eEML

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Business case – Vision, Targets, and Outline

Vision
Within the next 5 months, the Model list of Essential Medicines will be made available as a modern and comprehensive online information resource, and referred to as eEML (electronic Essential Medicines List). The vision is that the eEML will be accessible online for the purpose of data searches and downloads; in addition, editing and updating the EML and related information will also be carried online and greatly facilitated the efficiency and effectiveness of the EML review and dissemination process.
Targets
The project is based on the following targets:

- The EML will be transformed from a static PDF document into a modern web-based information solution, the eEML online platform.
- The project will be built upon the existing PAHO-PRAIS project, revamping it.
- The eEML platform will be based on a design concept which allows EML contents to be digitalized following a standardized and highly summarized information template, facilitating its future updates and integration with WHO Guidelines.
- The proposed eEML online platform will present two distinct key components: EML information and Expert Committee decisions (e.g. ATC codes, medicine first listed in year), and scientific information supporting the decisions (e.g. magnitude of benefit).
- The eEML will incorporate evidence from other WHO documents, such as guidelines and vaccine position papers. When there are no guidance documents developed directly by WHO, the eEML will be able to incorporate evidence from third parties (e.g. Cochrane).
- The reference information will serve as a knowledge repository, offering seamless integration of data shared with partner organizations (e.g. PAHO, Wikipedia).
- Access to the information provided in the EML platform will be public and free of charge and is subject to the WHO corporate and partners’ copyright and licensing schemes.

Project summary outline
The project covers the entire process from requirements gathering, design to testing and full implementation as a WHO online platform.

1. **Approach:**
Based on proven IT project and development methodologies, the project shall handle the full process for implementing a simple and yet efficient web-based business solution.

2. **Challenges and dependencies:**
The project identifies and addresses potential outside IT, and presents possible mitigation strategies and/or solutions. For example:
   - Availability of resources (scientific and editorial) and clearly documented process for maintaining all EML and related contents;
   - Establishing purpose and nature of linkages to external data sources and permissions for reuse/connecting to/integrating external resources from non-WHO entities.

3. **Solution design and deployment:**
The solution can be developed and implemented by a competent and reliable IT solution provider, either as Microsoft IIS or Apache/Linux, should be Internet browser independent (support IE10+, Firefox, Chrome latest versions, shall not require installation of software components on the client-side (i.e. the user’s computer/device).

4. **Timeframe:**
The solution shall be developed and deployed within a 5-month period, and released to the Internet (go-live) no later than 5 months after project start.
The eEML Project

The following chapters outline the project, providing descriptions of major functional and non-functional requirements for the development of the eEML online platform.

What has been done previously? EML and IT solutions

This is not the first time that the Department of Essential Medicines and Health Products (EMP) has endeavored to unlock the contents and information related to Essential Medicines to make them more accessible through digital data technologies. A previous IT solution existed from 2007 to 2010. The EML database was extended to incorporate information from the WHO Model Formulary, but ultimately failed due to content (high editorial workload, complex updates) and technology challenges (a slow web-based editor, browser dependent, with security limitations). The IT solution had been unsuccessfully outsourced, as it was passed to Pan America Health Organization (PAHO) in 2010 and abandoned in 2011. However some basic contents related to the EML can be still viewed and searched for on PAHO website: the WHO lists and evidence summaries. This former IT solution also allowed a basic comparison between the WHO Model List and National Lists. Some of the features of the former IT solution are still valid: presenting complex information in a plain-language and synthetic format. These can be editorially challenging, but are, at the same time, enhancing the value of the information by making it more easily understood by the user. Examples of previous web based essential medicines tools are presented at the end of this document.

The EML Revival Project needs to address lessons learnt from past experiences.

Background – The EML process

On behalf of WHO, the Department of Essential Medicines and Health Products EMP is responsible for maintaining the Model List of Essential Medicines (EML), a major reference document for healthcare systems, health practitioners and medicines supply organizations globally. The Model List is routinely revised by members of the Expert Committee on Selection and Use of Essential Medicines every 2 years. Following submission of applications for change of/addition to/removal from the list and the Expert Committee deliberations, an updated version of the EML is published as part of the WHO Technical Report Series with guidance and evidence information, on the WHO web site (2015 EML TRS) and in hard copy and distributed to various health related audiences. Each list has a unique number and highlights the changes compared to previous lists.

The WHO EML serves as a baseline for further modification (addition and deletion of new medicines), presentation of available dosage strength, and formulation depending upon the national priorities and available evidence. The WHO EML has steadily grown in terms of the number of medicines included in the list with each update. Initially in 1977, the WHO EML had 204 molecules and the current list of 2015 includes 409 unique molecules, with multiple occurrences across indications.

