

Welcome

The meeting was opened by Dr Jonathan Quick, Director of the Department of Essential Drugs and Medicines Policy (EDM) who welcomed more than 90 participants from all continents, from differing backgrounds, including public health, regulation, the innovative and generic pharmaceutical industry, government, and UN organizations. He spoke of the tremendous interest fuelled by fixed-dose combinations (FDCs) for antiretrovirals (ARVs) and also by recent experiences related to malaria and TB products.

He noted the long history of FDC production. One of the most far-reaching events of the 20th century occurred in May 1960 with the marketing of the first combined oral contraceptive (COC) in the USA. This was also one of the first widely marketed blister packed products. Maloprim (pyrimethamine + dapsone) was developed as a malaria prophylactic agent with activity against parasites that had become resistant to pyrimethamine alone in the early 1960s. In 1969 cotrimoxazole (Bactrim or Septrin) was launched as an FDC antibiotic which resulted from the cross licensing of components by Wellcome (now GSK) and Roche. This compound was the top antibacterial of its time (grossing more than US\$5 billion in sales).

During the 1960s the pendulum began to swing away from FDCs. The FDA was mandated to review the effectiveness of drugs approved between 1938 and 1962 in the Drug Efficacy Study Implementation (DESI) Programme. This resulted in medicines being withdrawn and new FDCs facing a difficult passage to registration.

In 1978, the first WHO Expert Committee on the Use of Essential Drugs laid down demanding criteria for inclusion of FDCs. These were:

- clinical documentation of efficacy
- therapeutic effect greater than the sum of the components
- cheaper than the sum of individual products
- improved compliance
- dosage adjustments possible for the majority of the population.

Every Expert Committee maintained this position until 2002, when it changed to: *"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, TB and HIV/AIDS."*

Jonathan Quick reminded participants that FDC products are not limited to AIDS, TB or malaria. One recent blockbuster has been an FDC asthma inhalant. And a recent controversial *BMJ* article has proposed a 4-FDC "polypill" for the

primary or secondary prevention of heart disease, which could be for everyone over the age of 55!

Especially in the area of HIV/AIDS but also for TB and malaria, FDCs have been identified as highly desirable in terms of adherence and ease of treatment, containment of resistance, reducing diversions and possibly reducing costs.

The purpose of the meeting was to bring together the many different groups with an interest in FDCs to share information and propose how WHO and its partners could work to address barriers and to optimize the benefits of FDCs. The areas to be discussed at the meeting were reviewed. These included the scientific issues around the production of FDCs, and issues of compliance and adherence, patents and licensing, production and formulation, and quality and regulation.

There had been debate on whether to have multiple small meetings for each of the three diseases or to have a single large meeting. It was decided to hold a large meeting because of the interaction between the issues and the actors. Individuals working on malaria, TB and HIV/AIDS were coming to EDM to discuss the same technical issues and were often unaware that problems had been solved by other disease groups.

Objectives of the meeting

The objectives of the meeting were:

1. To define the public health needs, and their evidence base, for FDCs for priority communicable diseases;
2. To determine the issues to be addressed from clinical, regulatory, intellectual property and production perspectives to overcome barriers to the availability of required/preferred FDCs.

Expected outcomes

He suggested that the expected outcomes of the meeting would be:

1. Analysis of the rationale for using FDCs for treating priority communicable diseases from a public health perspective;
2. Analysis of the existing evidence supporting use of FDCs for priority communicable diseases;
3. Analysis of the legal, regulatory and manufacturing possibilities and constraints in creating, producing and making available FDCs;
4. Identification of specific issues for which additional work is required, some of which may develop and be published in Expert Committee documents.

He acknowledged support received from the Rockefeller Foundation and the various WHO partnerships, particularly Stop TB, Roll Back Malaria and the 3 by 5 Initiative.

Dr Jim Kim brought greetings from WHO's Director-General and highlighted the interest of the D-G in the issues being discussed at the meeting. He emphasised that FDCs should be seen as one of the components of success and not as the only approach. He encourage participants to act quickly but not at the expense of quality or safety. Jack Chow greeted participants on behalf of WHO's HTM cluster. He pointed out that FDCs would be a crucial component of the fight against AIDS, TB and malaria. During the meeting, the Director-General of WHO, Dr LEE Jong-wook, intervened. He highlighted the need to act now, saying that the goal was to make products available and to resolve the intellectual property (IP) issues. He urged participants to work constructively to solve the difficulties that were being experienced by people in poor countries facing AIDS, TB and malaria epidemics.

