs remain the first choice when they are available, CBCs are a second choice and single products are a third, but least desirable choice.
 - b. FDCs/CBCs alone are not going to be enough; separate medicines will continue to be needed in specific circumstances, as discussed below.
 - c. FDCs/CBCs must be considered one element in an effort to ensure adherence that also includes supportive counseling, appropriate information, and other measures.
 - d. FDCs should be based on combinations of clinically proven safety and efficacy, and they must have demonstrated quality and bioequivalence. Where CBCs are used the

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requirement is for a logical combination of products of proven safety, efficacy and assured quality.

- e. To achieve “3 by 5”, many approaches will be needed. Thus, there will be a need for FDCs, CBCs, and single products under differing circumstances.

B. Experiences with Fixed Dose Combinations

Provisional observations

1. Combination treatment can be delivered in any of four presentations: (a) individual medicines in bulk; (b) individual medicines in blister packs; (c) co-blistering of the 2,3, or 4 needed medicines in a single pack (CBCs); (d) fixed dosage combination of the 2,3, or 4 active ingredients into one tablet or capsule (FDCs).
2. The possible benefits of FDCs and/or CBCs are that they can:
 - a. Increase patient adherence to treatment (especially FDCs)
 - b. Delay the development of resistance (especially FDCs)
 - c. Lower the total cost, including production, storage, transport, dispensing, and other health system costs
 - d. Reduce the risk of medication errors by prescribers, dispensers, or patients themselves
 - e. Simplify and increase security of supply systems (especially FDCs)
 - f. Facilitate patient counseling and education, reduce waiting time
 - g. Help in scaling up access to ARVs as their use has been associated with significant increase in enrollment in some pilot ARV programmes.
3. The strength of experiential and scientific evidence presented in support of these benefits varied among the possible benefits. Specifically, clinical trial evidence on the effect of FDC use on clinical outcomes, patient adherence, and resistance is limited; but what does exist supports a benefit from FDC use.
4. For FDCs, even where measured benefits are not seen, patients and providers appear to prefer them to loose combinations. No significant negative evidence is available against the use of quality assured FDCs.
5. Operational arguments for FDCs and the need for “common sense” approaches concerning cost, supply logistics, and patient counseling may be stronger in resource-limited settings.
6. In practice, pharmaceutical companies routinely have developed and marketed FDCs when combination therapy has proven advantages, companies have access to all components of the combination (through ownership or licensing), and a fixed dose combination is technically feasible.
7. It was noted, however, that it is, “not simple to make things simple.” FDCs/CBCs can create significant challenges for:
 - a. Toxicity management
 - b. Paediatric and weight-based dosing
 - c. Drug interactions (e.g., with rifampicin, nevirapine, other medicines)
 - d. Adjustment of regimens in response to resistance

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- e. Lead-in dosing
 - f. Dose and frequency adjustment for renal and hepatic impairment (this is not only true for FDCs but for all products)
 - g. Management of ARV therapies in child bearing women
 - h. Management of coinfections of HIV with TB and HBV.
8. Adherence depends on a combination of approaches, including counseling; packaging and labeling to promote understanding.
 9. In addition, there are a variety of dispensing options including “co-ziplocking”, “MEMS caps”, pill boxes, and unit dose packaging. These should be implemented in the context of Good Dispensing Practices.

Some ways forward

1. For HIV/AIDS, tuberculosis, and malaria, FDCs and CBCs should be developed according to standard treatment guidelines.
2. Each national programme needs to establish the role of FDCs, CBCs, and individual medicines within the context of its healthcare providers and healthcare system. WHO’s guidance may be crucial to support this needed development. National programmes should build in ways of overcoming or slowing antimicrobial resistance, FDCs are one of the important tools for achieving this objective.
3. There remains a place for combination dispensing packs according to individual patient needs.
4. Clinical and operational research is needed to expand the evidence base and, using natural experiments in combination with monitoring and resistance surveillance systems, including post marketing surveillance of FDCs when they are first introduced.
5. Pharmacovigilance need to be considerably strengthened, since these systems are not well-developed in many of the countries that are or will be using modern medicines for HIV/AIDS, malaria, and TB.
6. Monitoring outcomes of the programs in health care systems as a feedback to update and possibly modify treatment plans using FDCs and/or CBCs. This should include documentation of the role of FDCs in increasing enrollment in ARV treatment programmes.
7. The role of dispensing and co-packaging systems as complementary approaches to FDCs and CBC should be further developed.

