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30 October–3 November 2013
Palais des Congrès
Paris, France

PRACTICAL APPROACH TO WEIGHT BASED DOSING

Compounding in MSF

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MEDECINS SANS FRONTIERES

Managing Children with Drug-Resistant Tuberculosis
A Practical Approach
post-graduate course 31.10.2013

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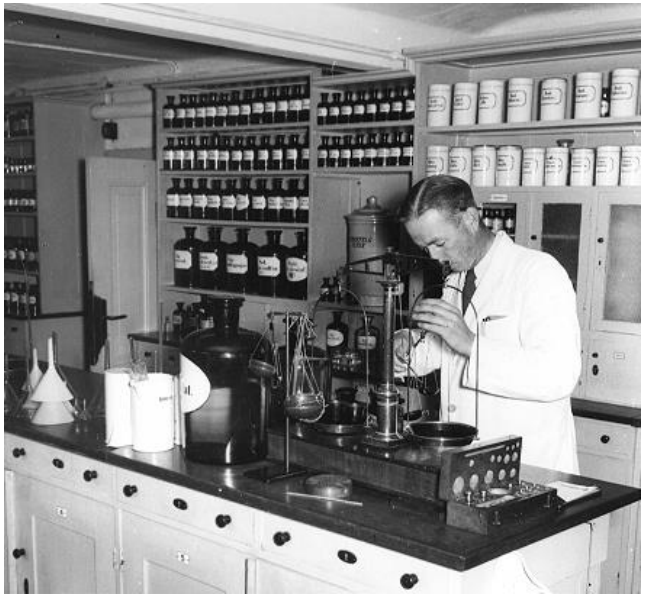

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THEORETICAL ASPECTS

Extemporaneous Preparation

- Medicines **prescribed by a physician** and **compounded by a pharmacist** to **fit the unique need of a patient** in the absence of a commercially available, authorized, **age-appropriate dosage** or form of a medicine

- **Mixture of a** active pharmaceutical ingredient or **commercially available finished product** - usually a solid dose form such as a tablet- with an appropriate vehicle(s)

- Preparations are based on **elaborated formulas and are manufactured through defined, standardized compounding procedures described in international pharmacopeias**

- **Stability limited to their period of storage and use**
- ***'Ad-hoc preparation'***

  Ad-hoc preparations are extemporaneous preparation meant to be **for immediate use** and cannot be prepared ahead

VERSUS

- ***'Manipulation***

  - Manipulation is not considered an extemporaneous preparation

  - **Dispersing** tablets in liquids, **crushing** tablets or **opening capsule** and **mixing the powder/content with food or a liquid vehicles** like juice, milk etc.

  - Immediate use

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Legal Aspects

- International and national laws
- Pharmacist entitled to compound and to dispense
- Prescription by licensed practitioner, patient-based

Country Specific

- Each country has own regulations for compounding in the pharmaceutical law
- Standards of preparations are set by the national/international pharmacopoeias

Risks and Limitations

- Explore alternatives
  a) Sourcing of commercially available pediatric products
  b) Therapeutic substitution
  c) Use of a preparation intended for a different route of administration
  d) Manipulation
- Lack of information on stability, bioavailability, safety and efficacy
- Risks minimized through evidence based formulas

Eligibility Criteria for Patients

- Accurate dosing of a substance
- Risk-benefit assessment based on over- and under-dosing of patients e.g. side effect, resistance profile
- Patient with swallowing problems

Quality Management in Projects

Quality Assurance System - Good Manufacturing Practices - Quality Control

Quality Assurance	Mean of control	Supervisor	Compounder	Dispensing Person
Protocols and procedures to use	Check lists of supervisor	**X**		
Starting material and compounding	Check lists and visual control	**x**	**X**	
Compounding	Check lists and visual control	**X**	**X**	
Stability of the preparation during shelf life	Visual control of preparation characteristics	**X**	**X**	
Stability of the preparation when dispensed	Visual control of preparation characteristics	**X**		**X**
Appropriate Dispensing Practices	Check lists of Supervisor and visual control of preparation characteristics	**X**		**X**

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PRACTICAL ASPECTS

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Liquid Vehicle: ORA-BLEND®

Brand name and Manufacturer	Composition/ Characteristics	Storage condition and stability
Ora-Blend® Fagron SAS	**- Composition:** Purified water, sucrose, glycerine, sorbitol, flavouring, microcrystalline cellulose, etc. **- Preserved** **- pH** 4.2	**Storage condition:** Room temperature (<25° C) **Use after opening:** 90 days
Ora-Blend® SF	**- Composition:** Sugar Free (Saccharine)	