Richard Wilder briefly introduced antitrust issues. He stressed that competing companies should not make any prior agreements which would reduce competition.

Presentations on TB FDC issues

FDCs for TB: lessons learned from a clinical, formulation and regulatory perspective was presented by Ramesh Panchagnula from NIPER in India.ⁱ (p. 29)

This extensive paper reviewed the history of the development of TB drugs, the rapid emergence of resistance, the use of combination therapy and the evolution of FDC products. He provided a detailed account as to how the WHO formulation for 2 and 4FDC products had been developed for TB. He highlighted the many benefits of FDCs but also identified related issues, such as the variable bioavailability of some products, resulting in the production of WHO Guidelines for establishing bioavailability of rifampicin.

Bernard Fourie from the MRC in South Africa highlighted the importance of quality in the production of TB 4FDCs, including issues around batch to batch variation. He also stressed the importance of clinical factors, such as drug interactions. He highlighted the fact that some patients may receive over doses of some products, pointing out that for patients at the extremes of weight determining the dosage of FDCs was difficult, and that there was a lack of evidence to address this issue. He suggested that a limited number of tablets was desirable but that tablet size was a factor.

ⁱ http://www.who.int/medicines/organization/par/FDC/Panchagnula_FDCs.ppt

Michiel de Goije of IDA Netherlands raised the relationship between dissolution and bioavailability. Ramesh Panchangula confirmed that dissolution served as a good proxy for bioavailability. The issue of variation in individual response was discussed.

Comparison of the product cost of FDCs in comparison with separate dispensing and/or co-blistering was presented by Robert Bwire.ⁱ (p. 67)

He provided data on the changes in the costs of TB FDCs, and presented a study on the differences between blistered TB FDC products and loose products. The balance between blister packs increasing costs compared to the savings in delivering products was discussed.

Erik Nordberg (IFPMA) discussed the issue of tariffs and anti-dumping duties as important factors in determining the end price. His organization opposed taxes or duties being applied to medicines.

Presentations and discussions on malaria FDC issues

FDCs for malaria: translating clinical recommendations to product supply was presented by Andrea Bosman from the Roll Back Malaria Programme.ⁱⁱ (p. 77)

He highlighted how many of the available drugs had been lost due to resistance, and pointed out that the shift from single to combination therapy had occurred later than for TB. Only since 2000 has there been a commitment to combination therapy. This new policy had created challenges because only one FDC product exists at present. The other products are only available as single products, and there is limited experience with the new drugs. The issue of malaria treatment was also complicated by a 10-fold increase in price. WHO had reached a special agreement on prices with Novartis, and had done collaborative work on packaging. The WHO Prequalification Project was working on issues around the new ACT products. In the first 17 months only one out of 26 products had been prequalified, creating a challenge for countries wishing to use these new products. An interim solution is to promote the procurement of individual products.

Another area of work for the RBM programme has been in forecasting for patients needing treatments and for individual treatments. He highlighted the fact that the Global Fund is the major funder of ACT purchases. Countries are following WHO's guidelines for malaria therapy.

In discussion Clive Ondari highlighted a key concern about the poor quality of antimalarial drugs used in Africa being a possible cause of drug resistance. He reported that seven countries were surveyed for the quality of chloroquine and

ⁱ <http://www.who.int/medicines/organization/par/FDC/Bwire.ppt>

ⁱⁱ <http://www.who.int/medicines/organization/par/FDC/FDC-Malaria1.ppt>

sulfadoxine/pyrimethamine (S/P). He reported that quality varied greatly, with a substantial number of products failing, in particular dissolution of SP. He pointed out that this problem was well recognized by regulators and manufacturers and was primarily due to poor quality APIs and the poor production process. He emphasized that as more complex FDCs are produced there is a need to ensure the quality of the APIs, to monitor the production and delivery process and to ensure a pharmacovigilance programme to monitor the quality of the new FDCs.

Susan Walters from Australia added that the method of manufacture was equally important as the formulation. This meant that GMP was critical. She pointed out that products change over time and that dissolution testing was needed to monitor changes in formulation or production. Roger Williams from USP in the USA commented that single dissolution tests cannot ensure bioavailability

The issue of access to antimalarials being delivered through other sectors was discussed. Andrea Bosman suggested that the rollout of new antimalarials should be through the public sector and should ideally include products that are not available as single products.

Developing combination drugs for malaria: examination of critical issues and lessons learnt was presented by Robert Taylor from WHO/TDR (p. 91)

He described the process of generating evidence through a series of clinical trials which demonstrated the efficacy of ACT products. He highlighted the demands for coordination that an overall programme to develop FDCs requires.

