COMMENTS FROM HIV/AIDS DEPARTMENT ABOUT THE DOCUMENTS SUBMITTED TO WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

A) COMMENTS ON BACKGROUND DOCUMENTS

1. Criteria for selection of essential medicines for children

The criteria as provided offer no specificity for infants and children, and therefore suggest that no specificity is required. In fact there are several special considerations in relation to children. Firstly those that relate to burden of disease, 'priority conditions' of infant and children are potentially different. Thus for neonates, it is sepsis, for under fives it is largely respiratory, diarrhoeal and other preventable communicable diseases. Pharmacokinetic (PK) and pharmacodynamic considerations are very different and mean that formulations suited to adults may not always be most appropriate, or contain proportions of active pharmaceutical ingredients best suited to dosing in children. The need for medicines to be given by care givers for younger children, and to children who may be unable to swallow solid forms, to tolerate alcohol excipient, or large volumes of some preparations based on age (e.g. 10 ml per dose is too much for a neonate) means specific products may be preferred for the paediatric population, and should be reflected in criteria for inclusion for children medicines.

For chronic diseases requiring continued adherence to a combined regimen of drugs single compounds are not preferred.

Fixed dose combination (FDC) therapies are usually cheaper. Some forms of medicines, including solid fixed dose combinations are much cheaper and offer significant advantages to national programmes for forecasting, procurement storage and distribution, and this is not currently recognized as criteria for selection.

2. Position paper on solid dosing forms to be included in the Model Essential medicines list for children.

The HIV department in expert consultation examining appropriate antiretroviral (ARV) formulations for paediatric patients agreed the to very similar criteria for ARV products (for meeting report see http://www.who.int/3by5/en/finalreport4Apr.pdf and see subsequent meeting reports from Paediatric ARV working group in http://www.who.int/hiv/events/paediatricmeetingreport.pdf.).

In general the policy statements outlined are suitable and meet the concerns of most HIV experts treating children. There were concerns that dividing a tablet beyond half led to less precision, and that all tablets that are intended for use in divided portions should be scored. Dissolvable film tablets and granules have been proposed and would also be considered useful.

Where liquids are used, and it is recognized they are useful even for ARV products, excipient should not be alcohol. This is a problem with all existing protease inhibitors liquid preparations. For use in low income settings, solid and liquid products should be stable at room temperature, have small dose/volume, have long shelf life at high humidity and temperatures, and be packaged to provide a complete course or a complete time period (e.g. for ARV medicines a minimum of 28-30 treatment days).

The HIV Department supports calls for suitable fixed dose combination (FDC) products in paediatric populations, as use of the same has led to massive scale up of antiretroviral therapy (ART) in adults. There are some examples of use of adult FDCs in paediatric populations[1] [2], and of new paediatric FDCs being used, with PK studies ongoing (see references [3]). There are considerable strategic, economic and programmatic advantages of FDCs.

Simplification of antiretroviral therapy by using FDC based ART is recommended in 2006 WHO antiretroviral treatment recommendations for adults, adolescents and children, and is particularly important in resource-limited settings. FDCs exist for the preferred adult 1st line regimens. Optimal use of ART requires high adherence of all drug components, and FDCs appear to contribute to good adherence as does reducing the total pill burden[4]. FDCs ensure availability of all three components at the same time; facilitate rational prescribing and compliance with national treatment guidelines. FDCs have increased access to ART at population level, and contribute to decentralization of service delivery.

Several studies in adults document successful clinical outcomes and confirm safety of FDCs in many countries. FDCs are cheaper to purchase if payment is required, and high cost of ART is one of the factors associated with decreased adherence. Where patients must purchase ART, FDCs may reportedly minimize use of dual or single ARV regimens. FDCs suitable for dosing in children are therefore urgently required.

Evidence is also accumulating that use of FDCs for ART is cost saving to the programme. The use of separate drug products increases costs of production, packaging, shipping, storage, dispensing, transport to the service facilities, stock maintenance and human resource utilization at the facility in dispensing and prescribing. Countries with limited health systems infrastructure and capacity need to have a limited but adequate formulary to facilitate sustainable supplies at the facility level, FDCs assist in achieving this.

