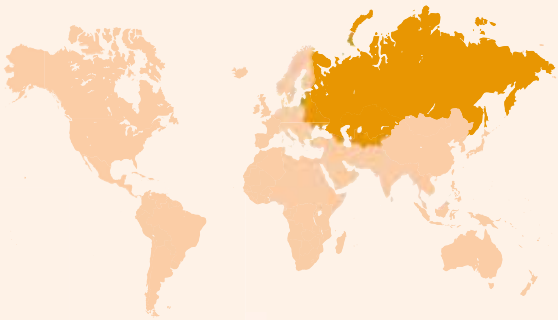

SURVEY OF THE QUALITY OF ANTI-TUBERCULOSIS MEDICINES CIRCULATING IN SELECTED NEWLY INDEPENDENT STATES OF THE FORMER SOVIET UNION

World Health Organization

WHO/EMP/QSM/2011.2

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

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The principal survey developers and organizers, and the report authors were Jitka Sabartova - Department of Essential Medicines and Pharmaceutical Policies, WHO, Geneva; Eva Nathanson - Stop TB Department, WHO, Geneva; and Olexandr Polishchuk, WHO Regional Office for Europe, Copenhagen.

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Abbreviations

API	Active pharmaceutical ingredient
BP	British Pharmacopoeia
BCS	Biopharmaceutical classification system
DL	Detection limit
E	Ethambutol
E. U.	Endotoxin units
EURO	World Health Organization Regional Office for Europe
FDC	Fixed-dose combination
FPP	Finished pharmaceutical product
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GLC	Green Light Committee
GDF	Global Drug Facility
GMP	Good Manufacturing Practice
H	Isoniazid
HPLC	High performance liquid chromatography
INN	International nonproprietary names for pharmaceutical substances
IMPACT	International Medicinal Products Anti-Counterfeiting Taskforce
IP	Indian Pharmacopoeia
IUATLD	International Union Against Tuberculosis and Lung Disease (now renamed “The Union”)
MDR-TB	Multidrug-resistant tuberculosis
MSF	Médecins sans Frontières
NGO	Nongovernmental organization
NIS	Newly independent states of the former Soviet Union
NLT	Not less than
NMRA	National medicines regulatory authority
NTP	National Tuberculosis Programme
OMCL	Official Medicines Control Laboratory
Ph. Eur.	European Pharmacopoeia
Ph. Int.	The International Pharmacopoeia
WHO-PQ'd	WHO-prequalified
R	Rifampicin
RRT	Relative retention time
RSD	Relative standard deviation
S	Streptomycin
SDS	Sodium dodecyl sulphate
SRA	Stringent regulatory authority
TB	Tuberculosis
TLC	Thin-layer chromatography
USP	United States Pharmacopeia
WHO	World Health Organization
WHO HQ	World Health Organization headquarters
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

Executive summary

The aim of this survey was to explore the quality of anti-tuberculosis medicines in use in selected newly independent states of the former Soviet Union (NIS), as one of the potential factors contributing to the high burden of multidrug-resistant tuberculosis (MDR-TB) observed in all of these countries.

Samples of selected first and second-line anti-TB medicines were collected from public and private sector procurement and treatment centres in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan. A total of 291 samples of medicines containing rifampicin, isoniazid, kanamycin or ofloxacin produced by 33 manufacturers were collected from 84 collection sites. Samples were tested by preselected reliable laboratories for appearance, identity, assay (content of active ingredient), related substances, dissolution and uniformity of mass. Injections, solutions, and powders for injection were also tested for pH value, sterility, and bacterial endotoxins.

No sample was suspected to be of a spurious, falsely-labelled, falsified or counterfeit product. There were no quality problems identified with samples of kanamycin powder for solution for injection, isoniazid solution for injections or ofloxacin solution for infusion. Isoniazid/rifampicin FDC was the only medicine of which WHO-prequalified samples were collected in this survey. Of 42 isoniazid/rifampicin FDC samples collected, 38 were of prequalified products and none of those failed to comply with pre-set specifications. Neither did any of the 42 samples supplied through the Global Drug Facility (GDF), 25 of which were of WHO-prequalified products.

Overall 33 samples (11.3%) failed to meet the specifications set for the survey. The highest failure rate was found for mono-component products containing rifampicin - more than a quarter of rifampicin samples (28.3%) failed to meet the specifications, and the predominant reason for this was that the content of active ingredient was below the acceptable limit. For the purpose of differentiating between deviations which are likely to impact the health of patients and those which are not, the category of extreme deviations was arbitrarily defined as the content of API deviating by more than 20% from the declared content and/or average dissolution value of tested units below pharmacopoeia Q value minus 25%.Focusing only on extreme deviations from specifications, the total failure rate reached 1.0%.

This seems to reflect relatively good overall compliance with quality standards, and the zero failure rate among WHO-prequalified samples and those supplied through GDF indicates that these mechanisms are effective in assuring the quality of anti-TB medicines. On the other hand, low content of rifampicin, substantial inconsistencies in ofloxacin dissolution, as well as batch-to-batch and intra-batch inconsistencies are of concern and need to be addressed. These findings may be caused by a combination of inconsistent application of Good Manufacturing Practices (GMP) and insufficient regulatory supervision. An impact of inappropriate distribution and storage conditions could not be excluded, but there was not enough information to relate the quality problems identified to specific distribution or storage problems.