Medicines on the EML are classified in core and complementary listings. Core list medicines are defined as efficacious, safe, and cost-effective medicines for priority conditions, based on public-health relevance and potential for safe and 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.

A further List was established in 2007 and continues to exist: the Essential Medicines List for Children (EMLc), which is a subset from the essential medicines list for adults. The EMLc specifically incorporates medicines for paediatric- and child-specific indications, and age-appropriate dosage forms and strengths of medicines (e.g., suspensions, dispersible tablets, etc.)

Medicines shown in the EML can be accompanied by a square box symbol. The intended purpose of the square box is to highlight pharmacological classes or groups of medicines from which health professionals or countries can assume homogenous efficacy and safety, and select the most appropriate single medicine based on price, local availability, patient’s value and preferences, etc.

An example of the final listing of medicines is provided in Table 1.
Table 1: Spreadsheet frame listing essential medicines.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10. MEDICINES AFFECTING THE BLOOD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>10.1 Antianaemia medicines</strong></td>
<td></td>
</tr>
<tr>
<td>ferrous salt</td>
<td>Oral liquid: equivalent to 25 mg iron (as sulfate)/ mL.</td>
</tr>
<tr>
<td></td>
<td>Tablet: equivalent to 60 mg iron.</td>
</tr>
<tr>
<td>ferrous salt + folic acid</td>
<td>Tablet: equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy).</td>
</tr>
<tr>
<td>folic acid</td>
<td>Tablet: 400 micrograms*; 1 mg; 5 mg.</td>
</tr>
<tr>
<td></td>
<td>*periconceptual use for prevention of first occurrence of neural tube defects.</td>
</tr>
<tr>
<td>hydroxocobalamin</td>
<td>Injection: 1 mg (as acetate, as hydrochloride or as sulfate) in 1- mL ampoule.</td>
</tr>
<tr>
<td><strong>10.2 Medicines affecting coagulation</strong></td>
<td></td>
</tr>
<tr>
<td>enoxaparin*</td>
<td>Injection: ampoule or pre-filled syringe</td>
</tr>
<tr>
<td></td>
<td>20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.</td>
</tr>
<tr>
<td></td>
<td>*Alternatives are limited to nadroparin and dalteparin</td>
</tr>
<tr>
<td>heparin sodium</td>
<td>Injection: 1000 IU/ mL; 5000 IU/ mL; 20 000 IU/ mL in 1- mL ampoule.</td>
</tr>
<tr>
<td>phytomenadione</td>
<td>Injection: 1 mg/ mL; 10 mg/ mL in 5- mL ampoule.</td>
</tr>
<tr>
<td>protamine sulfate</td>
<td>Injection: 10 mg/ mL in 5- mL ampoule.</td>
</tr>
<tr>
<td>tranexamic acid</td>
<td>Injection: 100 mg/ mL in 10- mL ampoule.</td>
</tr>
<tr>
<td>warfarin</td>
<td>Tablet: 1 mg; 2 mg; 5 mg (sodium salt).</td>
</tr>
<tr>
<td><strong>Complementary List [c]</strong></td>
<td></td>
</tr>
<tr>
<td>desmopressin</td>
<td>Injection: 4 micrograms/ mL (as acetate) in 1- mL ampoule.</td>
</tr>
<tr>
<td></td>
<td>Nasal spray: 10 micrograms (as acetate) per dose.</td>
</tr>
<tr>
<td>heparin sodium</td>
<td>Injection: 1000 IU/ mL; 5000 IU/ mL in 1- mL ampoule.</td>
</tr>
<tr>
<td>protamine sulfate</td>
<td>Injection: 10 mg/ mL in 5- mL ampoule.</td>
</tr>
<tr>
<td>warfarin</td>
<td>Tablet: 0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).</td>
</tr>
</tbody>
</table>

The process of maintaining the WHO EML as well as generation of the related publications consists of:

- Receiving the relevant and validated information with the order for required content changes from the WHO EML Secretariat
- Maintaining the EML in Excel by
  - Generating and preserving historical versions (e.g. 2011, 2013, 2015, etc.)
  - Editing/updating a latest version of the EML of Excel spreadsheet which holds all relevant changes derived from the decisions of the EML Expert Committee
  - Editing/updating a second Excel spreadsheet which summarises the history of changes related to single medicines (see Table 2)
- Publishing the latest version of the EML as a pdf file by using the data from the latest version of the Excel spreadsheet.

Table 2: Spreadsheet frame reporting EML history of changes.

