Reviewer No. 2 check list for Application for addition of 3-FDC rifampicin 150/isoniazid 75/ethambutol 275 mg (RHE)

(1) Have all important studies that you are aware of been included?
   Y [ ]    N [√]
   If “N”, add missing references with brief summary of key findings.
   No, please see the references in the Assessment Report.

(2) Is adequate evidence of efficacy for the proposed use?
   Y [ ]    N [√]
   If “N”, suggest what is needed.
   No, please see “The implication of evidence” in the Assessment Report.

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Y [ ]    N [√]
   If “N”, suggest what is needed.
   No, please see table 1 and references in the Assessment Report.

(4) Are there adverse effects of concern?
   Y [√]    N [ ]
   If “Y”, (list/describe)
   No special adverse effects of concern.

(5) Are there special requirements or training needed for safety/effectiveness use?
   Y [√]    N [ ]
   If “Y”, describe.
   Yes, for example patient’s classification, the dosage and usage.

(6) Is this product needed to meet the majority health needs of the population?
   Y [√]    N [ ]
   If “N”, is there a special reason why this should be on the Model List?

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Y [√]    N [ ]
   If “N”, give details.

(8) What action do you propose for the Committee to take?
   Please see “recommendation” of the Assessment Report.

(9) Additional comment, if any.
   Please see “recommendation” of the Assessment Report.
1. Summary of the application

a) Summary statement of the proposal
A proposal is made for the inclusion of rifampicin150/isoniazid75/ethambutol 275 mg fixed dose, combination oral tablets – 3-FDC R150H75E275 – in the WHO Model List of Essential Medicines (WHO EML) for treatment of category II tuberculosis.

b) Epidemiological information on disease burden
Tuberculosis continues to be a leading cause of death among adults and children worldwide. WHO estimates that 460,000 multidrug-resistant tuberculosis (MDR-TB) cases occur each year, among which one-half are previously treated patients. Appropriate administration and dosing of anti-tuberculosis medicines is essential to prevent from failure of therapy and increase of MDR-TB cases among re-treated patients. Rifampicin/isoniazid/ethambutol (RHE) is a component of standard therapy in Category II tuberculosis patients according to WHO treatment guidelines, but the fixed dose combination of RHE (FDC RHE) is not included in the current WHO Model List of Essential Medicines.

c) Assessment of current use
Fixed dose combination (FDC) is advantageous in treating tuberculosis and reducing noncompliance and development of multi-drug resistance. E275 complements R150/H75 are currently available only as separate formulations. However, RHE are used concurrently in the continuation phase of category II treatment, which supports inclusion of the FDC RHE tablet into WHO EML.

The advantages of this formulation include the ease of the logistics of treatment with RHE, the indication of RHE in treatment of Category II TB to prevent development of resistance, and the basis on 2:1:3 dosing guidelines. E275 is appropriate for daily dosing, which is demonstrated by pharmacokinetic assessment.

d) Target population
Adult category II tuberculosis.

e) Summary of comparative effectiveness in a variety of clinical settings
The applicant indicated that the search of published literature failed to identify any studies of treatment with FDC R150H75E275 in Category II patients for whom the standard re-treatment regimen with RHE throughout was recommended. The evidence for supporting this application is a study of bioequivalence assessment of two formulations of FDC R150H75E275 measured pharmacokinetic parameters in 22 healthy volunteers, but not category II tuberculosis patients.
2. External review

To be reassured that all the important studies are included in those high tuberculosis countries such as China, we searched Chinese Biomedical Database (CBM), Databases of CDSR and CENTRAL, DARE (via CRD website), MEDLINE (via PubMed), EMBASE (via EMBASE website), all up to 24 December 2006. Two investigators identified studies independently using the inclusion criteria of intervention (FDC R150H75E275) and population (category II tuberculosis). However, eligible studies were not identified.

Although there was no evidence of interest, we expected to address this issue, and we searched guidelines or technical documents from other grey sources to understand the regimens for category pulmonary TB patients and the relevant population in different settings, as shown in table 1.

The selection criteria were also re-defined to hopefully identify the relevant trials. The studies were considered eligible that involved the use of Rifampicin and Isoniazid and Ethambutol, regardless of patients, dosage and usage (single / combination use). The same search strategy was used, and twenty studies are found eligible.

3. The implication of evidence

The study included in the application has following limitations.