C. Public Health Priorities

Provisional observations

1. WHO has developed a public health approach to ART that has identified 4 first-line therapies using 5 specific medicines. These guidelines considered a range of factors including demonstrated efficacy, adherence potential, side effects, co-existing conditions such as TB or pregnancy, availability of FDCs, concomitant medications, presence of resistant viral strains, cost and availability and infrastructure needs including possibilities of rural delivery.

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2. WHO guidelines¹ indicate a preference for FDCs (or CBCs as interim) of proven quality and bioequivalence for first-line ART. This is an experience-based recommendation taking into account the total healthcare delivery system in developing countries.
3. Management of toxicities, resistance, and other treatment challenges will require alternative 3-drug FDCs, 2-drug FDCs, and single product formulations.
4. FDCs, co-blistering, and loose combinations will co-exist and can be transitional.
5. Paediatric preparations for HIV/AIDS are sorely lacking. While more clinical evidence is desirable, there is sufficient evidence to make operational paediatric treatment guidelines. The greater problem is that of convenient paediatric dosing. Issues around the treatment of mothers who have received ARVs to prevent MTCT remain unclear.
6. Recent developments for uncomplicated malaria have focused on combination therapies and there are at least seven new fixed dose combination therapies recently developed or under development.

Some ways forward

1. WHO treatment guidelines provide indications of desirable FDCs and CBCs. Guidelines, based on the best available clinical and public health evidence, should be widely communicated to national disease control programmes, procurement agencies, and the pharmaceutical industry.
2. It is essential to continue to build the evidence base within the healthcare system regarding procurement, distribution, use, and outcomes of FDCs and CBCs, moving from initial successful pilot projects to the practical to the proven.
3. Research is needed to develop and modify policy – e.g., malaria /ACT. This will include operational research.
4. Client perspective choice of delivery system preference for simplicity.
5. There is an urgent need for the development of pediatric formulations and specifically pediatric FDCs.
6. Special attention must be given to the packaging and dispensing of the “combination of combinations” needed for simultaneous treatment of HIV/AIDS and TB – perhaps through co-blistering of TB 4-FDCs and HIV/AIDS 3-FDC.
7. Tiered guidelines which provide practical information to health workers operating at different levels of the health system as to how to use the available medicines need to be developed within each country and within each health system.
8. There are multiple modalities to promote adherence which includes but is not limited to FDCs.
9. Operations Research needed to clarify options, particularly for the treatment of mothers who have received ARVs to prevent MTCT and the issue of women of childbearing ages or women who are pregnant and coinfecting with HIV and TB. The interactions between contraception and therapies for TB and HIV need to be investigated.

¹ Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach 2003. Revision http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf.

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10. Pharmacovigilance is required for new products and formulations releases.

D. IP and Legal Options

Provisional observations

1. For HIV/AIDS, WHO-recommended combinations involve one or more constituents that are widely patented in some countries, including some least-developed countries. Formulation of these FDCs, and perhaps CBCs with these constituents, may require licensing agreements or other arrangements that would enable legal production of these products.
2. Most existing active ingredients for combination products for tuberculosis and malaria are not patented, although some important ones are, such as the anti-malarial combination of artemether and lumefantrine known as Coartem/Riamet (Novartis). This situation may change over time as new chemical entities are developed. New FDCs and/or constituents in the pipeline may be patented and their IP will have to be properly managed to assure access.
3. Property holders may be reluctant to provide information about the number and nature of their IP portfolios. This lack of transparency as to the existence and scope of these IP rights creates uncertainty for potential competitors thereby decreasing the likelihood that such competition will occur. It is also often time consuming and difficult for procurement organizations to verify the existence and legal status of patents. Much of the relevant information should be available in the public domain, but in practice it can be difficult to obtain and/ or it is just not accessible in a form which is easily understood by non-experts.
4. Various mechanisms exist that can be used to ensure that patents and other intellectual property rights do not prevent but rather facilitate the development, *access* and marketing of FDCs and CBCs. These mechanisms can include voluntary and non-voluntary licensing, cross licensing, pooled licensing, and other measures consistent with TRIPS safeguards (interpreted in conjunction with the Doha Declaration on TRIPS and Public Health).
5. When specific needs and products are identified and collaborative negotiations are pursued, the IP problems may be overcome in a mutually acceptable fashion. Where collaborative negotiation does not lead to a voluntary solution however, it may be necessary to utilise public policy tools (including the TRIPS/Doha safeguards) to enable the necessary solution to the problem.
6. Post-2005, there will be a need to effectively manage access to certain future FDCs and constituents, including those using newly patented active ingredients, as the options for countries will have changed.
7. Least developed countries who are members of the WTO are under no obligation to enforce patents for any pharmaceutical products until at least 2016, as agreed by the World Trade Organization (WTO) Members in paragraph 7 of the Doha Declaration on Public Health and the TRIPS Agreement.