<table>
<thead>
<tr>
<th>ACTIVE INGREDIENT</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>abacavir + lamivudine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>acetazolamide</td>
<td>TRS615 (1977)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>acetic acid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>acetylcysteine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>acetylsalicylic acid</td>
<td>TRS615 (1977)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>aciclovir</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>adipodione meglumine</td>
<td>TRS615 (1977)</td>
<td>1</td>
<td>1</td>
<td>TRS685(1983)</td>
<td>TRS722(1985)</td>
<td>0</td>
</tr>
<tr>
<td>albendazole</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>TRS796(1990)</td>
</tr>
<tr>
<td>albumin, human</td>
<td>0</td>
<td>0</td>
<td>TRS685(1983)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>alcohol-based hand rub</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>alcuronium</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>all-trans retinoic acid (ATRA)</td>
<td>TRS615 (1977)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>aluminium acetate</td>
<td>TRS615 (1977)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>TRS770(1988)</td>
<td>0</td>
</tr>
<tr>
<td>aluminium diacetate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>TRS796(1990)</td>
</tr>
<tr>
<td>aluminium hydroxide</td>
<td>TRS615 (1977)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Current process of EML review and update - Changes envisaged

The Department wishes to overcome the current process which is time consuming, and entirely manual. EMP wishes to implement a web-based IT solution, which shall allow for efficient data management, data retrieval, and online searches dependent on user needs. The web-based IT solution has to link to other computerized (online) reference information such as medicines formularies/guidance and evidence information, INN and ATC databases.

Beyond EMP, other WHO allied technical programmes (e.g. UNITAID, UN Commission on Life-Saving Commodities) and external partners (e.g. The Cochrane Collaboration, Wikipedia) have expressed the desire to access the WHO EML information online, and in a user friendly and searchable manner.

Ideally, the new web-based IT solution shall therefore allow for updating and disseminating the EML information based on a WHO web site, and provides features for web based data maintenance, online data queries and reporting, generating PDF documents, and connecting to/with other scientific data resources.
Defining the requirements and scope

The web based tool should support the EML Secretariat workflow, enabling it to manage the decisions regarding essential medicines, tracking changes to the list more efficiently, creating multiple and HTML output documents (e.g. master list, children list, etc.) PDF based on user needs.

A scheme of the EML application management is presented in Figure 3.

Figure 3. Management of EML applications, outcomes and outputs.

Feature 1: web based tool for the EML management

The eEML project shall allow designing and implementing a web based tool for web based maintenance of the EML. The eEML shall be hosted by WHO and allow for managing, updating and tracking the applications of essential medicines, preparing the ground for the Expert review.

- Recording/viewing requests, applying requests and decisions
  - Background information for all changes are included and viewable
  - Relationships must preserve logic
    - List of EML applications and decisions (outcome) including rejected applications
    - EML List of applied decisions (these would not include rejected applications)

Versioning is enabled – all historical versions and actions are visible and can be shown in a meaningful manner.
It is important to notice that we are not primarily interested in a workflow management system for EML applications. Our primary goal is to offer to users a structured, quick and intuitive interface to navigate the EML contents. We acknowledge that the management of applications and the final list are parts of the same continuum.

**Feature 2: online management of Committee decisions and EML basic contents: applying and tracking additions, deletions, changes to the EML**

Managing APPLICATIONS and OUTCOME

- Addition: a new medicine or a combination is added to the list
- Deletion: a previously listed medicine (or combination) is de-listed for one or several medical uses
- Changes: class (e.g. anaesthetics), subclass (e.g. inhalation medicines), form (dosage, route, strength), ATC code

Business rules for including additions, alterations of data and or removals of points of information are established and need to be implemented by the eEML in controlled and auditable manner.

**Feature 3: online search and search options**

Customize requirements including options to search medicines using multiple tag, key words, years, etc., and superimposing limits to searches.

- Search bar
- Search Field Tags: terms qualified for search - field tags. A list of the available field names, tags, and brief field descriptions (search field descriptions and tags) should include: age, gender, indication, etc.

It is important that the tool provides a fast and flexible search and query engine, based on flexible search fields, using an ontology that will facilitate mapping data sources (see Figures 1 and 2).
Figure 1: Mock ups of the EML web search web page (adapted from Cochrane Linked data http://linkeddata.cochrane.org/).
Feature 4: Outputs, including EML & WHO Technical Report Series (TRS) publications

- HTML pages, including TRS Summaries divided in editorial sections (and references)
- Generation of EML body (PDF) for all or selected diseases and medicines
- Generation of TRS body (PDF) for all or selected diseases and medicines

The web-based tool will store the key information of few hundreds essential medicines and several levels of information aggregations to personalize the output. In addition, since the EML is global, the tool should be easily translated into different languages, ensuring that non-English speaking decision-makers can access the best available information without language barriers.

**Weighted relevance**: Computation of weighted relevance order in search outputs will be a preferred option when results of searches are presented to users.