✓ Only one study (n=22) included to establish FDC formulations as reference products for bioequivalence studies
✓ The objects are healthy male volunteers not category II tuberculosis patients
✓ The comparison is FDC containing the same drugs and doses as intervention but supplied by different Ltd
✓ The outcome is pharmacokinetic parameters not patient-oriented outcomes.

Since the direct evidence is not strong enough at present to support the inclusion of FDC RHE in WHO EML, we searched guidelines or technical documents from other grey sources, especially from high TB burden country such as India, China, and South African, which are ranked as first, second and fifth estimated TB burden country among the 22 high-burden countries in 2004 respectively. The indirect evidence from WHO and key countries including 3 high TB burden developing countries indicated that the guidelines included the recommendations for cases that met the definition of WHO category II tuberculosis. The regimens of continuation phase are RHE in these documents, but the dosage varies in different countries, and no country uses RHE as the FDC. These materials also indicated that the FDC of HRZE and HR (three different doses) have already been included in WHO guideline.

The study based on the indirect evidence involves the use of Rifampicin(R) and Isoniazid(H) and Ethambutol(E) demonstrate that the use of R&H&E, with or without
other drugs, is seen in the condition of extrapulmonary tuberculosis (EPTB), pulmonary disease caused by \textit{M avium intracellulare}(MAC), \textit{M malmoense}, \textit{M xenopi} or \textit{Mycobacterium kansasii}, newly diagnosed pulmonary tuberculosis, short-course chemotherapy for sputum-positive pulmonary tuberculosis, bioavailability or bioequivalence studies. The dosage of R&H&E is neither R150H75E275 nor the multiple of that, from the acquired studies, the dosage of E is usually applied based on body weight (for example, 15/25mg/kg/day), R is often used in two doses: 450mg for body weight less than 50kg and 600mg for 50kg and above, and the common dose of H is 300mg\textsuperscript{4-23}.

As the continuation phase treatment of category tuberculosis involves the use of RHE, there is need of the addition of FDC RHE to the WHO EML for more convenient use. However, the dosage still need to be decided based on further evidence.

4. Recommendation

It is recommended that FDC RHE be included in WHO EML for treatment of category II tuberculosis, but the dosage still need to be adjusted based on more clinical trials of high quality.

It is proposed to carry out clinical researches of the effectiveness, safety, economics and applicability of WHO guideline and national guidelines in high TB burden countries, so as to supplement high quality evidence.
References

1. IAP, Indian Pediatrics.net


### Appendix. Regimens for category pulmonary TB patients or similar from guideline of WHO/countries

<table>
<thead>
<tr>
<th>Country/Organization</th>
<th>Target population</th>
<th>Initial phase (IP)</th>
<th>Continuation phase (CP)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization, 2003</td>
<td>Category Tuberculosis Previously treated sputum smear-positive PTB (relapse; treatment after interruption; treatment failure)</td>
<td>2 HRZES/1 HRZE (daily or three times weekly)</td>
<td>5 HRE (daily or three times weekly)</td>
<td>FDC: H75 mg +R150 mg+ Z400 mg +E275 mg for daily use H 75 mg +R 150 mg/ H150 mg +R300 mg for daily use H 150 mg +R 150 mg for use three times weekly</td>
</tr>
<tr>
<td></td>
<td>Adults/Children: 2H3R3Z3Es + 1H3R3Z3Es+</td>
<td></td>
<td></td>
<td>Recommended Dosage (dose range), mg/kg</td>
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<td></td>
<td>Adults: H: Isoniazid (600 mg), R: Rifampicin (450mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). Patients who weigh 60 kg or more receive additional rifampicin 150 mg. Patients who are more than 50 years old receive streptomycin 500 mg. Patients who weigh less than 30 kg, receive drugs as per body weight. Children: Isoniazid 10-15mg/kg; Rifampicin 10mg/kg; Pyrazinamide 30-35mg/kg; Ethambutol 30mg/kg and</td>
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<tr>
<td>India, 2005</td>
<td>Sputum smear-positive Relapse</td>
<td>Adults/ Children: 2H3R3Z3Es + 1H3R3Z3Es+</td>
<td>Adults /Children: 5H3R3E3</td>
<td>Adults: H: Isoniazid (600 mg), R: Rifampicin (450mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). Patients who weigh 60 kg or more receive additional rifampicin 150 mg. Patients who are more than 50 years old receive streptomycin 500 mg. Patients who weigh less than 30 kg, receive drugs as per body weight. Children: Isoniazid 10-15mg/kg; Rifampicin 10mg/kg; Pyrazinamide 30-35mg/kg; Ethambutol 30mg/kg and</td>
</tr>
</tbody>
</table>