The results of the survey cannot be generalized to the overall anti-TB medicines market in the surveyed countries because of limitations in the sampling, and - although they are encouraging - they indicate that further efforts are required to facilitate access to medicines that meet international quality standards in order to ensure the provision of quality anti-TB medicines to patients in the region. The results of the survey were analysed with representatives of participating countries, and agreed recommendations on further steps to improve the situation are listed in Box 1.

Box 1. Recommendations from survey wrap-up meeting

Ministries of Health in participating countries:

- To shift towards the use of FDCs, especially for rifampicin-containing products
- To follow the WHO TB treatment guidelines and the WHO Essential Medicines List
- To introduce and reinforce rational use of anti-TB medicines through banning sales of anti-TB medicines without prescription and restricting the use of anti-TB medicines for other diseases
- To conduct investigation of failures with manufacturers and follow-up of corrective actions recommended
- To ensure the compliance of manufacturers with regulatory standards, including GMP
- To identify local manufacturers and encourage their participation in the WHO Prequalification of Medicines Programme
- To continue efforts to ensure proper conditions during distribution and storage of medicines both in pharmaceutical facilities (pharmacies and warehouses) and in health facilities

WHO:

- To publish the results of the survey in an objective and transparent manner (with Russian translation)
- To promote registration of medicines supplied by international organizations/mechanisms
- To further advocate for the participation of manufacturers in the WHO Prequalification of Medicines Programme
- To continue working with NMRAs to improve regulatory systems at country level

NMRAs and WHO:

- To investigate reasons for use of injectable forms of isoniazid, ofloxacin and other anti-TB medicines
- To support resource mobilization for strengthening of medicines regulatory systems, for example from the Global Fund and others

1. Introduction

1.1 Rationale

WHO estimates that nearly half a million multidrug-resistant tuberculosis (MDR-TB) cases emerge worldwide each year as a result of inadequate or poorly administered treatment regimens, insufficient supply or quality of anti-TB medicines, and transmission of drug-resistant strains. Newly independent states of the former Soviet Union (NIS) have the highest prevalence rates of MDR-TB, with reported proportions of MDR-TB as high as 28.3% among new and 61.6% among previously treated TB cases[1].

It has been hypothesized that one of the most important factors for the resurgence of TB, and for the high rates of MDR-TB, in the NIS, was the socio-economic crisis that followed the disintegration of the Soviet Union in 1991[2,3,4]. This crisis resulted in interruptions of drug supply and overall deterioration of the health sector, which had an impact on the transmission of and susceptibility to TB and MDR-TB. During this period regulatory mechanisms were in transition, and the quality of procured medicines was insufficiently monitored. The lack of standardized treatment regimens in many countries is also likely to have contributed to the development of drug resistance.

Limited research has been conducted into the factors contributing to drug resistance in this region, and into the marked regional and national differences in drug resistance rates. In particular, there has been little consideration of the extent to which substandard and spurious, falsely-labelled, falsified and counterfeit anti-TB medicines might circulate in this region. This survey aimed to investigate the quality of anti-TB medicines in use in selected NIS as one of the potential factors contributing to the development of drug resistance.

1.2 Background

1.2.1 Tuberculosis situation in the NIS

TB notification rates declined in the Soviet Union and Eastern Europe between 1950 and 1989, with a ten-fold decrease in notifications in urban areas and a threefold decrease in rural areas2. TB notification rates more than doubled in the NIS during the decade 1990-2000[5], fuelled by the deterioration of TB control services and the broader social and economic breakdown3. The rates have stabilized since 2000 yet still, in comparison to Western European countries where the estimated rate of new TB cases per 100,000 population is below 25, all NIS (except Belarus and the Baltic states) have high estimated rates between 100 and 299 per 100,000 population.

Box 2. Newly independent states (countries marked with * are designated high MDR-TB countries)

Armenia*	Kazakhstan*	Russian Federation*
Azerbaijan*	Kyrgyzstan*	Tajikistan*
Belarus*	Latvia*	Turkmenistan
Estonia*	Lithuania*	Ukraine*
Georgia*	Republic of Moldova*	Uzbekistan*