Feature 5: Integration with guidelines and other guiding documents

The proposal should present a strategy to export eEML contents to third parties (e.g. Wikipedia). This can be considered an automated way of transferring eEML contents: any system receiver (e.g. smartphone) can connect to the WHO eEML platform/database to import data/information and use the information in their own platforms (e.g. websites or smart phone applications). The EML should be able to send contents and links in a standardized and structured XML format. If the receiver is designed to be integrated with the eEML, the updates of the eEML will be read and processed by any third parties, and EML contents will efficiently populate target libraries.
One key strategy is about the **designation** of medicines as essential medicines. The business solution should automatically transfer the data related to the status of a medicine as an essential medicine to third parties governmental lists, such as National Formularies, National EMLs, National Guidelines or Regulatory agencies. This strategy should also target medical editorial products: medicines can be automatically flagged as essential on editorial products and services such as The Cochrane Library, Clinical Evidence, Dynamed, UpToDate, eTG, EBMeGuidelines, and electronic health records solutions. A similar strategy is already active for Wikipedia. However now updating of the status are not automated, and are under the responsibility of Wikipedia volunteers. The implications of a server-side Application Programming Interface (API, e.g. Java, PHP, .Net) web service will be considered as an element of primary importance.

A second key strategy regards the integration of WHO EML and WHO guidelines. Until now the contents of few WHO guidelines [Database of Evidence Profiles (DBEP - http://dbep.gradepro.org/search): Tuberculosis treatment guidelines (Delamanid and Bedaquiline) and Sexually transmitted Diseases guidelines (Gonorrhea, Syphilis and Chlamydia)] have been annotated and structured in XML format (see Figure 5). Annotations of WHO Guidelines contents and software development have been done by the GRADE – DECIDE Working Group.

This work is a prerequisite to integrate WHO EML contents and WHO Guideline contents. Particularly we envisage an Application Programing Interface (API, web service, etc.) that can handle the exchange of queries and responses messages, integrating Guidelines recommendations and Summary of Findings contents in the EML output. The system should ensure a timely automated transferring and updating of contents, as far as guidelines are developed using the API/web service. The final result should follow the same approach used when YouTube videos (or Google Maps) are embedded in different websites.

### Other relevant information

**Elements data**
The following lists basic specifications and requirements features of the future eEML.

We developed a strategy to use the EML similarly to what other authoritative scientific entities did. We considered as key examples the National Library of Medicine, the Cochrane Library and Clinical Evidence. The strategy provides the different potential components that can characterize a clinical question, and a related answer.

**Medicine Class**: A medicine class is a set of medications that are used to treat the same disease, example anesthetics, divided in additional sublevels (forming a hierarchy) based on route of administration, chemical structures, mechanism of action (i.e., bind to the same biological target), etc.

1. Anesthetics
   1.1 General anesthetics and oxygen
   1.1.1 Inhalational medicines
   1.1.2 Injectable medicines
**Medicine name:** International Nonproprietary Names (INN) to identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

**Individual/Square box:** the intended purpose of the square box is to highlight pharmacological classes or groups of medicines for which health professionals or countries can assume homogenous efficacy and safety, and select the most appropriate single medicine based on price, local availability, patient’s value and preferences. The square box is represented by a □ symbol.

**Selective square box:** In some circumstances, a selective square box listing may include an additional qualifying note to indicate that acceptable alternatives within the pharmacological class are limited to particular medicines. An asterisk may introduce alternatives.

**Formulation:** Medicine form (e.g. tablet, oral liquid, injection, etc).

**Dose strength:** The strength of a medicine, which indicates the amount of active ingredient in each dosage OR the proportion of active drug substance to excipient, measured in units of volume or concentration.

**Patient Group**

- **Children:** Distinguishing characteristic of formulation or medicine for children (age 0 – 14). The Children feature is represented by a [C] symbol, on a black background.

- **Adults:** Medicines and formulations for people having attained full growth or maturity.

**Age or weight restriction:** The [a] symbol indicates that there is an age or weight restriction on use of the medicine.

**Type of List**

- **Core List:** 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. At this moment the core list does not have specific symbol that characterizes it.

- **Complementary List:** Where the [c] symbol is placed next to the item it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children. Medicines in the complementary list are part of the Model List. Contents referring to medicines in the complementary list are in italic.

* : An asterisks signals additional relevant information about any aspect of the selection or use of the medicine.

**Type of medicines**

- Antidotes
- Blood Products
- Contraceptives
- Diagnostic Agents
- Disinfectants and Antiseptics
- Immunologicals
- Peritoneal Dialysis solution
- Vitamins and Minerals
**Vaccines:** Divided in four groups, i.e. Recommendations for all, Recommendations for certain regions, Recommendations for some high-risk populations, Recommendations for immunization programs with certain characteristics.