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	Syrspend SF liquide	Syrspend SF poudre	Syrsend SF Alka poudre	Kit Syrspend SF alka omeprazole
Produits				
Goût	Neutre, raisin, cerise	Neutre	Neutre	Neutre, cerise
Volume	450ml	100ml	100 / 200ml	100 / 200ml
Forme	Liquide	Poudre à reconstituer	Poudre à reconstituer	Poudre à reconstituer + oméprazole + seringue + Mode opératoire + notice
PH	4,2		>7	
Stabilité	**Actifs stables milieu acide**		**Actifs stables milieu basique**	

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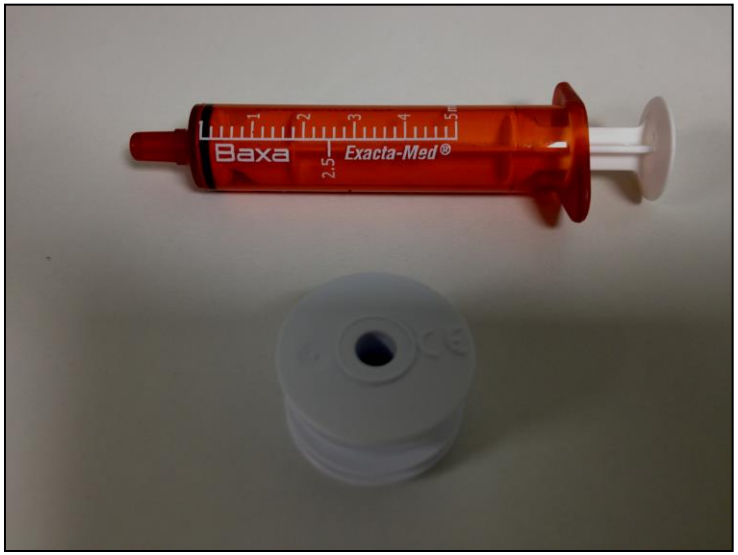
Compounding Material

Overview of basic compounding utensils (porcelain and Melamine mortar and mortar scrapers) and handling of the ‘stand for pallet knife’ (mortar scraper, pestle, pallet knife)

Dispensing Material



Orifice Reducer and oral syringes (1-10ml)

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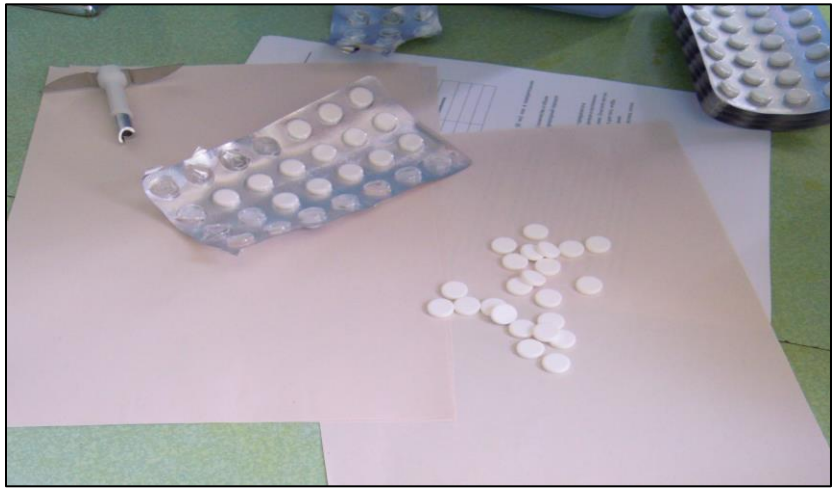
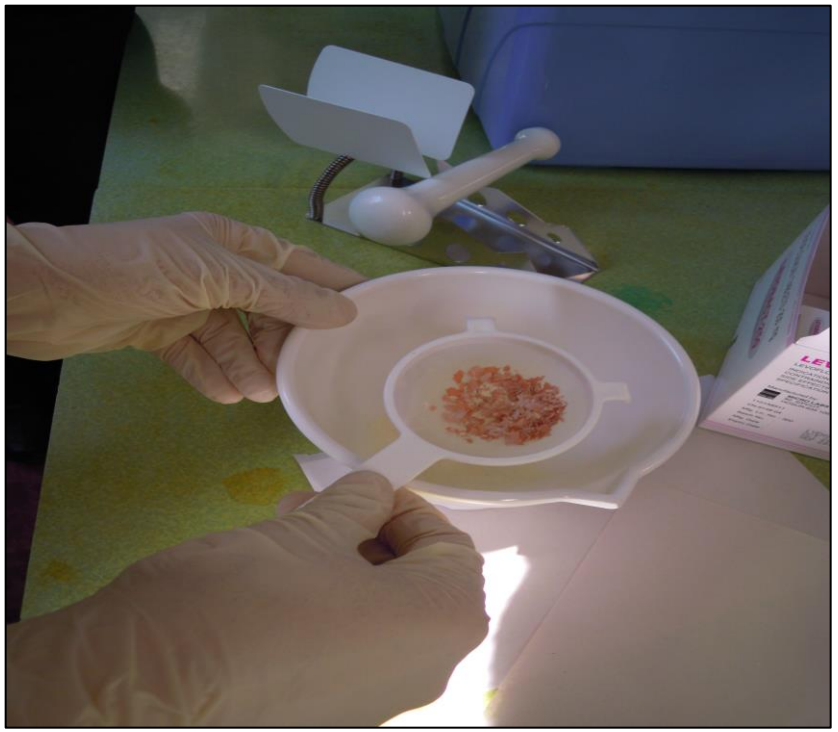
Compounding – Practice in the Field