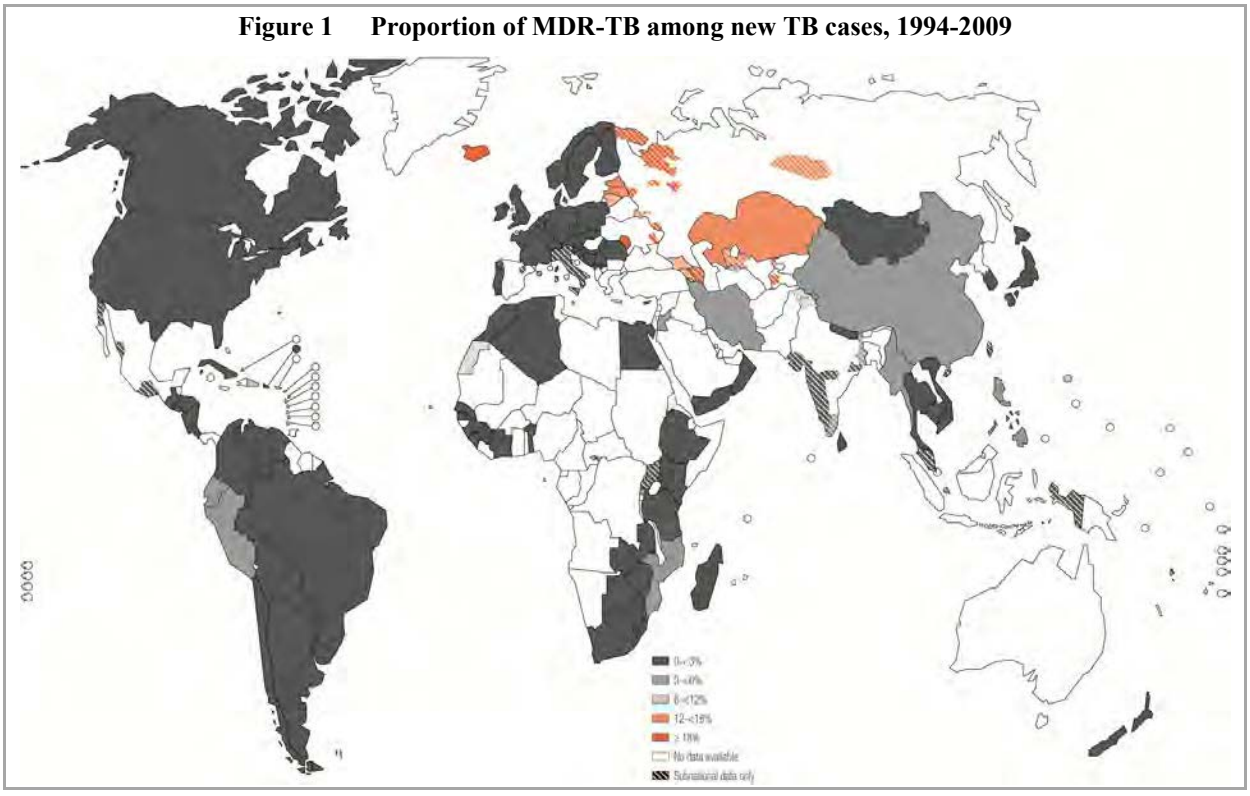
In 2008 an estimated 440,000 cases of MDR-TB emerged globally1. India and China carry the greatest burden of MDR-TB in absolute terms, together accounting for almost half of the world's total. However, the highest MDR-TB prevalence rates have been observed in the NIS. Of the 27 high MDR-TB burden countries that contribute 85% of the world's estimated MDR-TB burden, 14 are the NIS (Box 2)[6].

Since 2000, no country outside of Eastern Europe and Central Asia has reported proportions of MDR-TB among new cases exceeding 6% (for countries reporting more than 10 MDR-TB cases). The NIS, however, have consistently reported proportions above this threshold (Table 1 and Figure 1). Moreover, the proportion of MDR-TB among previously treated TB cases has exceeded 50% in several countries (Table 1).

In 2006 extensively drug-resistant TB (XDR-TB) was reported in all regions of the world and was rapidly classified by WHO as a serious emerging threat to global public health. By March 2011, 69 countries had reported at least one case of XDR-TB. Eight countries reported XDR-TB in more than 10% of MDR-TB cases (for countries reporting more than 10 XDR-TB cases); six of these are NIS6.

MDR-TB and XDR-TB are much more complex and costly to treat than drug-susceptible TB. Data from Estonia, Germany, Italy, and the Russian Federation (Arkhangelsk Oblast) between 1999-2006 have shown cure rates for MDR-TB of 39-72% and cure rates for XDR-TB of 36-48%, dependent on the precise resistance patterns and in particular sensitivity to capreomycin[7].

Figure 1 Proportion of MDR-TB among new TB cases, 1994-2009



Source: *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response*. Geneva, World Health Organization, 2010.