Andrea Bosman discussed the importance of multi-centre trials being undertaken at 10 sites for 4,500 patients. He highlighted the importance of keeping decision-makers involved in the development process and in providing information about future products. He identified a tension between marketing forces and the need to keep products available for treatment in other areas, also pointing out that PPV were driving much malaria work because of the limited interest in developed countries. He suggested that the research community need to be involved in issues around pricing, commenting that under some circumstances the development of new products that are not in the research mainstream may cause problems. He identified the need for Phase 4 studies related to specific aspects of the use of these drugs.

The choice between FDCs and co-blistering was discussed and issues related to formulation, registration and intellectual property were raised. Alan Schapira (WHO/RBM) highlighted the fact that most antimalarials are taken at home and that co-blistered preparations are frequently separated and shared between patients. The need for FDCs for short-course therapy was questioned. Conversely the suggestion was made that as malaria is an acute life-threatening disease therapy needs to be immediately accessible.

The issue of post-marketing surveillance for antimalarials was raised and Alan Schapira reported that due to the shortage of good quality products there were limited choices available. Andrea Bosman reported that about eight companies are involved in the prequalification process but that difficulties remain. Lembit Rago (WHO/QSM) reported that the WHO requirements are often higher than national standards, and that WHO is not willing to have different standards.

There was discussion to whether new antimalarials should be brought to registration as single entities or only as FDCs. The Medicines for Malaria venture (MMV) reported that the intention is to bring these molecules to market as FDCs.

Presentations and discussions concerning ARV FDCs

Fixed-dose combinations for HIV/AIDS: the pros and cons of experiences to date was presented by Sanjay Pujari, Director, HIV Project, Ruby Hall, Pune, India (p. 99)

He reported on the treatment of 1253 patients treated in two private tertiary care institutions in India with generic FDC products.ⁱ There had been a substantial increase in CD4 counts during the study. The incidence of mortality and morbidity of patients on these FDC products was 5.2 and 28.1 per 100 person years, which is comparable to results obtained with single ARV products.

Professor Joep Lange discussed the determinants of long-term HAART efficacy. He pointed out that if viral load is not monitored resistance may develop before clinical changes occur. He pointed out that DOT can increase positive outcomes from 70% to over 95%. There was lively discussion of the details of the clinical trial described by Dr Pujari, with the overall conclusion that, despite limitations, the report confirmed that FDC products were clinically effective in the relatively large cohort study.

Preferred fixed-dose combinations of ARVs for first-line use in HIV/AIDS was presented on the second day of the meeting by Jos Perriens (WHO, HIV/AIDS Department)

This was a detailed presentation on the preferred FDCs of ARVs for first-line use in HIV/AIDS.ⁱⁱ He emphasized the need to build systems that would allow the initiation and continuation of ARV therapy down to health centre level.

Andrew Clark (Bristol Myers Squibb) presented the slides prepared by Joep Lange,ⁱⁱⁱ highlighting the practical challenges faced in developing treatment regimens to cater for varied situations. He stated that although it is

ⁱ <http://www.who.int/medicines/organization/par/FDC/Pujari-WHO/FDC2003edited.ppt>

ⁱⁱ http://www.who.int/medicines/organization/par/FDC/1st_line_ARVinWHOGuidelines_JosPres.ppt

ⁱⁱⁱ <http://www.who.int/medicines/organization/par/FDC/FDCLangeFinal.ppt>

unquestionable that we need to simplify HIV treatment as much as possible to achieve the goal of treating the millions in need in a responsible manner, it is also true that it is not always simple to make things simple for everyone. There is a need for dosing-flexibility of antiretrovirals in relation to:

- antiviral potency/“robustness”
- toxicity management
- weight-based dosing
- paediatric dosing
- drug interactions
- overcoming drug resistance
- need for lead-in dosing
- renal and/or hepatic impairment.

He suggested that it may not be easy or possible to co-formulate some of the most desirable combination regimens, and that the most popular current FDCs are only partially active against HIV-2. He highlighted the need for dosing-flexibility in relation to toxicity management. He pointed out that rather than having to replace a whole regimen in the case of clearly identifiable single drug toxicity, it would be preferable to have the option to replace one of the agents. He also noted that there is a need for dosing-flexibility in relation to weight-based dosing to minimize toxicity and maximize the efficacy of some antiretrovirals. There was also a need for dosing-flexibility in relation to paediatrics, which implies a need for liquid formulations in infants; and weight-based dosing for virtually all ARVs until adolescence.