**ATC Code:** The Anatomical Therapeutic Chemical (ATC) Classification System. This pharmaceutical coding system divides drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. Each bottom-level ATC code stands for a pharmacologically used substance, or a combination of substances, in a single indication (or use). This means that one drug can have more than one code: acetylsalicylic acid (aspirin), for example, has A01AD05 (WHO) as a drug for local oral treatment, B01AC06 (WHO) as a platelet inhibitor, and N02BA01 (WHO) as an analgesic and antipyretic. On the other hand, several different brands share the same code if they have the same active substance and indications.

**Expert Panel recommendations:**

- **Addition:** medicine added to the list
- **Deletion:** medicine previously listed which is then deleted
- **Rejection:** medicine not previously listed which is not recommended for inclusion
- **Change:** change is a broad category that includes changes to dose, formulation, indication or restriction. New indications will be tagged as change.
- **Decision pending:** in few occasions decisions about listing/delisting have been postponed, as the ground to make the decision was in some respects problematic.

**Year:** year at which any decision has been taken.

**Indication:** the condition or illness that makes the medicine recommended, using organized computer processable collection of medical terms, such as SNOWMED CT [http://www.snomed.org/](http://www.snomed.org/).

**Ages:** Age option if the use is recommended or relevant to a specific age group. Age options should initially reflect MeSH age options ([https://www.ncbi.nlm.nih.gov/books/NBK3827/](https://www.ncbi.nlm.nih.gov/books/NBK3827/)).

**Sex:** sex option if the use is recommended or relevant to a specific gender.

**History:** all modifications related to one item.

**Evidence:** We will present brief summaries of evidence that supported the addition (or deletion/rejection) of medicines to the Model List designed to make key information quickly available for policy makers, in order to understand why a decision was made. It will be structured in a format dividing the key information in criteria (see Figure 4). The evidence section will replicate the information that is developed for the WHO TRS, and will be prepared and updated by the EML Secretariat.

The criteria include the following:

- Benefits
- Harms
- Additional evidence
- WHO Guidelines
- Cost / cost effectiveness
- Availability
EMP is in the process of preparing a template for about 90 medicines. In fact, all EML applications presented and reviewed at the Expert committee for the 2017 EML will have a companioning template prepared by the EML Secretariat. We therefore intend to launch the new eEML based upon the renew template; in fact, it is planned that all 90 templates will be copy-edited by May 2017.

After launch of the eEML with the initial selection of 90 medicine records, we will cover the remaining medicines listed in the EML following two strategies. Medicines that have an evidence summary template presented in the PAHO website will be reconciled to the new template, adding data elements that are lacking. The same approach will be followed for medicines presented in the 2015 TRS 994. This will allow having complete templates for about half of all medicines listed in the EML. The additional batch of templates will be finalized by the end of 2017 and is not part of the IDEAS BED proposal.
**Figure 4**: Example of key information on essential medicines – prepared and updated by the EML Secretariat.