Table 1 Proportion of MDR-TB among TB cases tested for resistance

In bold: Resistance rates > 6% in new cases, >50% in previously treated cases

Period:	1994-1997		1997-2000		2000-2002		2002-2007		2007-2009	
Type of TB cases: / Country / Region	New	Previously treated	New	Previously treated	New	Previously treated	New	Previously treated	New	Previously treated
Armenia							**9.4%**	43.2%		
Azerbaijan							**22.3%**	**55.8%**		
Estonia	**10.2%**	19.2%	**14.1%**	37.8%	**12.2%**	45.3%	**13.3%**	**52.1%**	**22.0%**	**51.6%**
Georgia							**6.8%**	27.4%	**10.3%**	31.1%
Kazakhstan					**14.2%**	**56.4%**				
Latvia	**14.4%**	**54.4%**	**9.0%**	23.7%	**9.3%**	27.1%	**10.8%**	36.3%	**13.4%**	35.8%
Lithuania					**9.4%**	**53.3%**	**9.8%**	47.5%	**10.6%**	**51.5%**
Rep. of Moldova							**19.4%**	**50.8%**		
Russian Federation										
Arkhangelsk Oblast									**23.8%**	**58.8%**
Belgorod Oblast									**19.2%**	**51.6%**
Bryansk Oblast									**12.9%**	27.8%
Ivanovo Oblast	4.0%	27.3%	**9.0%**	26.7%			**12.3%**	**58.1%**	**20.0%**	**57.7%**
Kaliningrad Oblast									**19.3%**	43.1%
Mary El Oblast							**12.5%**	-	**16.1%**	37.7%
Murmansk Oblast									**28.3%**	35.7%
Orel Oblast					2.6%	42.4%	**8.8%**	16.7%	5.4%	48.3%
Pskov Oblast									**27.3%**	50.0%
Chuvashia Repub.									**14.2%**	45.7%
Tomsk Oblast			**6.5%**	25.9%	**13.7%**	43.6%	**15.0%**	-	**13.0%**	**53.8%**
Vladimir Oblast									**14.0%**	32.7%
Tajikistan									**16.5%**	**61.6%**
Turkmenistan					3.8%	18.4%				
Ukraine							**16.0%**	44.3%		
Uzbekistan					**13.2%**	40.2%	**14.8%**	**60.0%**		

Source: World Health Organization/International Union Against Tuberculosis and Lung Disease (WHO/UNION). *Global Project on Anti-Tuberculosis Drug Resistance - Surveillance results for countries of the former Soviet Union (1994-2008)*[1, 6, 8, 9, 10, 11]

1.2.2 Quality problems of medicines

Although reports on medicines quality problems – with their serious health repercussions – appear to be on the increase, the exact magnitude of the problem is unknown. The diversity of sources of information makes compiling statistics a challenge. Sources include reports from national medicines regulatory authorities (NMRA), enforcement agencies, pharmaceutical companies and nongovernmental organizations, as well as *ad hoc* studies of specific geographical areas or therapeutic groups. The different methods, especially sampling, used in the studies and the varying approaches to preparing reports compound the difficulties in compiling and comparing data. Furthermore, studies can only give snapshots of the immediate situation. Counterfeiters, by contrast, are extremely flexible in the methods they use to mimic products and prevent detection of their activities.

Medicines quality problems are particularly prevalent where regulatory and legal oversight is absent or weak (which is the case in about 30% of countries worldwide); where prices of

medicines are high; and where the official supply chain fails to reach some communities. Although precise and detailed data on spurious, falsely-labelled, falsified or counterfeit medicines is difficult to obtain, estimates range from about 1% of sales in developed countries to over 10-30% in developing countries, depending on the geographical area[12].

The circulation of substandard and spurious, falsely-labelled, falsified or counterfeit medicines has been acknowledged to be a serious clinical and public health problem[13,14,15,16], however there is limited evidence as to how prevalent and widespread the problem is. Scientific study in this area has been hampered by the confusion over the distinction between spurious, falsely-labelled, falsified or counterfeit and substandard medicines. Counterfeiting can arise with both branded and generic medicines; substandard, spurious, falsely-labelled, falsified or counterfeit medicines may include those with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.

Many NIS have a proportion of counterfeit medicines which is above 20% of market value. A 2006 report suggested that counterfeit drug production was worth an estimated $300 million per year in the Russian Federation and, although the government claimed that counterfeiting was on the decrease, it admitted that up to 10% of medicines were counterfeit[17]. According to the same report, 70% of counterfeit medicines in circulation in the Russian Federation were produced inside the country, and an estimated 70% of those were copies of foreign medications.

1.2.3 Quality problems of anti-tuberculosis medicines

The existence of substandard, spurious, falsely-labelled, falsified and counterfeit anti-TB medicines has been documented in surveys from a number of countries (Table 2). Whilst these studies give some information as to the existence of the problem, the data are not sufficient to establish its scale or distribution.

There are limited data about the quality of anti-TB medicines from NIS. One survey listed in Table 2 included samples from Estonia and Latvia but there was no breakdown by country on the results of the quality testing[18].

The majority of quality problems for anti-TB medicines were due to inadequate content of the active ingredient. A further problem has been identified with poor bioavailability of anti-TB medicines, primarily rifampicin, both in mono-component products and fixed dose combinations (FDC)[19,20,21]. Evidence suggests that for FDCs, and particularly for formulations of rifampicin, isoniazid and pyrazinamide, the absorption of rifampicin can be significantly impaired if the FDCs are manufactured under suboptimal conditions[22]. It is therefore vital to use only rifampicin-containing FDCs that have proven rifampicin bioavailability[23]. One bioavailability study from Estonia of two generic rifampicin mono-component formulations demonstrated bioequivalence to the standard formulation[24].

The cause of altered bioavailability of rifampicin from certain formulations is not clearly understood. Various hypotheses have been proposed, including changes in the crystalline structure during processing, adsorption by excipients, decomposition of rifampicin in the formulation, decomposition of rifampicin in the gastrointestinal tract, and inherent variability in absorption and metabolism[22,25,26,27,28,29]. Particle size, in the presence of magnesium stearate, can also affect the bioavailability and dissolution rate of rifampicin[30,31,32].