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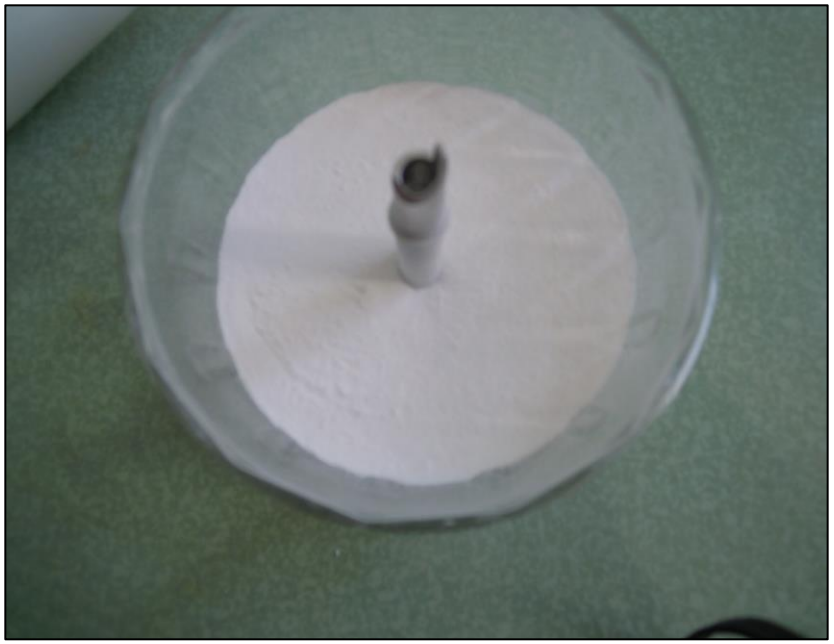

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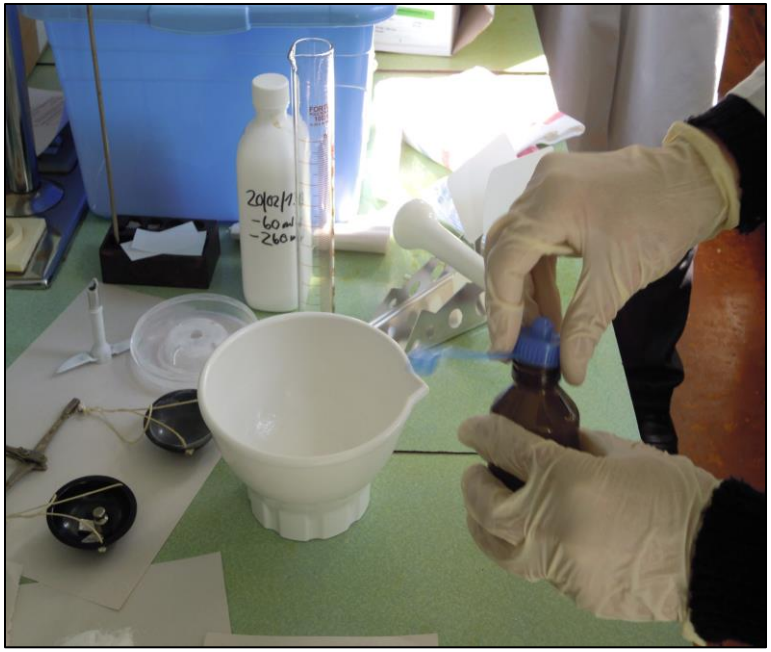