There was also a need for dosing-flexibility in relation to drug interactions in that dosages of ARVs may need to be adapted in the case of co-medication. The need for dosing-flexibility in overcoming drug resistance was mentioned, as was the suggestion that drug-resistance is not an absolute phenomenon and that pharmacological boosting (of protease inhibitors with ritonavir) may overcome it. Depending on the setting, it may be desirable to have available some of the PI in non-boosted as well as boosted form. The issue of lead-in dosing specifically for nevirapine, where failure to adhere to a step-up scheme may lead to a considerable increase in severe (life-threatening) toxicities was highlighted as a serious issue for FDCs containing nevirapine. The problems of severe renal or hepatic impairment requires adjustment of dosages of particular frequently used ARVs. He mentioned possible drug interactions with herbal preparations that patients may be taking in addition to ARVs.

He concluded that "one size does not fit all" and that even in mass treatment programmes, where one may have to “cut corners” and allow for casualties to save as many lives as possible, the need for the availability of various individual drug formulations will not be negligible.

David Hoos (Columbia University, USA) spoke about the MTCT+ programme and client’s perspective concerning dosing-flexibility. He highlighted that blister packs and FDCs play complementary roles. He emphasized the value of pill

holders and other simple adherence devices for prompting patients to take their medicines regularly.

Bernard Pécoul (MSF) commented on MSFs experience with trying to deliver ARVs in constrained environments. He said that MSF had organized a recent consultation on delivery approaches in Nairobi and that he was reporting on the consensus reached. He highlighted that the existing infrastructure is very limited and that patient loads are high. He suggested that the ideal product would be stable in tropical climates, not need laboratory monitoring, be low-cost and fully efficacious. Such a product does not yet exist but the FDC products that have been developed come closest to the ideal. He suggested that we needed more FDCs, particularly those containing efavirenz. He identified a need for new tools for the future which would include new combinations, paediatric formulations, lower dose products and a review of products that had been discarded during the development process.

Extensive discussions followed the presentations. Leonard Sachs (FDA,USA) expressed concern that using NNRTI FDCs could lead to broad resistance to NNRTI. Hanne Bak-Pedersen (UNICEF) was concerned that there were no appropriate formulations of paediatric medicines. If FDCs could not be produced she strongly urged that other formulations be developed. Renee Ritson (Gates Foundation, USA) expressed concern about mothers who had previously received NVP for MTCT prevention. Dr Pujari (India) emphasized that the first therapy is the most important and highlighted the importance of adherence. He pointed out that the first-line regimen may promote resistance. He said that in India many patients are not naïve and will need adaptation of their regimens. He also pointed out that side effects such as dyslipidaemia and lipodystrophy were common. David Hoos expressed support for the WHO guidelines because they provide clear information to national programme managers as a basis for making national policies. He agreed that infant and child regimens and formulations were needed.

Andrew Clark (BMS) responded to concerns about the use of NNRTI regimens. He reported that in optimum conditions good outcomes with such regimens occurred for up to two years. He agreed that where NVP is used for MTCT resistance does occur at significant levels. He suggested that many women will start to receive full HAART and that they will not receive monotherapy. He reported on the difficulty of developing formulations and undertaking clinical trials for children. He expressed surprise at the Indian reports of lipodystrophy and AMI.

Jos Perriens (WHO) commented on the presentations and discussions. He reiterated all of the concerns expressed by Joep Lange but highlighted the emphasis of the treatment committee on treating as many patients as possible. He confirmed that the guideline committee had considered PI regimens but had decided that the non PI regimens remained the most practical choice. He confirmed that the committee had struggled with the issue of paediatric formulations. The committee had agreed to organize a consultation in 2004

before the next guidelines were produced. The committee had considered the issue of NVP for the prevention of MTCT. A consultation document was posted on the web for public comment. The durability of NNRTI regimens is a serious concern. He commented that where programmes had good adherence levels the outcomes were positive, and he highlighted the importance of treatment support.

Issues around treatment of co-infection for TB and HIV were discussed. The issues of providing FDCs containing EFZ and the need for a combined ARV FDC with a TB 4 FDC as a co-blister was suggested. The question as to whether NVP was an absolute contraindication during rifampicin regimens was raised as a research question.

Further discussion of the paediatric preparations occurred. The example of TB experience with dispersible tablets was quoted as an example that the ARV industry could duplicate. Bernard Pecoul suggested that clear recommendations about formulation and type of products were needed by the industry. Warren Kaplan highlighted the need for operational research. The question was raised as to whether new trials would be needed for registration of these paediatric formulations.

