



PRELIMINARY QSM PROPOSALS FOR CONSIDERATION BY THE WHO EXPERT COMMITTEE ON THE SELECTION AND USE OF ESSENTIAL MEDICINES

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WHO Model List of Essential Medicines (EML) **WHO Model List of Essential Medicines for Children (EML-C)**

Preliminary QSM proposals

Considering the importance of the EMLs, it is proposed that the **Explanatory Notes** are expanded to provide more information and guidance to users of the lists on interpretation of certain aspects. Two issues on which it is considered that guidance would be beneficial are dosage form terminology and the expression of medicine strength. Separate draft texts are provided on these issues for consideration for inclusion in the Explanatory Notes.

The publication of new editions of the EMLs is also an opportunity to communicate a key tenet of WHO Medicines policy - that quality, safety and efficacy are inseparable. Safety and efficacy of medicines can only be assured if due attention is paid to quality throughout the life cycle of a medicine from "patent to patient". Inclusion in the Explanatory notes of a link to the Quality Assurance area of WHO Medicines website would allow users of the EML to easily access the extensive advice and guidance that WHO has to offer in this area.

A draft revision of the Explanatory Notes, illustrating how the above aspects might be incorporated and with other suggested changes is provided for consideration.

Dosage form terminology

The draft text provided for consideration for inclusion in the Explanatory Notes (as Annex 1) gives terms for "Principal dosage forms used in EML" and "Other dosage forms" and indicates what is and is not covered by each term. It is recommended that in describing dosage forms within the EML the "main terms" given in the draft text are used, whenever appropriate.

Medicine strength

While for many entries in the EMLs the statements concerning the strengths available are straightforward and clear, there are some for which the situation is complicated and for which clarification is required. It is strongly recommended that the EMLs provide users with guidance on the interpretation of the statements and that the entries are checked to ensure that they are consistent with such guidance. The draft text provided for consideration for inclusion in the Explanatory Notes (as Annex 2) gives guidance in a relatively brief form.

The following discussion is intended to provide additional background information, to set out the issues in some detail and to draw some conclusions/make some recommendations.

Background information

The EML has a clinical/treatment basis - it is essentially a list of medicines! The main message to be conveyed is that provided in the left-hand column.

The "medicine" entries in the left-hand column in the EML are for active moieties that is, they normally use the International Nonproprietary Name (INN) alone*.

[***Note:** A few of these entries specify the chemical form of the API by using the INN.M. When they do, it is because the form is considered to have a significant effect/ to be a different medicine (e.g. procaine benzylpenicillin).]

Entries in the right-hand column of the EML are intended to provide information on the dosage forms and on the strengths (for example, the weight per tablet) of products available in the WHO Member States. An active substance used in manufacturing a dosage form, the active pharmaceutical ingredient (API), may be the active moiety *per se* or it may consist of the active moiety together with one or more additional chemical groups/ radicals, depending on the nature of the molecule. Commonly APIs are salts, esters or hydrates of the active moiety. In naming many APIs it is therefore necessary to use a Modified International Nonproprietary Name (INN) which consists of the name of the active moiety plus the name of the group/ radical. Many of the APIs used in manufacturing the dosage forms mentioned in the EMLs are defined within monographs (quality specifications) in *The International Pharmacopoeia*.

The way that the strengths of dosage forms are expressed in the entries in the right-hand column of the EML reflects the way that the strength of products available on the market in WHO Member States is declared, that is, how currently available products are labelled. This in turn should, of course, be consistent with how doses are expressed. It is emphasized that WHO has no control over product labelling.

Because an active substance used in making a pharmaceutical product (APIs) may be the active moiety itself or a modified form of the active moiety and because some active moieties may exist in several different modified forms as APIs, different cases can be described in increasing order of complexity:

- In cases **where the API is the active moiety**, the expression of strength of all products will be in terms of the active moiety and the right-hand column entry in the EML is straightforward.
An amount given in the right-hand column is to be interpreted as an amount of the active moiety listed in the left-hand column.

Example: For paracetamol, the tablet strength of 100 mg to 500 mg is to be interpreted as 100 mg to 500 mg of paracetamol.

- In cases **where the API is not the active moiety**, the entry in the right-hand column in the EML indicates the form of the API used in the dosage form (by specifying the name of the salt, ester etc in brackets).
 - Where the strength of products available in the Member States is expressed in terms of the active moiety, the name of the salt, ester etc specified in brackets is preceded by the word "as".
An amount given in the right-hand column of the EML is to be interpreted as an amount of the active moiety listed in the left-hand column.