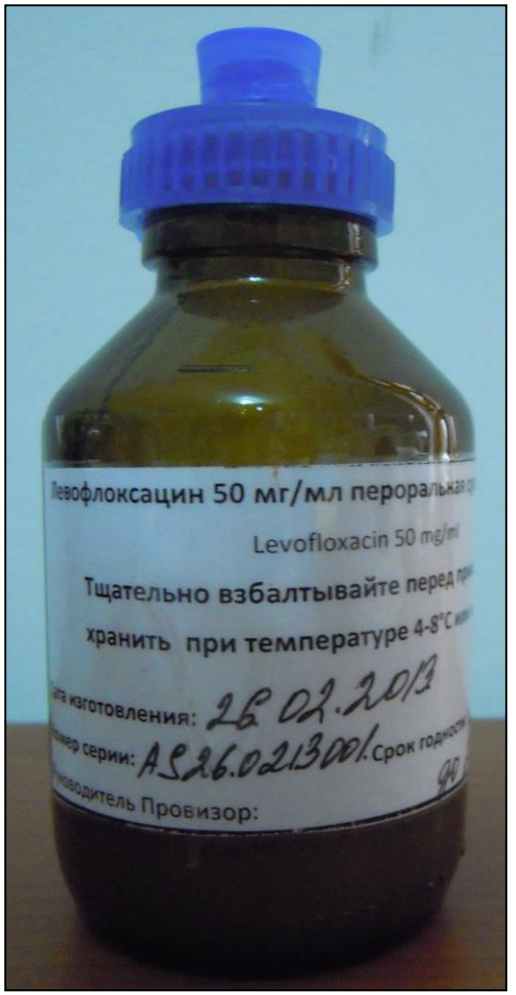

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MSF COMPOUNDING GUIDELINES

Moxifloxacin 24 mg/ml oral suspension – 100 ml

The preparation must be compounded respecting European or US Good Manufacturing Practice guidelines and following good compounding procedures as described in the European or United States Pharmacopoeias.

Formula

Ingredients	Quantity
Moxifloxacin 400 mg tablet	6 tablets
Ora-Blend® (Paddock Laboratories)	100 ml
Total	100 ml

Compounding procedure

Crush6 moxifloxacin tablets in a porcelain mortar and reduce to a fine, uniform powder. Transfer the powder to a synthetic mortar, if necessary sieve the powder from coating remnants. Add a small amount of Ora-Blend® to the powder and mix to a uniform paste. Then continue mixing while adding the vehicle in incremental proportions to 100 ml for a smooth homogenous suspension. Scrape the pestle and mortar at least twice with a plastic card or a spatula to make sure that no powder sticks to the surface, rinse mortar with vehicle and then continue mixing. Transfer the suspension into a 100 ml amber bottle. Close the bottle with a paediatric dosing cap and shake the suspension.

Storage Conditions: amber glass; below 25°C
Shelf life: 90 days

Dispensing Instructions: shake well before use

Description: milky, homogenous suspension; easily resuspendable

Available presentation (MSF ITC catalogue)**:** 400 mg tablets

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MOXIFLOXACIN

Dosage

– Patient < 30 kg: 7.5 to 10 mg/kg once daily
– Patient ≥ 30 kg: 400 mg once daily
– Maximum daily dose: 400 mg

Age	Weight (kg)	Daily dose (mg)	Available presentation	Compounded oral suspension 24 mg/ml
			400 mg tablet	
	3	22.5-30		1.0 ml
1 month	4	30-40		1.5 ml
2	5	37.5-50		2.0 ml
3	6	45-60		2.0 ml
4-6	7	52.5-70		2.5 ml
7-9	8	60-80		3.0 ml
10-11	9	67.5-90		3.5 ml
1 year	10	75-100	¼ tab	3.5 ml
	11	82.5-110	¼ tab	4.0 ml
	12	90-120	¼ tab	4.5 ml
2 years	13	97.5-130	¼ tab	4.5 ml
	14	105-140	¼ tab	5.0 ml
3 years	15	112.5-150	¼ tab	5.5 ml
	16	120-160	¼ tab	6.0 ml
4 years	17	127.5-170	¼ tab	6.0 ml
	18	135-180	½ tab	6.5 ml
5 years	19	142.5-190	½ tab	7.0 ml
	20	150-200	½ tab	7.5 ml
6 years	21	157.5-210	½ tab	
	22	165-220	½ tab	
	23	172.5-230	½ tab	
7 years	24	180-240	½ tab	
	25	187.5-250	½ tab	
	26	195-260	½ tab	
8 years	27	202.5-270	½ tab	
	28	210-280	½ tab	
	29	217.5-290	½ tab	