In further discussion of the logistics issues around the WHO model, Jos Perriens reported that the intention was that routine treatment might be delivered by CHWs who would monitor for common toxicities or side-effects. Those patients identified would be referred up the system to a health centre or district hospital. Simple algorithms will be developed to cope with these eventualities.

Presentation and discussion of cross-cutting issues related to logistics, adherence and resistance with FDCs

Analysis of the impact of the introduction of FDCs on supply management and security when compared with separate dispensing and/or co-blistering was presented by Jane Masiga from MEDS Kenyaⁱ (p. 113)

She identified the many advantages of FDCs from a procurement standpoint. She suggested that selection of products and suppliers would be simplified. Drug registration and inspection, import clearance and contract negotiation would all be facilitated by the use of FDCs, as would distribution and storage. She suggested that FDCs improved prescribing and dispensing and could reduce costs to patients. She provided data to show how the uptake of ARVs had been related to cost in Kenyan church facilities.

Cecile Mace (MSF France) highlighted the importance of including FDCs on the national EDL and the need for paediatric formulations to be developed. She stressed the importance of the prequalification project in helping the procurement process. She emphasized that one obstacle to registration was the

ⁱ <http://www.who.int/medicines/organization/par/FDC/MasigaFDC.ppt>

lack of monographs. She highlighted the present short shelf-life of FDCs, and pointed out that the prices of FDCs have been reduced through using pooled procurement.

There was a general discussion of the process in changing from single products to FDCs. This has been a problem in some situations as FDCs have been very popular and single products have not been used, risking expiry. This rapid shift has caused problems in maintaining stocks.

Sabine Kopp (WHO/QSM) reported that WHO is working to produce monographs and to work on developing standards and methods for ARV products.

Review of the evidence on better compliance and treatment outcomes with FDCs when compared with separate dispensing and/or co-blistering was presented by Jennie Connor from the University of Auckland, New Zealandⁱ (p. 119)

She reported that there were very few trials but that what evidence is available tends to indicate the benefit of FDCs and clear instructions or packaging in improving adherence. She confirmed that there was a need for rigorously organized trials to evaluate the benefits of FDCs and medication promoting measures.

Review of the evidence on effect of FDCs on the development of clinical resistance when compared with separate dispensing and/or co-blistering was presented by Warren Kaplan, Boston University, USAⁱⁱ (p. 119)

He pointed out there are vertical (DNA changes) and horizontal (transfer of DNA) mechanisms for generating resistance. He suggested that there were many factors related to the development of resistance and that FDCs or co-blistered packs only addressed some of the factors. From his review of the literature he reported that there were very few well conducted studies but what evidence did exist tended to suggest that FDCs were beneficial in preventing resistance.

David Lee (MSH, USA) commented on the two papers. He pointed out the need to focus on the two areas of adherence and AMR. He pointed out that adherence was affected by many factors, and that factors other than the product were often determinant. He highlighted the opportunity for natural experiments with the distribution of ARVs. There was extensive discussion of the value of attempting to link ARV resistance patterns with the types of ARVs provided. There was a brief discussion as to whether medication monitors are more useful than well organized questionnaires.

ⁱ http://www.who.int/medicines/organization/par/FDC/Connor_revisedslidesdec18.ppt

ⁱⁱ http://www.who.int/medicines/organization/par/FDC/Kaplan_resistance.ppt

Jane Kangeya Kanyondo spoke about the work that she was doing in regard to co-blistering and the delivery of antimalarial products.ⁱ She emphasized that co-blistering and unit dosing could use FDCs to improve outcomes. She suggested that two systems are likely to run in parallel, and said that blistering does not add substantially to the cost of medications. She pointed out that liquid preparations for children were associated with under-dosing and over-dosing and that paediatric blister packs achieved more reliable results.

David Hoos (Columbia University, USA) demonstrated a simple blister packing system that was being used within the MTCT programme. He pointed out that this system was flexible, blistering could be carried out locally and allowed for dosage changes. Participants expressed concerns about quality assurance issues and about the stability of the materials used.

Procurement experiences

Hanne Bak Pedersen (UNICEF, Copenhagen) presented the experiences of UNICEF in procuring ARV products. She emphasized the need for joint procurement plans involving nationals and donors. She suggested that more work is needed on the area of forecasting. It is not enough to know the number of patients, there is a need to know the patient profile mix and the different regimens being used. There is a problem in that some countries are not willing to fast-track registration of these FDC products. Concerns exist within both innovative and generic companies about IP issues. At present LDCs are not making full use of TRIPS safeguards, although Malawi has invoked paragraph 7 of the Doha Declaration for their procurement.