<table>
<thead>
<tr>
<th><strong>Dolutegravir</strong></th>
<th><strong>ATC code: J05ZA12</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EML / EMLc</td>
<td>EML</td>
</tr>
<tr>
<td><strong>Section:</strong></td>
<td>New sub-section: 6.4.2.4 Integrase inhibitors</td>
</tr>
<tr>
<td><strong>Dose form(s) &amp; strengths(s):</strong></td>
<td>Tablet: 50 mg</td>
</tr>
<tr>
<td><strong>Core / Complementary:</strong></td>
<td>Core</td>
</tr>
<tr>
<td><strong>Individual / Square box listing:</strong></td>
<td>Individual</td>
</tr>
<tr>
<td><strong>Background:</strong> (if relevant, eg. resubmission, previous EC consideration)</td>
<td>Single-agent integrase inhibitors had not previously been considered by the Expert Committee. A separate application to this meeting requested the addition of an alternative integrase inhibitor, raltegravir, for second-line treatment.</td>
</tr>
<tr>
<td><strong>Public health relevance:</strong> (burden of disease)</td>
<td>Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% living in low- and middle- income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving antiretroviral therapy in 2015 (1).</td>
</tr>
<tr>
<td><strong>Summary of evidence:</strong> benefits (from the application)</td>
<td>The application presented the results of three randomized controlled phase III studies in support of the efficacy of dolutegravir in ART-naive patients: The SPRING-2 non-inferiority study compared dolutegravir and raltegravir over 96 weeks regardless of baseline viral load and nucleoside reverse transcriptase inhibitor (NRTI) backbone (2). At 96 weeks, dolutegravir was found to be non-inferior to raltegravir with 81% of patients in the dolutegravir group having HIV RNA &lt; 50 copies per mL compared with 76% in the raltegravir group (adjusted mean difference 4.5%, 95% CI -1.1% to 10%). The SINGLE study compared dolutegravir in combination with abacavir+lamivudine with emtricitabine+efavirenz+tenofovir disoproxil fumarate in 833 participants who had not received previous treatment for HIV infection (3). The dolutegravir combination met the criterion for superiority with a greater proportion of patients achieving a HIV RNA level of less than 50 copies per mL at 48 weeks (88% versus 81%; adjusted treatment difference 7%, 95% CI 2% to 12%). The dolutegravir group also had more favourable outcomes for the secondary end points of time to viral suppression, changes in CD4+ T-cell count from baseline, safety and antiviral resistance. The FLAMINGO study compared dolutegravir with ritonavir-boosted darunavir, each dosed with two NRTIs (4). At 96 weeks, a statistically significantly greater proportion of the dolutegravir group had HIV-1 RNA less than 50 copies per mL (adjusted mean difference 12.4%, 95% CI 4.7% to 20.2%; p = 0.002). The application also presented the results of two phase III studies of dolutegravir in ART treatment-experienced adult patients. The SAILING study compared dolutegravir and raltegravir (with background therapy). The proportion of patients with treatment-emergent integrase-inhibitor resistance was a pre-specified secondary endpoint. At 48 weeks, the proportion of patients in each group with HIV-1 RNA &lt; 50 copies per mL was 71% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%, 95% CI 0.7% to 14.2%), and superiority was concluded. In addition, significantly fewer patients in the dolutegravir group had virological failure due to treatment-emergent resistance (4 versus 17 patients; adjusted difference -3.7, 95% CI -6.1 to -1.2) (5). In the VIKING-3 single-arm study, twice daily dolutegravir in combination with other ART was demonstrated to be effective in ART-experienced patients demonstrating...</td>
</tr>
</tbody>
</table>
Integrase inhibitor resistance with 69% of patients with prior virologic failure and resistance to other integrase inhibitors achieving virological suppression at week 24 (6).

The IMPAACT P1093 clinical trial of dolutegravir plus two NRTIs in treatment-experienced children and adolescents assessed the pharmacokinetics and efficacy of dolutegravir in treatment experienced adolescents. Among the 12-18 years age cohort, 70% and 61% of patients had HIV RNA < 50 copies/mL at weeks 24 and 48, respectively (7).

**Summary of evidence: harms**

The safety profile of dolutegravir compared favourably to other antiretrovirals in the abovementioned clinical trials. The most common clinical adverse observed in the SPRING-2 and SINGLE studies were nausea, nasopharyngitis, diarrhoea and headache. The occurrence of adverse events leading to treatment discontinuation was low and comparable across treatment groups (2, 3). Dolutegravir has also been associated with hepatotoxicity and hypersensitivity reactions (8).

**Additional evidence:**

N/A

**WHO Guidelines:**

Dolutegravir 50 mg is included in the 2016 WHO **Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection** as an alternative first-line treatment option in combination with a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone for adults and adolescents (8).

A systematic review and network meta-analysis of 71 trials involving 34 032 patients was conducted to inform the WHO guidelines and assessed the comparative evidence of the efficacy and safety of integrase inhibitors (INSTI, dolutegravir, raltegravir and elvitegravir+cobicistat) and efavirenz in adult patients with HIV. The review found moderate quality evidence that two NRTIs + INSTI was a generally more effective regimen than two NRTIs plus efavirenz 600 mg. Dolutegravir and raltegravir had comparable effects, but were better than elvitegravir+cobicistat in terms of viral suppression and treatment discontinuation.

Compared with efavirenz 600 mg, dolutegravir has advantages including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier.

The WHO guidelines note the limited availability of data regarding the safety and efficacy of dolutegravir in pregnant women and patients with tuberculosis co-infection.

**Costs / cost-effectiveness:**

The unit price for dolutegravir 50 mg averages US$0.127. In comparison, the average unit price for efavirenz 600 mg is US$0.111. The application claims that with increasing volumes and generic manufacture, the unit price of dolutegravir is expected to decline, and pricing agreements be refined.

**Availability:**

Viiv Healthcare, United Kingdom; Aurabindo Pharma Limited, India. Generic versions of dolutegravir 50 mg received tentative approval from the FDA in August 2016. Dolutegravir 50 mg is also included on WHO List of Prequalified Medicinal Products.