(alternatives)

the dosage

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Child's weight (kg)	Total daily dose (mg)		Oral suspension 24 mg/ml	
	7.5 mg/kg	10 mg/kg	Total volume to administer per day (ml)	Corresponding administered dose (mg)
3	22.5	30	**1.0**	**24**
4	30	40	**1.5**	**36**
5	37.5	50	2.00	48
6	45	60	2.00	48
7	52.5	70	2.50	60
8	60	80	3.00	72

Compo

Moxifloxacin 24 mg/ml oral suspension – 100 ml

Patient	
Project	
Name of Compounder	
Name of Supervisor	

Manufacture Date	
Batch Number	
Shelf life	90 days
Expiry date (dd/mm/yy)	

Manufacturing utensils	**Packaging**
Porcelain Mortar & Pestle	100 ml or 250 ml amber glass bottle
Synthetic Mortar & Pestle	Paediatric dosing cap
100 ml or 200 ml graduated cylinder	Label
Plastic cards **OR** spatula	**Signature of Supervisor**
Spatula holder	

Starting material			
Ingredients	***Manufacturer***	***Batch Number***	***Expiry date***
Moxifloxacin 400 mg tablet			
Ora-Blend® syrup	Paddock Lab.		

Quantities	**Original**	**Calculated**	**Measured**	**Quality Control Signatures**	
Ingredients	*Formula*	*Quantity to be compounded*	*Quantity to be compounded*	*Compounder*	*Supervisor*
Moxifloxacin 400 mg tablet	6				
Ora-Blend® syrup	100 ml				
TOTAL	100 ml				

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Compounding:

- ☐ Count the total number of tablets and put them on a paper towel
- ☐ Measure the corresponding quantity of Ora-Blend® using a graduated cylinder.
- ☐ Have supervisor checked the number of corresponding tablets and syrup volume (before starting the compounding process. (*sign on 'compounding protocol'*)
- ☐ Crush the tablets in a mortar to reduce to a fine, uniform powder *(show to supervisor for validation)*
- ☐ Transfer the powder into the synthetic mortar
- ☐ If necessary sieve the powder from coating remnants to improve pharmaceutical elegance.
- ☐ Add a small amount of Ora-Blend® to the powder and mix to a uniform paste. Continue mixing while adding vehicle in incremental proportions to the final volume for a smooth homogenous suspension. Scrape the pestle and mortar at least twice with a plastic card or a spatula to make sure that no powder sticks to the surface, and then continue mixing.
- ☐ Rinse mortar with vehicle, use the plastic cards or the spatula to gather the suspension from the mortar and pestle and transfer the suspension into the suitable amber bottle.
- ☐ Close the bottle with a paediatric dosing cap and shake the suspension.

Compounding observation:

.....

.....

.....

Copy of the label:

Moxifloxacin 24 mg/ml oral suspension – 100 ml
Shake Well Before Use – Store below 25°C

Patient's Name:.....

Dosing Instructions: .....

Batch No:..... **Expiry Date**:...../...../.....

Supervisor: .....

Packaging: .....

Storage Conditions: amber glass; below 25°C

Signature of Compounder **Signature of Supervisor**

....

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TADJIKISTAN FIRST PILOT PROJECT

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- Children with MDR-TB
- Dushanbe and Kulyab
- Post-Sowiet context
- In- and out-patient care of MoH with MSF support
- Preparations: E, Z, Lfx, Mfx, Cs, Pto

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Challenges in the Field

- **Eligibility criteria for patients**
- **Quality management**, e.g. supervision and training of health staff for drug administration counselling
- Higher ADE under syrup (nausea and vomiting)
- Storage conditions and shelf life of syrups, when working in remote areas (home based care)
- Outsourcing of the compounding to national laboratory

NEXT STEPS

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Swaziland, pilot project

- Training and implementation in November 2013
- Compounding will be done in MSF
- Participation of NGOs and MoH at the training

R&D

- Stability studies for higher temperature (>25˚C) out sourced to *Fagron*
- New formulas to be included
- New vehicle of *Fagron* shows promising characteristics

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Special thanks to my MSF colleagues for their support during development , implementation and evaluation of the compounding project

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