*Example: for the active moiety **ampicillin**, ampicillin sodium is used as the API in manufacturing the powder for injection; the strengths of "500 mg and 1 g (as sodium salt)" are to be interpreted as 500 mg and 1g of ampicillin.*

[**Note:** In such cases, any monograph for the specific dosage form(s) in *The International Pharmacopoeia*, will include a Labelling statement to the effect that the quantity should be indicated in terms of the equivalent amount of [active moiety].]

- Where the strength of products available in the Member States is expressed in terms of the API, the name of the salt, ester etc specified in brackets is given alone.
An amount given in the right-hand column of the EML is to be interpreted as an amount of the salt ester etc (specified in brackets) of the active moiety listed in the left-hand column.

*Example 1: for the active moiety **codeine**, codeine phosphate is used as the API in manufacturing the tablets; the strength of "15 mg (phosphate)" is to be interpreted as 15 mg of codeine phosphate.*

*Example 2: for the active moiety **ethambutol**, ethambutol hydrochloride is used as the API in manufacturing the tablets; strengths of "100-400 mg (hydrochloride)" are to be interpreted as 100-400 mg of ethambutol hydrochloride.*

Note: For clarity and consistency, however, the entries for combinations including ethambutol need amendment to the right-hand column to add "(hydrochloride)" after the relevant weight; eg for isoniazid + ethambutol, tablet strength should read 150 mg + 400 mg (hydrochloride).

- In some cases **several different APIs exist for a single active moiety**; the different APIs may be used in manufacturing different types of dosage forms or in the same type of dosage form supplied as different products by one or more manufacturers.

Example: for morphine, the injection strength of 10 mg (morphine hydrochloride or morphine sulfate) is to be interpreted as 10 mg of morphine hydrochloride or 10 mg of morphine sulfate, depending on which API was used in the manufacture of the product.

In the more complex cases above, confusion occurs when product labelling is not clear as to what the strength refers and/or when different expressions of product strength are used in different Member States or by different manufacturers within a single Member State. In certain instances such confusion can give rise to serious problems; the potential for medication errors can impact upon patient safety and treatment outcomes. The seriousness of the problem will depend on a number of factors concerning the use of the medicine including the disease/condition that it is used to treat/prevent and how widely and by whom it is prescribed and administered.

Confusion and problems are most likely in relation to certain long-established medicines for which different salts are used as APIs and/or where there is non-equivalence of the strengths available. Confusion and problems can also occur where there are significant difference between the molecular weight of the active moiety and the API.

During the 4th UN Prequalification stakeholders meeting held in February 2009, UNICEF used the example of the confusion relating to the strength of amodiaquine products to illustrate challenges they faced in relation to product labelling and package inserts.

Conclusions/recommendations

WHO cannot be expected "wave a magic wand" and remove all inconsistencies that have arisen over time in relation to pharmaceutical products currently available across the world. Such inconsistencies may reflect local or regional differences or long established practices.

As noted above WHO has no control over product labelling; as with other aspects of pharmaceutical products labelling is the responsibility of the manufacturers and the Drug Regulatory Authorities (DRAs).

WHO can be expected to:

- Provide clarity and transparency within WHO publications (EML, Treatment Guidelines, Formulary, International Pharmacopoeia etc). In the EML this could be achieved by providing:
 - general guidance on interpretation of statements
 - specific warning notes for entries where there is known to be confusion, inconsistencies or problems (an indication of the problem could be included in the relevant entry of the EML or in the WHO Model Formulary with a cross-reference in the EML)

WHO might also be expected to work with partners (DRAs*, manufacturers, suppliers (eg UNICEF) pharmacopoeial authorities, professional bodies etc) to:

- Offer guidance on correct approach *for new APIs*
- Encourage and improve consistency for all medicines

*raise at next ICDRA ?

Background documents consulted

EML 15th edition (March 2007)

http://www.who.int/medicines/publications/08_ENGLISH_indexFINAL_EML15.pdf

Explanatory notes to EML 14th edition (March 2005)

http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf

WHO Model Formulary, 2008 http://www.who.int/selection_medicines/list/WMF2008.pdf

The International Pharmacopoeia, Fourth Edition including First Supplement 2008

<http://www.who.int/phint>

Preface to International nonproprietary Names (INN) for pharmaceutical substances: Names for radicals, groups & others, comprehensive list, WHO/PSM/QSM/2007.1

International Nonproprietary Names Modified, INN working document 05.167/3

British Pharmacopoeia 2009, TSO (especially Supplementary Chapters I F: Declaration of content, I G: Labelling and II B: Monograph titles for Formulated Preparations)

United States Pharmacopeia, USP 31 2008

Martindale 35th Edition, Pharmaceutical Press, London

APPENDIX 1

16th edition

QSM revision proposals Essential Medicines

WHO Model List (revised March 200)

Explanatory Notes

The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol** () is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price. Medicines are listed in alphabetical order, within sections.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable. For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website
http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/index.html.