**Other considerations:**

Weight restriction of >40 kg

Age restriction of >12 years

**Committee Recommendations:**

References
Our aims in choosing data elements have included the following:

- Key information for essential medicines.
- Use of codes, terms, synonyms and definitions that makes the EML a searchable tool.
- Limit searches that can be applied to single medicine or group of medicines.
- Structured in a way that allows essential medicines to be linked to other documents of WHO.
- Indexing can be completed for all essential medicines (100%) in a limited time.
- Potential for integration with vocabularies already in use by scientific and health information related institutions outside WHO, including, but not limited to, Wikipedia, Cochrane, UpToDate, and the British National Formulary.

Maintenance
To maintain accuracy, validity and relevance, the data contents must be regularly updated as changes are implemented. Our strategy includes formal plans for updating since inception. The data elements are divided in two main categories, what will be updated as part of the duties of the Secretariat, and what will be updated if additional resources are available.

The proposed business solution will initially contain a limited number of descriptors. These will be updated and reviewed biannually, using the same timeline of the EML. The maintenance workload is compatible with the actual capacity of the EML team. For instance, the new version of the ATC index will be downloaded from the website http://www.whocc.no/, changes will be made by EMP to the EML database and immediately applied to the live EML database. Currently, this work is also carried out, but by recording all changes in MS Excel spreadsheets which are not visible online.

With our new EML management approach, which relies on a web based eEML online platform, any changes will be immediately applied to the online database.

Therefore, this new process, while requiring approximately the same amount of content maintenance work, will allow EMP to carry out EML maintenance much more efficiently and faster.

The evidence section might pose challenges in being regularly updated as evidence cumulate over time. To keep updating manageable, we decided to have updates only under specific circumstances (e.g. additional important evidence that corroborate the decision of the panel, working group on cancer that updates an EML chapter), or particular criteria (i.e. updating links to most recently published WHO guideline).

Integrated data model and annotation
We are looking to be supported in choosing elements data and specific controlled vocabularies: other entities that have more experience in annotating contents, such as OHDSI (Observational Health Data Sciences and Informatics) or Cochrane Linked Data already worked in creating strategies to structure information related to computerized medical records, adverse drug reaction reports submitted to regulators, systematic reviews that identify drug risks and benefits. There is a great potential to integrate some vocabularies (e.g. SNOMED CT, MeSH, LOINC and ATC) to the EML, facilitating mappings from one vocabulary to another using linking terms.

For instance, many domain concepts of Cochrane PICO (Population, Intervention, Comparison, Outcome) fit well with the elements data that we would like to adopt for the EML, e.g. their P - Population would be part of our indication, Intervention would fit with our Medicine, etc. Cochrane
possibly has identified, or created, and mapped a vocabulary to other vocabularies for medicines, including the WHO's ATC vocabulary.

In addition to precise annotations using terms from controlled vocabularies, we will be annotating medicines following the EML classification, using clear categories that define the status of medicines as essential.

Proposals should highlights how the EML Secretariat will be supported in the annotation phase (i.e. assigning meta-data to element data), making the annotation as automatic and complete as possible. The application should also facilitate organizing and locating information of interest from the original repository.

**Dissemination and knowledge translation**

The proposal should present the format to present and deliver our contents on the WHO main website, including coding solution that should be transferred to WHO. We will value the search functionality, the web interface, how contents will be prioritised, customised, and how different data elements will be linked. Examples of a possible formats presented in [Figure 1 and 2](#).

We require that the proposed solution is able to be searched and presents contents at different level of granularity, from individual medicine, to medicines aggregated by disease or indication, to the whole list.

The main objective is to create the optimum environment for partners to efficiently and effectively explore the Model List. The EML explorer website should be designed to last for a period of five years without major updates, and with a minimal workload to be maintained.

**Permissions for reuse/connecting to/integrating external resources from non-WHO entities**

The eEML will be released under the terms of a CC BY-NC-SA 3.0 IGO licence. This license allows for redistributing and re-using eEML contents for different purposes, including commercial purposes. Extracts or the entire eEML can be integrated in Drug Formularies and evidence-based clinical textbooks (e.g. BMJ Clinical Evidence, eTG – Therapeutic Guidelines).

We will also explore how to obtain the permission to re-use or republishing figures, tables, and extracts about key evidence from external sources which are included in/referred to by the eEML. For instance, we will draft an Agreement Proposal Form outlining terms and conditions of the re-use of evidence syntheses extracts (forest plots, plain language summaries). Evidence (systematic reviews, meta-analyses, guidelines) pertinent to essential medicines will be possibly published as supporting evidence in the eEML.
Figure 5. HTML versions of WHO guidelines, available from the Database of Evidence Profiles. APi developed by Evidence Prime Inc.
**Implementation Notes**

Adds evidence profile to the DBEP database on random UUID. The evidence profile document is documented at DBEP Schema. See:

- Diagnostic evidence profile schema documentation.
- Management evidence profile schema documentation.