Bernard Pecoul (MSF) presented the experience of MSF in procuring ARVs. He highlighted the problem that many national treatment programmes have not incorporated FDCs into national treatment guidelines. He stressed that political will at national level was critical to ensure efficient procurement. He reported that when FDCs were available they were able to shift patients to the new regimens and to increase the uptake. Erik Nordberg reported that the Accelerated Access Initiative was treating large numbers of patients and that lessons could be learned from these programmes

ⁱ <http://www.who.int/medicines/organization/par/FDC/Co-packaging-FDC%20meeting-Finaldec18.ppt>

Intellectual property and industry issues

Legal options for overcoming patent barriers of fixed-dose combinations was presented by Warren Kaplanⁱ (p. 155)

He reviewed the range of legal and IP issues that arise with the production of FDCs, suggesting a range of possible approaches addressing these constraints, with different mechanisms be useful under different circumstances and he made a series of recommendations to the meeting.

Richard Wilder (USA) made the case that IP protection was important for incentivizing companies to invest in research. He suggested that IP is something to be managed rather than be seen as a barrier to overcome. Ellen 't Hoen (MSF) suggested that the prime issue is political and not legal, stating that there are many reasons to have FDCs available from a public health standpoint. She commented that where possible voluntary licences are preferable but that compulsory licences may be needed. She suggested that the idea of patent pools might be useful and that WHO could be involved in defining what these patent pools should contain. She reminded participants of the danger of regulatory barriers from regulatory agencies only considering products for which patents have been granted. Cecilia Oh (WHO/EDM) pointed out that as TRIPS comes into force more widely countries will need to deal with these issues. Cynthia Cannady (WIPO) discussed the range of options to deal with IP barriers and stressed the importance of voluntary licences in resolving these issues. She pointed out that considerable experience exists in other technological fields in dealing with such issues.

Industry perspectives on FDC production

After these IP discussions industry representatives spoke of a meeting held the previous week in Washington DC and reviewed the different technical issues in producing FDCs. John Morris from Abbott Laboratories presented an industry perspective on FDC issues. He started by pointing out that several aspects must be considered for successful combination of multiple active pharmaceutical ingredients (APIs) into a single dosage unit. This included:

- formulation development
- chemical & physical stability – compatibility
- manufacturability
- analytical methodology
- *In vivo* performance (bioavailability and PK parameters)
- regulatory approval.

ⁱ http://www.who.int/medicines/organization/par/FDC/Kaplan_IP.ppt

He reminded participants that a co-packaging was always an alternative. In describing FDC formulation development he confirmed that the basic formulation approach can vary significantly based upon API chemical and physical properties and that *in vivo* performance of BCS Class I compounds (high solubility – high permeability) is not dependent upon the formulation composition, whereas, BCS Class IV compounds (low solubility, low permeability) are highly dependent upon the formulation to achieve bioavailability. This problem could be encountered in developing an FDC product containing compounds from the various classes of therapy (PI, NRTI, NNRTI). A combination of multiple APIs of distinctly different properties can result in complex formulation development to target bioequivalence to individual marketed products. In addition all APIs must be compatible with each other and with formulation excipients, the size and number of dose units needs to be considered and some therapeutic regimens require relatively larger doses, resulting in multiple FDC dosage units of an acceptable size.

With regard to chemical and physical stability there must be both chemical stability with no significant change to degradation rates or introduction of new impurities over shelf-life and physical stability in which the products maintain the desired solid form or solution state of the respective APIs over the shelf-life of the product. Changes in solid form or physical properties may impact bioavailability and some API's may have limitations with respect to exposure to air, light, humidity, or temperature. The packaged FDC dosage unit must be chemically and physically stable over shelf-life as studied under a wide variety of use conditions.

A robust manufacturing process must be developed to ensure routine production of a quality FDC product. The complexity of the formulation and levels of the respective APIs in the dosage unit will be major factors, in addition the uniformity of the respective APIs could represent a challenge, especially if the APIs are present at significantly different levels in the formulation. The goal is always to maximize production efficiency.

When addressing FDC analytical methodology there is a need to develop analytical procedures to accurately monitor identity, strength, uniformity, quality, and purity attributes of respective API's in the FDC product and this will usually present a major challenge because each API will be controlled through appropriate specifications, the complexity of the FDC product leads to more complex test methods and the difficulty in the determination of related substances of a smaller API component in the presence of other API components at much larger concentrations.

