



## EUROPE

### **Survey of the quality of anti-tuberculosis medicines circulating in selected countries of Eastern Europe and NIS WHO/Europe workshop, Copenhagen, 17-18 June, 2010**

Limited research has been conducted into the causes of drug resistance and the marked regional and national differences in drug resistance patterns by investigations into the extent and magnitude of substandard anti-TB drugs. This survey therefore aimed to investigate the quality of anti-TB drugs circulating in the countries with the highest rates of MDR-TB in the world i.e. the countries of the former Soviet Union.

In 2008, a pre-survey was conducted on anti-TB drugs used in the following nine countries: Armenia, Azerbaijan, Belarus, Estonia, Kazakhstan, Moldova, Latvia, Ukraine and Uzbekistan. The pre-survey asked for the first and second-line anti-TB drugs, including fixed-dose combinations (FDCs), that were used in the countries during the same year in both public and private sectors, the volumes used, the manufacturers of these drugs and also which institutions that were involved in the importation and distribution of the drugs. The results of the pre-survey indicated little use of FDCs and considerable use of injectable forms of isoniazid and ofloxacin in some countries.

Following the pre-survey, Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine and Uzbekistan were included in the drug quality survey because they had the widest choice of anti-TB drug products in the country. Agreements were obtained from the Ministries of Health of the six countries and each country nominated a focal point from the National Drug Regulatory Authority (NDRA) for the sampling and shipment of drugs to the testing laboratories. The anti-TB drugs selected for the quality survey were the following (other second-line anti-TB drugs were excluded because they were predominantly originating from 1-2 sources and supplied by the Global Drug Facility):

- isoniazid tablets and injections
- rifampicin capsules
- isoniazid/rifampicin tablets
- kanamycin powders for injection
- ofloxacin tablets, capsules and solutions for infusion

A survey protocol was developed, as well as standard operating procedures for the collection and shipment of samples. All samples were testing in four WHO quality controlled laboratories in Western Europe and according to specifications in the International, British or United States Pharmacopoeia. Prior to the sampling, a preparatory meeting was held with the country focal persons, appointed by the Ministries of Health, in Minsk, Belarus, 21-22 May 2009.

The objectives of the Copenhagen meeting were to discuss:

- Survey benchmarks, lessons learned by country focal persons.
- The outcomes of the anti-TB medicines quality survey:
  - What proportion of anti-TB medicines samples, including fixed-dose combination products, collected at approved procurement and treatment centres fails quality testing?
  - Are any of the deficiencies critical, i.e. could they affect treatment efficiency and/or cause harm to the patient?
  - Which specific quality tests do the samples fail, if any?
  - Appropriate quality assurance strategies needed, based on the survey results, for anti-TB medicines in the six participating countries.
- Publication of the results, including WHO report and scientific publication in peer-reviewed journal.

During the meeting all presentations were followed by live discussions of the survey methodology and results. Representatives of member states and country focal persons presented country related challenges and experience gained during their participation in the survey.

A total of 291 samples were collected from 90 collection sites in the six countries (mostly public TB treatment centres at national and regional level but also from private pharmacies and warehouses). The samples were originating from 33 manufacturers from the following 12 countries: 10 from India, 5 each from Russia and from Ukraine, 3 from Kazakhstan, 2 each from Belarus and from China, and 1 each from Cyprus, France, Palestine, Syria, Turkey and Uzbekistan.

In total, 11% of samples failed in one or more tests. The failure rate per product in the set of samples collected was the following:

- rifampicin capsules: 28,3%
- isoniazid tablets: 16,7%; isoniazid injection: 0%
- rifampicin/isoniazid tablets: 2,4%
- ofloxacin tablets: 15,8%; ofloxacin capsules: 0%; ofloxacin solution for infusion: 0%
- kanamycin powder for injection: 0%

Of the total of 291 samples, 38 (13%) were from WHO prequalified products. All these samples were of isoniazid/rifampicin FDCs from three Indian manufacturers. All WHO prequalified products complied with specifications as did all samples supplied by the GDF. 51 collected samples (18%) were of products not registered in the respective country, mostly supplied as humanitarian aid by international organizations, as allowed by national legislations. Two of these samples of non-registered products, were found non-compliant.

Conclusions of laboratory testing:

- The overall percentage of anti-TB drugs failing the quality standards was lower than expected. However, the proportion of rifampicin and isoniazid samples failing is concerning.
- The different quality testing results revealed not too many major failures but significant inconsistencies in quality were found. This indicates that there are problems with Good Manufacturing Practices (GMP) and other regulatory systems.
- For rifampicin, the lower content (assay) for some samples is worrying.
- The dissolution of rifampicin containing product did not provide clear information on bioavailability. Assessment of bioequivalence studies within the registration process of procurement of not registered products is therefore essential.

The summary of the survey results was accepted by all participants of the meeting.

### **Recommendations of the meeting and follow-up points:**

#### **Ministries of Health of participating countries:**

- To shift to the use of FDCs, especially for rifampicin containing products.
- To follow the WHO TB treatment guidelines and Essential Medicines List for selection of anti-TB products.
- To introduce and reinforce rational use of anti-TB medicines through banning sales of anti-TB drugs without prescription and restricting the use of anti-TB drug for other indications.
- To conduct investigations of manufacturers failing to conform with international quality standards and follow-up of corrective actions recommended.
- To support manufacturers to meet regulatory standards, including GMP.
- To identify local manufacturers and encourage their participation in the WHO Prequalification Programme.

#### **WHO:**

- To publish the results of the survey in an objective/transparent manner within three months. The text will not link any failure to a specific manufacturer but the full data of the 291 samples will be available as an annex (including the names of the 33 different manufacturers per sample). The report will reflect the limitations of the survey and cautions in extrapolating the results and drawing systematic conclusions. Participating countries and individuals will be acknowledged. The report will be translated into Russian.
- Following the finalization of the WHO report, a manuscript should be prepared for submission to a peer-reviewed journal.
- To promote registration of medicines provided by international organizations/mechanisms.
- To further advocate for the participation of manufacturers in the WHO Prequalification Programme.
- To continue working with NDRAs to improve regulatory systems at country level.

#### **National Health Authorities and WHO:**

- To investigate reasons for use of injectable forms of isoniazid, ofloxacin and other anti-TB drugs not recommended by WHO.
- To support resource mobilization for strengthening of medicines regulatory systems, for example from the Global Fund and others.