Dosage forms of medicines are listed in alphabetical order and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

Dosage form terminology

The main terms used for dosage forms in the Essential Medicines List are as shown below (Annex 1). Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* <http://www.who.int/medicines/publications/pharmacopoeia/en/index.html>

[Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.] *this text can be deleted as moved to Annex 1.*

[Crushable, chewable and dispersible tablets may be easier to administer to paediatric populations and to the elderly.] *this text can be deleted as moved to Annex 1.*

Medicine strength

Guidance on the interpretation of information given in the Essential Medicines List for strengths (for example, the weight per tablet) of products available in the WHO Member States is shown below (Annex 2).

APPENDIX 2

WHO Model List of Essential Medicines (EML) WHO Model List of Essential Medicines for Children (EML-C)

Explanatory Notes: Annex 1

Dosage form terminology

A. Principal dosage forms used in EML

Oral administration

Tablets

Entries in which the term **tablet** is used without further qualification, are intended to allow/cover the following types of tablet:

- uncoated or coated (film-coated or sugar-coated)
 - those tablets that are intended to be swallowed whole*
 - unscored
 - scored*

*Scored tablets may be divided for ease of swallowing, provided dose is a whole number of tablets.

and also to allow/cover, where appropriate:

- those tablets that are intended to be chewed before being swallowed
- those tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed
- those tablets that are intended to be crushed before being swallowed

The term **tablet** is qualified with an additional term (in parentheses) in entries where one of the following types of tablet is *specifically* intended:

- **chewable** - tablets that are intended to be chewed before being swallowed
- **dispersible** - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed
- **soluble** - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed
- **crushable**¹ - tablets that are intended to be crushed before being swallowed
- **scored**² - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet

Note: Crushable, chewable and dispersible tablets may be easier to administer to paediatric populations and to the elderly.

Entries in which the term **tablet** is used without further qualification, are *never* intended to allow any type of modified-release tablet. The term **tablet** is therefore *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended:

- **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release)
- **prolonged-release**
- other modified-release form

The term **tablet** is *always* qualified with an additional term (in parentheses) in entries where the following type of tablet is intended:

- **sublingual** - those tablets that are intended to be placed beneath the tongue

Capsules

Entries in which the term **capsule** is used without further qualification, are intended to allow hard or soft capsules.

Entries in which the term **capsule** is used without further qualification, are *never* intended to allow any type of modified-release capsule. The term **capsule** is therefore *always* qualified with an additional term (in parentheses) in entries where one of the following types of capsule is intended:

- **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release)
- **prolonged-release**
- other modified-release form

Granules

Entries in which the term **granules** is used without further qualification, are intended to allow preparations that are issued to patient as granules to be swallowed as such, to be chewed, or to be taken in or with water or another suitable liquid

Entries in which the term **granules** is used without further qualification, are *never* intended to allow any type of modified-release granules. The term **granules** is therefore *always* qualified with an additional term (in parentheses) in entries where one of the following types of granules is intended:

- **gastro-resistant** (such granules may sometimes be described as enteric-coated or as delayed-release)
- other modified-release forms

Oral powder

Entries in which the term **oral powder** is used are intended to allow preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid

Oral liquid

Entries in which the term **oral liquid** is used are intended to allow liquid preparations intended to be *swallowed* i.e.

- oral solutions, suspensions, emulsions and oral drops
 - including those constituted from powders or granules

but *not* those preparations intended for *oromucosal administration* e.g. gargles and mouthwashes

Note: Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

Parenteral administration

Injection

Entire in which the term **injection** is used are intended to allow

- solutions, suspensions and emulsions
 - including those constituted from powders or concentrated solutions

The term **injection** is qualified by (**oily**) in relevant entries.

In some entries the route of administration is indicated (in parentheses).