When addressing FDC *in vivo* performance all ADME parameters must be considered (absorption, distribution, metabolism and excretion). Producers must understand the importance of AUC, C_{max} , C_{min} , $t_{1/2}$ for each API with respect to daily dosing regimen (QD, BID, TID). They must understand the effect of food on PK profile and there may be situations where some drugs should be taken with food while others should not. Based upon product characteristics (solubility,

permeability), some APIs will require more complex formulations (reduced particle size, stabilized amorphous systems, or solutions) to achieve acceptable bioavailability. In some circumstances complex formulation may not be appropriate for some APIs with very different properties – in some cases, certain combinations may not be possible. If an API is typically dosed in an immediate release formulation, incorporation into a modified release formulation may significantly alter the pharmaco-kinetic profile which could have a significant impact on bioavailability (increased or decreased). In this situation regulatory approval through bioequivalence becomes more challenging. In addition interactions between APIs or formulation excipients may alter PK profile.

When dealing with FDC regulatory approval the goal is to approve FDCs through bioequivalence to individual marketed products, as this allows bridging to existing safety and efficacy data. If PK profiles in the FDC product are significantly altered from the individual products, then the bioequivalence approach may not be feasible. This would result in additional safety / efficacy trials being required by regulators.

He suggested that a co-packaging approach could provide a viable alternative to an FDC approach. This would allow therapeutic agents from different classes (different properties) to be easily combined through packaging, while avoiding many of the development challenges. It would also allow individual drug products to be taken under conditions that are most suitable for optimum performance with respect to food and dosing regimen (QD, BID). This approach would mean a substantially reduced development time, and would provide increased flexibility to create various combination therapies and adapt to evolution of prescription strategies

Regulatory issues

Development of FDCs; pharmaceutical considerations Susan Walters presented her keynote paper that addressed the many issues related to the sustained quality of products once they have been produced, stored and distributedⁱ (p. 169). She emphasized the importance of validation after any changes are made in the manufacture of a product.

Vinod Arora (Ranbaxy, India) presented information on his experience with the production of ARV FDCs.ⁱⁱ He made a detailed presentation of the methods used to establish bioequivalence and to assure the quality of FDCs as compared to originator products.

Witold Wieniawski (Polish Pharmaceutical Society) emphasized the need to identify what products are needed before the formulators are asked to produce the required products. Regulators will be assisted by having external validation.

ⁱ <http://www.who.int/medicines/organization/par/FDC/WHOGenevaSMW1203.ppt>

ⁱⁱ <http://www.who.int/medicines/organization/par/FDC/VKAroraWHOGenevaDec.ppt>

In addition to the prequalification scheme, he suggested that there is also a need for specifications and quality standards to be produced. These standards are expensive and need to be managed in cooperation with organizations such as the USP and European Pharmacopoeia.

János Podgorny (Hungary) reported in detail on the WHO prequalification scheme.ⁱ He presented detailed case studies on the prequalification of the 4FDC TB product and FDC ARVs. He concluded that there were no regulatory obstacles to the production of quality assured FDCs.

Lembit Rago (WHO/QSM) reviewed the WHO prequalification project.ⁱⁱ He emphasized that sampling for QC testing was at the post-marketing level.

Leonard Sachs (FDA, USA) highlighted the many issues around the approval of FDCs.ⁱⁱⁱ He pointed out that assuring the quality of the product affected clinical factors.

Roger Williams (USP, USA) discussed the issue of comparator products.^{iv} He pointed out that individuals may respond to drugs in different ways. He emphasized that packaging was an important component of product quality.

Jérôme Barré (France) confirmed that for well established drug combinations, all the regulatory authorities agree that there is no need to perform extensive studies. Proper pharmaceutical development and a study demonstrating that the components in the FDC are bioequivalent to the components administered in the free combination are sufficient. In the situation where one active component should be administered with food and the others without food, the food effect on the FDC has to be investigated. He pointed out that the regulatory requirements for new drug combinations with which we lack experience were not addressed in this session. In this situation things are much more complex, especially with regard to toxicology and safety pharmacology requirements. Unfortunately these points are often overlooked although safety problems are at stake.