The International Union Against Tuberculosis and Lung Disease (The Union) and WHO jointly recommend that rifampicin-containing FDCs are rigorously registered and that the results of bioavailability tests (from a testing site of proven proficiency) are provided. Also on

submission of tenders, comparative bioavailability studies for rifampicin and dissolution tests for all other components should be required[33,34,35,36,37].

Table 2 Surveys of anti-TB medicines quality

Country	Reference	Survey methodology	Tests*	Medicines tested*	Sample size	Proportion of samples substandard
Nigeria	38	Random selection 35 pharmacies; specific medicines purchased	Assay (HPLC)	R H Z S	15 4 3 19	33% 100% 100% 53%
Thailand	39	Random selection 52 hospitals; random selection 20 tabs/caps from dispensary	Assay (HPLC) Dissolution	R H Z E	50 51 46 51	Assay / Dissolution 0 / 0 0 / 62% 14% / 26% 0
Not specified	40	Convenience sample 13 FDC products	Assay (TLC, confirmatory testing by UV for R and HPLC for H)	HR HRZ HRZE	5 6 2	20% 17% 100%
Colombia Estonia India Latvia Russian Federation Vietnam	18	Convenience sample from hospital & local pharmacies	Assay (TLC, confirmatory testing of selected samples by UV for R and HPLC for H)	R H HR HRZ HRZE	14 2 21 1 2	14% 0 14% 0 100%
India	41	Random selection from 52 pharmacies; specific medicines purchased	Screening (semi-quantitative TLC and disintegration)	R H	118 84	9% 12%
Myanmar Vietnam	42	Non-random selection survey sites; random selection of medicines outlets within survey site	Assay (not specified)	R	42	24%
India	43	Non-random selection of pharmacies; non-random selection of medicines	Assay (HPLC)	HR HRZ HRE HRZE	3 2 3 3	0 0 0 0

*HPLC, high performance liquid chromatography; TLC, thin layer chromatography; UV, ultraviolet spectrophotometry; R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; E, ethambutol

1.2.4 WHO response to quality problems of medicines

Development of international norms and standards

WHO's mandate is to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products" (Article 2, WHO Constitution). WHO Member States rely on WHO for advice, expertise and guidance in regulation, safety and quality assurance of medicines through development and maintenance of international up-to-date norms, standards, guidelines and nomenclature.

The increasing globalization of manufacturing, including the merging of pharmaceutical companies, related to both starting materials and finished pharmaceutical products, are internationalizing pharmaceutical commerce. International pharmaceutical norms and standards are thus more important than ever before since they serve as global tools for a harmonized approach aiming to ensure safety and quality of medicines. One of WHO's roles is to continue to develop such international norms and standards, and to help countries implementing them.

Important key elements are quality assurance guidance texts and guidelines in the areas of production, testing, and distribution of medicines. These include guidance on good manufacturing practices, quality assurance for regulatory approval and prequalification of medicines, laboratories and supply agencies, quality control testing, the International Pharmacopoeia and International Chemical Reference Standards, and the programme on International Nonproprietary Names (INN). All these elements are ready for use by national regulatory authorities, manufacturers, and other interested parties, including international organizations. Based on the feed-back from the users, WHO undertakes all efforts to maintain the standards and guidelines up to date and to complement them as necessary.

Prequalification of Medicines Programme

The Prequalification of Medicines Programme, set up in 2001, is a service provided by WHO to facilitate access to medicines that meet unified standards of quality, safety and efficacy primarily for HIV/AIDS, malaria, TB, and reproductive health[44]. From the outset, the programme was supported by UNAIDS, UNICEF, UNFPA and the World Bank as a concrete contribution to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines. WHO keeps a list of prequalified medicinal products on the internet. The products listed (manufactured at specified manufacturing sites according to accepted specifications) are those for which, at the time of assessment, the product data and information submitted were found to meet the norms and standards recommended by WHO and for which, at the time of inspection, the relevant manufacturing and clinical sites were found to be in compliance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). Compared to the other categories of medicines, the list of WHO-prequalified anti-TB medicines is limited for various reasons - fewer manufacturers worldwide, their lower interest to participate in competition in a less profitable area, and frequent problems with GMP compliance and with the quality of medicines dossiers. However, the list has increased in the past two years and as of June 2011 it contained 11 first-line mono-component anti-TB medicines, 12 first-line FDCs, and eight second-line products[44].

International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT)

WHO activities in the prevention and control of substandard, spurious, falsely-labelled, falsified and counterfeit medicines form a part of its work in the area of quality and safety of medicines. In order to mobilize awareness and action in the fight against counterfeit medicines, in February 2006 WHO created a global partnership known as the International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT)[12]. From 2007 to 2009, the taskforce resulted in the more active involvement of WHO in this area than in preceding years, with a strong new planning and coordinating role.

In 2009, following discussions at the Sixty-first World Health Assembly and the 124th session of the Executive Board, and the questions raised about the involvement of WHO in the Taskforce, WHO formally re-established its own programme to combat spurious, falsely-labelled, falsified and counterfeit medicines within the Essential Medicines and

Pharmaceutical Policies Department. A Working Group of Member States on Substandard/spurious/falsely-labelled/falsified/ counterfeit medical products was mandated in May 2010 by the Sixty-third World Health Assembly[45,46].