Some ways forward

1. Explore feasibility and mechanisms for public listing of license, patent, and registration status. This may involve more cooperation between countries, international organisations, national organizations (including patent offices) and companies.
2. Licensing and other IP arrangements for FDC and CBC would be facilitated by a clear identification of the priority products and formulations to be selected for license negotiations.

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3. The feasibility of expanded IP licensing arrangements should be explored with WHO and WIPO, including identification of (a) the IP needed, (b) potential licensors (IP holders), and potential licensees (other producers). Other mechanisms for technology transfer may also be possible.
4. Explore the possibility of consultations between individual industries and other stakeholders on specific IP issues for specific products.
5. If used, voluntary licensing, patent pools, and other IP sharing arrangements generally should be implemented in a manner that stimulates competition among various qualified producers. Such arrangements should include the necessary IP to manufacture specifically defined products.
6. Explore other mechanisms that would effectively address the multiple IP ownership issues of FDCs and promote innovation, which may include mechanisms for joint or collective management of IP rights.

E. Pharmaceutical Development, Quality Assurance, and Regulatory Requirements

Provisional observations

1. Quality must be built into the product – it cannot be tested, inspected, or assessed into the product. Scientifically-based formulation and production will minimize problems with product quality. Quality assurance needs to extend beyond product quality to include program quality.
2. Serious product quality problems have been documented for several malaria, TB, and ARV single ingredient products as well as fixed-dose combinations. This has not occurred for WHO prequalified products.
3. FDCs are more technically demanding than single-ingredient preparations to develop and to produce – scientific basis for production - e.g., two-layer tablets.
4. The WHO-managed UN Prequalification Project assesses the quality of selected medicines for HIV/AIDS, tuberculosis and malaria to produce a positive list of pre-qualified products and manufacturers assessed according to establish criteria of safety, efficacy, and quality (including bioequivalence). WHO prequalification work and standard setting are clearly endorsed by established regulators.
5. Targeted sampling and testing to monitoring the market should be actively expanded. Test results conducted by procurement agencies should be shared with national regulatory authorities.
6. A single comparator based on the original single dose innovator product should be used to determine the bioequivalence of FDCs. In general, this should be the product (s) that was used for the original clinical trials
7. The Prequalification Project includes ongoing monitoring of prequalified products and manufacturers; strengthens local regulatory and production capacity; provides innovator companies with a fast-track process when their product has been already evaluated by a stringent agencies.
8. As yet, too few products meet WHO Prequalification standards, especially in the case of tuberculosis and newer antimalarials.

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9. In addition to the WHO Prequalification Project, quality specifications need to be made available to national drug regulatory authorities (NDRAs). WHO has developed an abbreviated protocol for TB bioequivalence testing. Such protocols may be necessary for ARV and malarial FDCs.
10. Countries are encouraged to use the results of WHO prequalification to do fast track registration.

Some ways forward

1. Improved medicines quality requires substantial political commitment and commitment of resources, both nationally and internationally.
2. Development of CBCs is a practical step toward development of FDCs; a step that may avoid some of the more time-consuming and costly steps in product development and regulatory approval.
3. Specifications for APIs and finished products as well as methods of analysis and reference standards need to be made available to national drug regulatory authorities.
4. Under some unusual circumstances, a new product study may be needed when a new FDC is produced. This may require both preclinical and clinical trials to be undertaken.
5. Packaging is also an important part of quality. Defining the storage conditions for new products, especially FDCs and CBCs, should be a priority.