He commented that Roger Williams had presented a very comprehensive review on comparator products stressing the importance of a good choice for comparator. Formulations of brand products which are used as reference drugs can vary slightly from one country to another. In Susan Walters' presentation, she mentioned some of the reasons for these variations including new source of excipients, new manufacturing equipment, new site of manufacture etc. These variations may produce different *in vitro* dissolution profiles. In some cases, these changes in dissolution profiles do not translate into different bioavailability while in other cases they do and with confidence intervals beyond the usually accepted

ⁱ http://www.who.int/medicines/organization/par/FDC/Janos_FDCFPPs_Experience_LaingRv1.ppt

ⁱⁱ <http://www.who.int/medicines/organization/par/FDC/Lembit-FDC2003adec18.ppt>

ⁱⁱⁱ <http://www.who.int/medicines/organization/par/FDC/WHOSacksFDCs.ppt>

^{iv} <http://www.who.int/medicines/organization/par/FDC/19-comparatorproduct-williamsdec18.ppt>

ranges, as regulatory authorities have sometimes noted. For some pharmaceutical products there are publications reporting substantial differences in bioavailability of the same brand product sold in various countries and showing slight variations in the formulation. This is why there is a need to be very stringent when choosing the reference drugs to be administered in loose combination to demonstrate the bioequivalence with the test FDC. The reference drugs should originate from the country in which the clinical trials were performed to evaluate the efficacy of the free drug combination. This will avoid having FDCs with sub-optimal efficacy.

Concluding session

At the end of the meeting there was a general discussion of a draft of an executive summary document that had been prepared by the secretariat. This session allowed meeting participants to highlight important issues discussed at the meeting. Many of the comments have been incorporated into the final version of the executive summary.

Ramesh Panchangnula (NIPER, India) urged that a single drug comparator be used for quality control of FDCs. He called on WHO to develop a rapid protocol for testing, as had occurred for bioequivalence testing of TB FDCs and he suggested that surrogate markers for FDCs should be developed and agreed. He called for operational research (OR) on all aspects of the use of FDCs.

Roger Webber (USP, USA) highlighted the need for bioequivalence testing to be an integral part of the approval process. He suggested that under some circumstances new product studies might be necessary.

Bernard Pécoul (MSF, France) stressed that from an operational standpoint there was a clear hierarchy of needs. The first priority was for FDC products, the second priority was for co-blistered products and the third priority was to have single products. In discussion the point was made that there may be a need to co-blisten FDCs to deal with different therapeutic eventualities, such as simultaneous treatment of TB and AIDS. Jeff Sturchio (Merck-USA) pointed out that to achieve WHO's 3 by 5 goals many routes were needed and a range of different approaches would have to be tried. He stressed that the innovative pharmaceutical industry could contribute their expertise once it was clear what they were being asked to do. He stressed as Professor Joep Lange had previously stated that "It is not simple to make things simple!"

Hemadri Sen (Lupin, India) focused his comments on practical technical issues. He agreed with prior comments that the comparator product should have been used for validating clinical products. He stressed that formulation and packaging were an important part of quality and could facilitate effective dispensing. He mentioned the need for storage conditions to be defined so that manufacturers can produce products suitable for the expected markets. Hanne Bak-Pedersen (UNICEF, Copenhagen) expressed concern at the lack of emphasis on

procurement issues in the meeting and executive summary. She pointed out that with the limited number of prequalified producers there were difficulties in procuring all the products that were requested, particularly for malaria and TB.

Renee Ritson (Gates Foundation, USA) suggested that many different approaches would be needed for effective treatment programmes, and many different options would need to be considered. Operational research (OR) was required on topics such as MTCT and treatment, dealing with women in treatment programmes, co-infection with TB in child bearing women, rifampicin and nevirapine interactions. She stressed the need for pharmacovigilance to be built into any programme to proactively collect information on drug reactions or treatment failures. Leonard Sachs (FDA, USA) expressed doubts that combination therapy was always required for malaria. He stressed that in the same way that there was a need to test the quality of products there was also a need to monitor the quality of programmes.

William Haddad (Cipla, USA) stressed the need for an adverse event report system that would allow early recognition of problems. He called for an agreement on a first line regimen, and for a statement of support for the WHO prequalification scheme. He mentioned his concern about the effect of Hepatitis B co-infection with HIV and the use of lamivudine causing possible fatal interactions. David Stanton (Department of State, USA) suggested a need for OR on the interaction between contraception and AIDS therapy. Jaideep Gogtay (Cipla, India) urged that existing FDCs should be used more widely. Ellen t'Hoën (MSF, France) called on participants to remember the background to the meeting. The 3 by 5 Programme aims to dramatically increase the number of AIDS patients under treatment. At present, very few of these patients are on ARV treatment and the widespread provision of FDC ARVs is a critical component of treatment expansion.

The meeting ended with thanks extended to participants by the co-chairs (David Hoos and Jonathan Quick). They expressed appreciation for the constructive atmosphere created by the willingness of everyone to interact in a frank, respectful manner. Participants agreed to continue work on the topics discussed.