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[1] Pharmacokinetics of nevirapine in HIV-infected children receiving an adult fixed-dose combination of stavudine, lamivudine and nevirapine. Chokephaibulkit,K. Plipat, N. Cressey, T. Frederix, K. Phongsamart, W. Capparelli, E. Kolladarungkri, T. Vanprapar, N. AIDS 2005, 19*:*1495–1499.

[2] In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy. Daniel P. O'Briena, Delphine Sauvageotb, Rony Zachariaha and Pierre Humbleta for Medecins Sans Frontieres. AIDS 2006, 20:1955–1960

[3] Pharmacokinetics of Nevirapine, Stavudine, and Lamivudine in HIV-infected Children in Zambia Treated with Pediatric Fixed-dose Combination Tablets. Kabamba D, L'homme R , Ewings F, Mulenga V , Kankasa C , Thomason M, Walker S, Chintu C, Burger D , Gibb D, and The CHAPAS study group *CROI 2007 Session 103* Poster Abstracts 580

[4]Adherence to Long-Term Therapies - Evidence for Action available at: http://www.who.int/medicinedocs/collect/edmweb/pdf/s4883e/s4883e.pdf

3. **WHO Guidelines Review - Essential medicines for children**

The HIV department notes from the useful review that 4 ARV products recommended in the 2006 ART treatment recommendations for ART in children are not listed on the 14th EML and will work with HTP/PRU to ensure that all ARV products deemed essential are included or submitted in the EML and or children's Model list. Recent additions to the 15th Model list may have included some of the products and should be considered by the committee (Emtricitabine [FTC] as an alternative to 3TC, Efavirenz [EFV 600mg], FDC of AZT/3TC, and FDC of d4T/3TC/NVP).

4. **Position paper on Paediatric age Categories to be used in differentiating between listing on a model essential medicine list for children.**

The paper does not provide any evidence for the proposed categorisations, and refers to non primary sources as references. There is no reference to existing UN WHO definitions of terms e.g. infant, child, adolescent and inconsistency with those already recognized.
The table included provides little clarity and is not based on any of the parameters identified in the first section as being useful to guide selection of medicines. A simpler classification would be more useful as most countries with limited capacity, resources and infrastructure are not able to carry a large range of product forms and may even choose to avoid liquid forms wherever possible (e.g. Malawi national programme for child health and basic IMCI does not include liquid medicines).

5. **Off label use of medicines in the paediatric Populations: Recommendations for assessing appropriateness**

It will be important to include flexibility for inclusion of some medicines in an off label fashion, but also to ensure safeguards. Some antiretroviral medicines are now recommended to be used in an off label way based on more recent pharmacokinetic analysis (e.g. zidovudine and nevirapine). The proposed consideration of risk benefits analysis to identify where medicines could be included appears to be practical and pragmatic.

B) INDIVIDUAL PRODUCT APPLICATIONS FOR CHILDRENS MODEL LIST

Lamivudine- 150 mg tablet scored

HIV department welcomes the submission of a scored 150 mg Lamivudine tablet and recognizes it would be useful for treatment according to most recent WHO treatment recommendations (see Annex E page 83 in WHO recommendations available at http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf).

Abacavir -300mg tablet scored

HIV department welcomes the submission of a scored 300 mg Abacavir and recognizes it would be useful for treatment according to most recent WHO treatment recommendations (see Annex E page 91 in WHO recommendations available at http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf).

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Zidovudine/ Lamivudine tablet - 300mg/150mg scored

HIV department welcomes the submission of a fixed dose combination of 300 mg Zidovudine (azidothymidine) and 150 mg of Lamivudine scored, and recognizes it would be useful for treatment according to most recent WHO treatment recommendations (see Annex E page 114 in WHO recommendations available at http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf). This dual AZT/3TC FDC delivers the recommended preferred NRTI backbone that is required for 1st line ARV regimens in current WHO guidelines and can be used safely in children, even in children with common co-morbidities as tuberculosis and hepatitis B co-infection. Safety and efficacy data are available from single products to support the use of these drugs in combination. Data from adult populations suggest there are no drug-drug interactions, or other problems leading to reduced bioavailability of one or other agent in the FDC product.