**Response Class (Status 200)**

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{
  "id": "string",
  "message": "string",
  "errors": [
    
    "message": "string",
    "path": "string"
  ]
}
```

**Response Content Type** (application/json)

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<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
<th>Parameter Type</th>
<th>Data Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>body</td>
<td>(required)</td>
<td>Evidence profile to add.</td>
<td>body</td>
<td>undefined</td>
</tr>
</tbody>
</table>

**JSON-LD Type: ManagementRecommendation**

Represents a guideline recommendation for management questions.

**Fields:**

<table>
<thead>
<tr>
<th>Field name</th>
<th>Possible types</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>author</td>
<td>Person</td>
<td>The author of the document.</td>
</tr>
<tr>
<td>consequencesBalance</td>
<td>string</td>
<td>Consequences balance (optional field).</td>
</tr>
<tr>
<td>decisionText</td>
<td>string</td>
<td>Decision from Panel Members. (Optional field but one of recommendationText or decisionText must be present in document.)</td>
</tr>
<tr>
<td>decisionType</td>
<td>string</td>
<td>Decision type if it suggests intervention/intervention test, comparison/comparator test or neither option. (Optional field but one of recommendationType or decisionType must be present in document.)</td>
</tr>
<tr>
<td>guidelineSubject</td>
<td>PICO</td>
<td>The PICO that this recommendation is for.</td>
</tr>
<tr>
<td>header</td>
<td>ManagementEldHeader</td>
<td>The header of the diagnostic table.</td>
</tr>
<tr>
<td>justifiction</td>
<td>string</td>
<td>Justification of the recommendation or decision.</td>
</tr>
<tr>
<td>modificationTime</td>
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<td>Modification timestamp in ISO 8601 format: yyyy-MM-dd'T'HH:mm:ss.</td>
</tr>
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<td>Monitoring and evaluation (optional field).</td>
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<tr>
<td>recommendationText</td>
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<td>Recommendation type if it suggests intervention/intervention test, comparison/comparator test or neither option. (Optional field but one of recommendationType or decisionType must be present in document.)</td>
</tr>
<tr>
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Exhibits of previous web based tools.
Online Applications for the WHO Model List of Essential Medicines

Applications submitted to and accepted by WHO no later than 15 October 2006 will be discussed at the 45th session of the WHO Programme Committee on 3/15/2007

Review application > Add medicine > Creating the dosage forms and strengths

tenofvir

Proposed dosage forms and strengths

<table>
<thead>
<tr>
<th>Strength</th>
<th>Dosage Form</th>
<th>Type of List</th>
<th>ATC Code</th>
<th>WHO Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>Tablets</td>
<td>Unknown</td>
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<td>NAD9290</td>
</tr>
</tbody>
</table>

Create a new dosage form and strength

Strength

Dosage Form

Type of List

ATC Code

WHO Section

Create formulation

MODEL FORMULARY INFORMATION

GENERAL INFORMATION

Adverse effects: nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, alopecia.

Precautions: use in pregnancy only if clearly needed. Do not use in breastfeeding women. Do not use in patients with renal impairment.

Dosage: Adult dose: 300 mg once daily. Children: 10 mg/kg once daily.

Contraindications: allergy to any component of the formulation.

Interactions: use with caution with other drugs that may cause hepatotoxicity.

Reconstitution and administration: inject slowly over 30 seconds. Store at 2°C to 8°C. 

Pregnancy: Category B. Do not use in breastfeeding women.

Breastfeeding: use only if clearly needed.

Pediatric use: dose adjustment required.

Renal impairment: dose adjustment required.

Hepatic impairment: use with caution.

Clinical trials: not required for this drug.

Carcinogenicity: not applicable.

Mutagenicity: not applicable.

Teratogenicity: not applicable.

Drug interactions: use with caution with other drugs that may cause hepatotoxicity.

Adverse reaction: nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, alopecia.

Pharmaceutical: store at 2°C to 8°C. Protect from light. 

Stability: 18 months unopened. 3 months if opened. 

OVERDOSAGE: there is no specific antidote.

Substitution: not applicable.
1. Benzoyl peroxide for treating mild-moderate acne
   Context: Acne vulgaris.
   Question: Should children or adults with mild to moderate acne be treated with benzoyl peroxide compared to other topical preparations for acne?
   View details...
   Medicine(s)
   * benzoyl peroxide

2. H2-antagonists versus proton pump inhibitors for gastro-esophageal reflux in adults
   Context: Gastro-esophageal reflux disease.
   Question: Should adults with gastro-esophageal reflux be treated with H2-antagonists compared to proton pump inhibitors?
   View details...
   Medicine(s)
   * ranitidine
   * omeprazole