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Note: a) The target population is for patients who have never received treatment for tuberculosis. b) The dosage is recommended for patients who weigh 60 kg or more. c) The dosage is recommended for patients who weigh less than 30 kg. d) The dosage is recommended for patients who are more than 50 years old. e) The dosage is recommended for patients who weigh more than 60 kg.
<table>
<thead>
<tr>
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</tr>
</thead>
</table>
| China, 2002          | Smear-positive pulmonary TB, and Retreatment - including Relapse, Treatment failure, Treatment after interruption, and others (treatment after interruption less than two months and immigrant previously treated for more than 1 months by clinicians in other district) | 2H₃R₃Z₃S₃E₃ / 3H₃R₃Z₃E₃                      | 6H₃R₃E₃                                             | Adults, Weight<50kg: H: Isoniazid (500 mg), R: Rifampicin (600mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1000 mg), S: Streptomycin (750 mg). 
Adults, Weight≥50kg: H: Isoniazid (600 mg), R: Rifampicin (600mg), Z: Pyrazinamide (2000 mg), E: Ethambutol (1250 mg), S: Streptomycin (750 mg). |
<p>| South African, 1998  | Smear positive retreatment cases (failure, relapse and return after interruption)   | 2 Months Initial Phase (5 times a week): FDC-RHZE 120/60/300/200 mg + streptomycin | 5 Months Continuation Phase (5 times a week): FDC-RH150/100 mg+ E400mg or FDC-RH300/150 mg+ E400mg | &lt;50 kg  IP: FDC-RHZE 4tabs+ streptomycin 750mg  3rd month: FDC-RHZE 4tabs  CP: FDC-RH150/100 mg 3tabs+E400mg 2 tabs  &gt;50 kg  IP: FDC-RHZE 5tabs+ streptomycin 1000mg  3rd month: FDC-RHZE 5tabs  CP: FDC-RH300/150 mg 2tabs+E400mg 3 tabs |</p>
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<tbody>
<tr>
<td>USA, 2003</td>
<td>Culture-positive pulmonary TB caused by drug-susceptible organisms</td>
<td>2HRE or 5d/wk for 2 months/</td>
<td>R/H seven days per week for 31 weeks or 5d/wk for 31 weeks/</td>
<td>R(capsule 150mg 300mg): 10mg/kg(max 600 mg) for daily or 1x/wk or 2x/wk or 3x/wk</td>
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<td></td>
<td></td>
<td></td>
<td>H(tablet 50 mg 100mg 300mg): 5mg/kg(max 300 mg) for daily and 15mg/kg(max 900 mg) for 1x/wk or 2x/wk or 3x/wk</td>
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<td>E(use estimate lean body weight of 40-55kg as example) (100 mg 400mg):</td>
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<td>Daily: 800mg(14.5-20.0 mg/kg)</td>
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<td>Thrice weekly:1200mg(21.8-30.0 mg/kg)</td>
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<td>Twice weekly:2000mg(36.4-50.0 mg/kg)</td>
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</tbody>
</table>

- **H** = Isoniazid; **R** = Rifampicin; **E** = Ethambutol; **Z** = Pyrazinamide; **S** = streptomycin; **PTB** = pulmonary tuberculosis; **FDCs** = Fixed-dose combinations
- **a** Whenever possible, drug sensitivity testing is recommended before prescribing Category II treatment in failure cases. It is recommended that patients with proven MDR-TB use Category IV regimens.
- **b** Direct observation of drug intake is required during the initial phase of treatment in smear-positive cases, and always in treatment that includes rifampicin.
- **C** In rare and exceptional cases, patients who are sputum smear-negative or who have extra-pulmonary disease can have Relapse or Failure. This diagnosis in all such cases should always be made by an MO and should be supported by culture or histological evidence of current, active TB. In these cases, the patient should be categorized as ‘Others’ and given Category II treatment.
- **d** Patients in Categories I and II who have a positive sputum smear at the end of the initial intensive phase receive an additional month of intensive phase treatment.
- **e** The guideline define this phase as a separate phase between Initial Phase and Continuation Phase.
- **f** This is one of the four regimens for this kind of population.
References for table data
5. American Thoracic Society, CDC, and Infectious Diseases Society of America, Treatment of Tuberculosis, MMWR Recommendations and Reports, June 20, 2003/52(RR11);1-77