Global Drug Facility (GDF)

The Global Drug Facility (GDF) was launched in 2001 and is an initiative of the Stop TB Partnership which aims to increase access to quality-assured TB medicines[47,48]. GDF is housed at WHO HQ in Geneva and managed by the Stop TB Partnership secretariat. GDF acts as a procurement agency and offers three core services:

- Grant Service (first and second-line anti-TB medicines and diagnostics) for countries and nongovernmental organizations (NGOs) that are donor-dependent for some or all of their drug supply
- Direct Procurement Service for countries, NGOs and donors wanting to buy first-line anti-TB medicines and diagnostics, or second-line anti-TB medicines for Green Light Committee (GLC)-approved projects
- Technical assistance service for grant and direct procurement recipients through annual and ad hoc missions for in-country drug management monitoring and training

In 2008, GDF initiated a revision and expansion of its Quality Assurance Policy and Procedures in line with the new policies of major donor and international organizations involved in TB control (i.e. the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID, UNICEF, The Union and Médecins sans Frontières) in order to ensure global consistency in quality standards for procurement and supply of anti-TB medicines and medical items, and to avoid duplication of effort among organizations involved in TB control.

With the mission of guaranteeing the safety, efficacy, and quality of products provided by GDF, the quality assurance system[49] is based on:

- WHO treatment guidelines
- Authorization for use by recipient countries
- Recommendation by the relevant WHO programmes, i.e. for anti-TB medicines the Prequalification of Medicines Programme; or authorization for marketing by a stringent national medicines regulatory authority (SRA)* in the country of use
- Recommendation for procurement purposes by an Expert Review Panel, for a specified time period where there are no WHO-prequalified or SRA-approved products available
- Monitoring of the quality of supplied products including independent random quality control and post-delivery surveillance

* *Stringent Regulatory Authority (SRA)* means a regulatory authority (in case of the European Union both EMA and national competent authorities are included) which is (a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH (as specified on its website); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).
Source: Guideline on Submission of Documentation for Prequalification of Multisource (generic) Finished Pharmaceutical Products (FPPs) approved by Stringent Regulatory Authorities.
http://www.who.int/prequal/info_applicants/Guidelines/PQProcGenericSRA_June2009.pdf

1.3 Aim of this survey

The aim of this survey was to evaluate the pharmaceutical quality of widely used first- and second-line anti-TB medicines obtained at public and private sector procurement and treatment centres in selected NIS. The specific questions addressed were:

1. Which anti-TB medicines are mostly used?
2. What proportion of anti-TB medicine samples (including FDC products), collected at approved procurement and treatment centres, fail quality testing?
3. Which specific quality tests do the samples fail, if any?
4. Are any of the deficiencies critical, i.e. could they most likely affect treatment efficacy and/or cause harm to the patient?

The results of this survey are expected to assist responsible authorities in the countries to develop appropriate quality assurance strategies for anti-TB medicines. They also provide information for WHO to adapt its prequalification procedures. Finally, the results will be of use in awareness and advocacy programmes around quality issues in anti-TB treatment in general.

2. Methodology

2.1 Pre-survey

In 2008, a pre-survey was conducted in the following nine countries: Armenia, Azerbaijan, Belarus, Estonia, Kazakhstan, Moldova, Latvia, Ukraine and Uzbekistan. The aim of the pre-survey was to discover the range and manufacturers of medicines circulating in the countries, and to identify facilities where samples could be collected.

A questionnaire was developed (Annex 1 to Appendix 1) to determine the availability in the countries of key first- and second-line anti-TB medicines. Based initially on the WHO Guidelines for Treatment of Tuberculosis, the questionnaire was expanded to include other anti-TB medicines which were identified in pre-surveyed facilities.

NMRAs, with which the WHO Regional Office for Europe is cooperating on a long-term basis, were asked to perform the pre-survey in facilities in which a representative range of anti-TB medicines used in the particular country could be expected (taking into account the national system of supply and provision of anti-TB medicines). The pre-survey asked for an overview of anti-TB medicines (first- and second-line, mono-component and FDCs, with specific focus also on paediatric formulations) that were in stock in the selected facilities in July 2008, including their volumes and manufacturers.

Table 3 shows the types of facilities included in the pre-survey in individual countries. As the systems of supply and provision of anti-TB medicines differ in the countries, various approaches were taken. In both Azerbaijan and Belarus the pre-survey was performed in a single facility in the capital city. In Estonia and Latvia the information was collected by the national TB Programme in Tartu and the State Agency of TB and Lung Diseases in Riga region respectively. In Kazakhstan and Uzbekistan the pre-survey was performed in two facilities (in Kazakhstan both were located in the capital city, in Uzbekistan the two facilities were in separate regions). In Armenia four facilities in the capital city were pre-surveyed and in Ukraine the information was received from 26 facilities throughout the country (25 regions and the capital Kiev).