Zidovudine and Lamivudine and Nevirapine (AZT/3TC/NVP) 60mg/30mg/60mg as a fixed dose scored tablet

HIV department welcomes the submission of a fixed dose combination of 60 mg Zidovudine (azidothymidine), 30 mg of Lamivudine and 60 mg of Nevirapine, and recognizes it would be useful for treatment according to most recent WHO ART treatment recommendations. This triple FDC delivers the recommended preferred 1st line ARV regimen. There is extensive experience with this combination, although not always as an FDC. An expert group, the WHO paediatric ARV working group (PAWG) has recognized this to be a preferred priority product, and has provided recommendations of safe dosing for this product in the meeting report of October 2006 (see annex VII in meeting report available at http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf).The dosing schedule proposed is the same as that proposed by the working group. It is noted that this is a product in development and bioavailability, dissolution and other quality dimensions for the actual product will be required.

Stavudine and Lamivudine and Nevirapine (d4T/3TC/NVP) 40mg + 10mg + 70 mg and 20mg + 5mg + 35 mg as fixed dose tablets

The HIV department welcomes the submission of the solid dispersible scored fixed dose products containing Stavudine (d4T), Lamivudine and nevirapine and note that the application is for use in children weighing 9- 31kg. This is an alternative first line ART regimen, and extensive data suggests good clinical efficacy, tolerability and acceptability. There is an increasing concern about the long-term toxicity (due to mitochondrial toxicity).This product was developed prior to the development of expert recommendations characterizing optimal or priority ARV fixed dose combination ARV products and so contains slightly different proportions of each active pharmaceutical agent than the products identified as optimal for simplified dosing. Other manufacturers

(e.g. CIPLA, Emcure and the Thai manufacturers GPOvir) have also now produced similar products with slightly different rations of API. The PAWG working group reviewed this product and modelled using a simple dosing assessment tool (http://www.who.int/hiv/paediatric/generictool/en/index.html) to determine what dosing would be expected to deliver safe and efficacious amounts of each active component (see also annex VIII in meeting report available at http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf). The experts concluded that this FDC could be used but have proposed a slightly different dosing schedule, mainly due to concerns about under dosing Nevirapine. (The recommended dosing proposed by the expert group for this ARV product is attached as annex). The expert group recommended that this product should not be used in children under 8.0 kg as in order to achieve adequate nevirapine and Lamivudine, Stavudine over dosing results.

The application includes tables that examine the requirements for the lowest weight at any given weight band with respect to nevirapine (provides range of 160- 200mg/$m^{2)}$ but do not include calculations for the larger child (e.g. for 9 kg the range of Nevirapine required is given as 67.9- 84.9 mg/m^2which is true for the 9.0 kg child but the requirement for a 9.9 kg child would be 72-90 mg/$m^{2,}$ and the actual amount delivered would be 70mg). The proposed dosing schedule could result in under dosing for selected children in 10-15 kg weight bands if dosed according to schedule provided.

OTHER COMMENTS ON ARV PRODUCTS:

The HIV Department would also like to note that there is need to include Lopinavir in a fixed dose combination with ritonavir **(LPV/r)** to the CEML. It is included on the EML for adults, and is the preferred protease inhibitor ARV for 2nd line ART. There is a new formulation available that has programmatic advantages as it is now heat stable tablet, and can be transported and stored without refrigeration. It is available in different dose strength as 200 mg/50 mg and a paediatric form 100mg/25mg, and both need to be included, as other protease inhibitors are not suitable for use in children or have inferior efficacy or safety profiles. This is not yet reflected in the 15th EML.

Other products

Proposal to include drugs for treating upper and lower respiratory infections.

A detailed systematic review of the paper and all the indications has not been undertaken by the HIV department The paper title suggest that there is special consideration of the HIV infected child, however this is not reflected in the text. Co-trimoxazole is however noted to be necessary as treatment for pneumocystis pneumonia, but this is not included in the indications for use. Dosing is not provided for prophylaxis. Evidence and further details of dosing are summarized in recently published WHO guidelines for use of co-trimoxazole available at http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf [5] and reviewed in BMJ clinical evidence. http://www.clinicalevidence.com/ceweb/conditions/hiv/2501/2501_I1.jsp.

[5] Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. WHO 2006

http://www.clinicalevidence.com/ceweb/conditions/hiv/0908/0908.jsp

Proposal to include drugs for treating fungal infections in children including opportunistic and inter current fungal infection in those infected with HIV.

This is a useful review and clearly identifies the lack of evidence for use of a range of newer agents against fungal infections in paediatric populations. The HIV department has not had time to do a systematic or thorough review of the paper; however key comments are summarized below.