Intravenous infusion

Entries in which the term **intravenous infusion** is used are intended to allow

- solutions and emulsions
 - including those constituted from powders or concentrated solutions

B. Other dosage forms

Administration to the eye

Use following terms -

- **Eye drops**
- **Eye ointments**

Topical administration

Use following terms -

for semi-solids

- **Cream**
- **Ointment**

for liquids

- **Lotions**
- **Paints**

Rectal administration

Use following terms -

- **Suppositories**

Vaginal administration

Use following terms -

- **Pessaries or Vaginal tablets**

For administration by inhalation

Use following terms -

- **Powder for inhalation**
- **Pressurized inhalation**
- **Nebuliser solution**

EML may wish to allow choice between these three types of preparation for inhalation

Notes and questions from QSM

At its October 2007 meeting the Expert Committee on Specifications for Pharmaceutical Preparations agreed that the general monographs for dosage forms in *The International Pharmacopoeia* should be reviewed and, where necessary, revised. In reviewing the general monograph for Tablets, the need to provide specific requirements for additional types of tablet will be considered. Attention is drawn to the following points on which comment would be appreciated.

1. **Crushable tablets** It is understood that "crushable tablets" are proposed as being suitable for administration to children. What is the definition of a crushable tablet? How are the crushed tablets intended to be administered? Are they intended to be swallowed as such, to be chewed, or to be taken in or with water or another suitable liquid?

Alternatively, are they intended to be sprinkled on or mixed with food? Could this give rise to problems such as (1) not receiving full dose of medicine - if food not all eaten or (2) being put off food if medicine has unpleasant taste?

2. **Scored tablets** In reviewing the general monograph for Tablets it is intended to consider the need for inclusion of a section dealing with scored tablets. Many tablets are presented with break-marks (scored).

If the break-mark(s) is/are intended to facilitate breaking the tablet simply for ease of swallowing a dose consisting of one or more whole tablets, the scoring is not critical.

However, if the break-mark(s) is/are intended to permit accurate sub-division of the tablet in order to provide doses of less than one tablet, the scoring is critical. In these cases the manufacturer must address the effectiveness of break-marks during the development of a product and be able to satisfy the appropriate regulatory authority with regard to this aspect of product quality. The manufacturer needs to be able to demonstrate the uniformity of mass of the subdivided parts in order to ensure that the patient receives the intended dose. This is important for both efficacy and, for drug substances with a narrow therapeutic range, safety.

APPENDIX 3

WHO Model List of Essential Medicines (EML) WHO Model List of Essential Medicines for Children (EML-C)

Explanatory Notes: Annex 2

Medicine strength

The medicines listed in the left-hand column of the EML are usually named as the active moieties, using the International Nonproprietary Name (INN), wherever applicable.

Entries in the right-hand column of the EML are intended to provide information on the dosage forms and on the strengths (for example, the weight per tablet) of products available in the WHO Member States.

An active substance used in manufacturing a dosage form, the active pharmaceutical ingredient (API), may be the active moiety *per se* or it may consist of the active moiety together with one or more additional chemical groups/ radicals, depending on the nature of the molecule. Commonly APIs are salts, esters or hydrates of the active moiety and are named using an appropriate Modified INN (INNM).

The way that the strengths of dosage forms are expressed in the entries in the right-hand column of the EML reflects the way that the strength of products available on the market in WHO Member States is declared, that is, how the products are labelled.

In cases where the API is not the active moiety, the entry in the right-hand column in the EML indicates the form of the API used in the dosage form (by specifying the name of the salt, ester etc in brackets).

- Where the strength of products available is expressed in terms of the active moiety, the name of the salt, ester etc specified in brackets is preceded by the word "as". An amount given in the right-hand column of the EML is then to be interpreted as an amount of the active moiety listed in the left-hand column.

Example: for ampicillin, the powder for injection strengths of 500 mg and 1 g (as sodium salt) are to be interpreted as 500 mg and 1g of ampicillin.

- Where the strength of products available is expressed in terms of the API, the name of the salt, ester etc specified in brackets is given alone. An amount given in the right-hand column of the EML is then to be interpreted as an amount of the salt ester etc (specified in brackets) of the active moiety listed in the left-hand column.

Example: for codeine, the tablet strength of 15 mg (phosphate) is to be interpreted as 15 mg of codeine phosphate.

- For a small number of medicines, in particular certain long-established medicines for which different salts are used as APIs, there are significant differences in the way that

products available in WHO Member States are labelled with respect to strength. Where necessary, in these and other instances of potential confusion, a warning note is included. In such cases further guidance may be found in the WHO Model Formulary.

Draft for consideration