The answers from the pre-survey questionnaires gave a snapshot of the medicines available in the selected facilities as of July 2008. Although it could not provide a complete picture of anti-TB medicines used in the countries, and the different countries provided various levels of detail, the pre-survey was useful to broadly identify medicines used in the country, to estimate numbers of manufacturers located in a stringent regulatory environment or supplying at least one product registered in such an environment, numbers of manufacturers producing at least one WHO-prequalified products, and the availability of FDCs and paediatric formulations.

The number of products stated to be in stock in the pre-surveyed facilities ranged from 14 in Estonia and Latvia to 30 in Ukraine. Some respondents mentioned only the products included in the questionnaire; others provided information about additional TB medicines.

Table 3 indicates the numbers of manufacturers of anti-TB medicines mentioned to be in stock at the pre-surveyed facilities, differentiating between manufacturers operating in or exporting to a stringent regulatory environment (as defined in the footnote on page 16), manufacturers of WHO-prequalified products, and others. Countries were preferentially selected for inclusion in the main survey if medicines produced by the last group were found to be circulating in their territories.

Table 3 Overview of pre-survey outcomes

Country	Types of facilities pre-surveyed	Number of products pre-surveyed	Manufacturers of available anti-TB medicines specified in the questionnaire*				
			Operating in / exporting to a stringent regulatory environment	Producing at least one WHO-prequalified product	Other		
					Total	**Domestic**	**Foreign: Countries of manufacture of imported products**
Armenia	P/H, W, 2 Ph	20	8	2	**7**	**-**	**Belarus, China, Egypt, India, Syria, Ukraine**
Azerbaijan	P/H	19	3	3	**10**	**-**	**India, Russian Federation, Turkey**
Belarus	P/H	16	2	1	**10**	**3**	**India, Russian Federation, Ukraine**
Estonia	P/H	14	7	1	**-**	**-**	**-**
Kazakhstan	2 P/H	17	1	2	**8**	**3**	**India, Russian Federation, Ukraine**
Latvia	P/H	14	6	-	**1**	**-**	**India**
Moldova	P/H, W	23	3	4	**9**	**1**	**China, India, Russian Federation, Ukraine, Viet Nam**
Ukraine	26 P/H	30	-	3	**10**	**6**	**India**
Uzbekistan	2 P/H	15	5	3	**5**	**-**	**China, India**

P/H –Public hospital; W – Warehouse; Ph – Pharmacy;
* Each manufacturer was counted only once regardless of the number of different products found in the pre-survey.

First-line products

In principle, all first-line mono-component anti-TB medicines selected for the pre-survey were available in the selected facilities in all countries at the time of pre-survey.

Injectable formulations were available in addition to oral formulations in certain countries:

- Isoniazid solution for injection in Azerbaijan, Belarus, Kazakhstan and Ukraine
- Rifampicin powder for solution for injection in Latvia and Ukraine
- Ethambutol solution for injection in Latvia

First-line FDC products were less frequently found in the pre-surveyed countries than mono-component products. No FDC products were reported from Belarus and very few from Ukraine, despite the large number of facilities surveyed in that country. In the other countries the following combinations were found:

- Isoniazid/rifampicin in Armenia, Azerbaijan, Estonia, Kazakhstan, Latvia, Moldova and Uzbekistan
- Ethambutol/isoniazid/rifampicin in Kazakhstan
- Ethambutol/isoniazid/pyrazinamide/rifampicin in Armenia, Azerbaijan, Kazakhstan, Uzbekistan

Small volumes of FDC products were generally reported to be available in the pre-surveyed facilities, and although a total of 13 local manufacturers were identified in the pre-survey,

none of the FDC products reported was produced domestically. The vast majority had been produced in India, with one product produced in Germany.

Second-line anti-TB medicines

Most second-line anti-TB medicines selected for the pre-survey were available in the selected facilities in the majority of the countries. The exceptions were products containing ethionamide (reported from Kazakhstan and Moldova only), levofloxacin (reported from Armenia, Belarus, Ukraine and Uzbekistan only) and moxifloxacin (reported from Armenia, Belarus, Latvia and Uzbekistan only). Similarly to first-line mono-component anti-TB medicines, second-line products were also available in injectable formulations:

- Ofloxacin solution for infusion in Belarus and Ukraine
- Levofloxacin solution for infusion in Ukraine
- *p*-aminosalicylic acid (PAS) solution for infusion in Ukraine

Paediatric anti-TB medicines

Very few medicines intended specifically for use in children were reported within the pre-survey. There were no paediatric formulations identified in Armenia, Azerbaijan, Belarus and Kazakhstan. Only mono-component medicines containing 100mg of isoniazid were reported from Estonia, Latvia, Moldova, Ukraine and Uzbekistan. One region in Ukraine reported the availability of paediatric FDC isoniazid/rifampicin 60mg/60mg.

Additional TB medicines not included in the pre-survey questionnaire

Four of the nine countries also reported the availability of additional anti-TB medicines not in the questionnaire:

• Belarus:	Rifabutin	150mg capsules
• Estonia:	Amoxicillin/clavulanic acid	875/125mg tablets
	Clarithromycin	500mg tablets
• Latvia:	Amoxicillin/clavulanic acid	500/125mg tablets
	Clarithromycin	500mg tablets
• Ukraine:	Clofazimine	100mg capsules
	Gatifloxacin	0.2%; 0.4% solution for infusion
	Lomefloxacin	400mg tablets
	Pefloxacin	400mg tablets
	Rifabutin	150mg capsules
	Rifapentine	150mg tablets/capsules
	Sparfloxacin	400mg tablets

No information in this respect was received from Armenia, Azerbaijan, Kazakhstan, Moldova and Uzbekistan. The above list therefore does not represent a complete picture of additional medicines used in the pre-surveyed countries.