Drug	**Comments**
Fluconazole	Agree should be included
Itraconazole	Advantages over and above fluconazole not clear
Amphotericin B	Required
Caspofungin	Further evidence required
Nystatin	Not clear why included as clotrimaxole and or micanozole already included
Clotrimazole, Terbinafine, Gentian violet, Potassium iodide, and Whitfield ointment	Agree should be included

ANNEX 1.
WHO Paediatric ARV working group dosing recommendations for Zidovudine / nevirapine/ Lamivudine FDC combination (60/60/30mg)

Weight range (kg)		Formulation	DOSE (tablets)	
			AM	PM
3	3.9	60/60/30 mg tablets	1	0.5
4	4.9	60/60/30 mg tablets	1	1
5	5.9	60/60/30 mg tablets	1	1
6	6.9	60/60/30 mg tablets	1	1
7	7.9	60/60/30 mg tablets	1.5	1.5
8	8.9	60/60/30 mg tablets	1.5	1.5
9	9.9	60/60/30 mg tablets	1.5	1.5
10	10.9	60/60/30 mg tablets	1.5	1.5
11	11.9	60/60/30 mg tablets	1.5	1.5
12	13.9	60/60/30 mg tablets	2	2
14	16.9	60/60/30 mg tablets	2	2
17	19.9	60/60/30 mg tablets	2.5	2.5
20	24.9	60/60/30 mg tablets	3	3
25	29.9	200/300/150 mg tablets	1	1
30	34.9	200/300/150 mg tablets	1	1

ANNEX 2.

WHO Paediatric ARV working group dosing recommendations for Ranbaxy FDC products of Nevirapine, Stavudine, and Lamivudine

COMBINATION (NVP/d4/3TC) FDC 5 (NVP/d4/3TC 35/ 5/20mg) FDC 10 (NVP/d4T/3TC 70/10/40 mg)

Weight range (kg)		Formulation	DOSE (tablets)		Formulation	DOSE (tablets)		Formulation	DOSE (tablets)	
			AM	PM		AM	PM		AM	PM
3	3.9	35/5/20 mg tablets	not recommended*		35/5/20 mg tablets	not recommended*		70/10/40 mg tablets	not recommended*	
4	4.9	35/5/20 mg tablets	not recommended*		35/5/20 mg tablets	not recommended*		70/10/40 mg tablets	not recommended*	
5	5.9	35/5/20 mg tablets	not recommended*		35/5/20 mg tablets	not recommended*		70/10/40 mg tablets	not recommended*	
6	6.9	35/5/20 mg tablets	2*	2*	35/5/20 mg tablets	2*	2*	70/10/40 mg tablets	1*	1*
7	7.9	35/5/20 mg tablets	2*	2*	35/5/20 mg tablets	2*	2*	70/10/40 mg tablets	1*	1*
8	8.9	35/5/20 mg tablets	2	2	35/5/20 mg tablets	2	2	70/10/40 mg tablets	1	1
9	9.9	35/5/20 mg tablets	2	2	35/5/20 mg tablets	2	2	70/10/40 mg tablets	1	1
10	10.9	35/5/20 mg tablets	2.5	2.5	35/5/20 mg tablets	2.5	2.5	70/10/40 mg tablets	1.5	1
11	11.9	35/5/20 mg tablets	2.5	2.5	35/5/20 mg tablets	2.5	2.5	70/10/40 mg tablets	1.5	1.5
12	13.9	35/5/20 mg tablets	3	3	35/5/20 mg tablets	3	3	70/10/40 mg tablets	1.5	1.5
14	16.9	70/10/40 mg tablets	2	2	35/5/20 mg tablets	3.5	3.5	70/10/40 mg tablets	2	2
17	19.9	70/10/40 mg tablets	2	2	35/5/20 mg tablets	4	4	70/10/40 mg tablets	2	2
20	24.9	70/10/40 mg tablets	2.5	2.5	35/5/20 mg tablets	4.5	4.5	70/10/40 mg tablets	2.5	2.5
25	29.9	200/30/150 mg tablets	1	1	35/5/20 mg tablets	6	6	70/10/40 mg tablets	3	3
30	34.9	200/30/150 mg tablets	1	1	35/5/20 mg tablets	6	6	70/10/40 mg tablets	3	3
		* stavudine (d4T) doses consistently high			* stavudine (d4T) doses consistently high			* stavudine (d4T) doses consistently high		