2.2 Participating countries and study period

Based on the results of the pre-survey, the main quality testing survey focused on countries with a wide range of domestic and imported first- and second-line anti-TB medicines, including a substantial proportion produced by manufacturers who were not operating in a stringent regulatory environment nor supplying WHO-prequalified products. Accordingly,

Estonia and Latvia were excluded from the project because the vast majority of the available medicines were produced in a stringent environment. Moreover both these countries follow European Union regulations for medicine quality and have various mechanisms for market surveillance in place. Moldova was not included as the reply to the pre-survey questionnaire was received too late to allow inclusion in the main survey.

Consequently six countries were included in the survey, namely **Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine and Uzbekistan**. Agreements for participation were obtained from the National Ministries of Health, and each country nominated a focal person from the NMRA or the Ministry of Health to coordinate the sampling and shipment of medicines to the testing laboratories.

The survey was conducted according to a common protocol (Appendix 1) developed in cooperation with all involved parties.

A preparatory meeting was held with the focal persons from the six countries in Minsk, Belarus, from 21-22 May 2009. Following this meeting the samples of anti-TB medicines were collected in the three-month period from June to August 2009. Collected samples were sent to five preselected reliable testing laboratories, and testing was performed between September 2009 and February 2010. In June 2010, WHO met with representatives of the participating countries in Copenhagen, Denmark and analysed the survey outcomes.

2.3 Anti-TB products surveyed

The following criteria were considered when selecting medicines for the quality survey:

- Medicines available in the majority of countries in significant volumes
- Medicines produced by various manufacturers, preferably from non-stringent environment
- Medicines susceptible to quality deterioration

With regards to first-line mono-component anti-TB medicines, the above criteria were fulfilled by products containing isoniazid and rifampicin. As mentioned previously, FDCs did not seem to be widely available and the only combination found in the majority of selected countries was the FDC containing isoniazid/rifampicin. Second-line anti-TB medicine products containing kanamycin and ofloxacin were selected. Products containing isoniazid and ofloxacin were available in some countries in oral and injectable formulations; both these formulations were included in the survey.

As the result, the following first and second-line anti-TB medicines were included in the project:

- **Isoniazid** — 300mg and 100mg tablets; 10% solution for injection (5ml)
- **Rifampicin** — 300mg and 150mg capsules
- **Isoniazid/rifampicin** — 150mg/300mg, 150mg/150mg, 75mg/150mg, 60mg/60mg, and 30mg/60mg tablets
- **Kanamycin** — 1g powder for solution for injection
- **Ofloxacin** — 200mg and 400mg tablets or capsules; 0.2% solution for infusion (200ml).

2.4 Selection of sample collection sites

All selected countries used centralized government procurement and supply of anti-TB medicines at the time of the survey. Sale in pharmacies was prohibited by regulations for first-line anti-TB medicines in Azerbaijan and for all anti-TB medicines in Belarus. In Armenia, Kazakhstan, Ukraine and Uzbekistan, anti-TB medicines could be obtained in pharmacies, but this was not the major source of anti-TB medicines for patients. Almost all countries used donor assistance in addition to centralized procurement. All supplies came through licensed wholesale companies, both in the public and private sector.

The aim of the survey was to evaluate the quality of medicines available to patients, i.e. in treatment facilities. It was clear from the pre-survey results that in some countries it would not be possible to collect all planned samples at primary healthcare level or hospitals only. Therefore the following principles for selecting sampling sites were agreed:

- The sampling should be done as close to the patient as possible, and
- the facility should have a large range of the selected medicines in sufficient amounts available for sampling.

Priorities for selection of sampling sites were defined as follows:

1. Treatment facilities (hospitals/primary healthcare level)
2. Pharmacies (public and private)
3. Wholesale/warehouses (public and private)
4. Manufacturers (only if sampling not possible at levels 1. to 3. above)

This sampling method could not ensure collection of a representative set of all anti-TB medicines used in these countries. However, in countries using centralized government procurement and supply of anti-TB medicines it provided a broad picture on the medicines available to patients.

The approach to selection of sampling sites was discussed and agreed with country focal persons during the preparatory meeting in Minsk. Draft national sampling plans were developed by the focal person in each country based on the above algorithm and reviewed and approved by WHO pharmaceutical experts.

2.5 Sample collection

For the purposes of this survey, a sample was defined as an item of each presentation collected from the same site. This means that an identical product (the same name, content of APIs, the same dosage form, same strength, same batch and produced by the same manufacturer) collected in two different sites represented two samples.

Samples were collected by the staff of the NMRAs (except Kazakhstan, where National TB Programme staff were involved), in cooperation with the WHO country office staff. Detailed national sampling plans were used (Annex 2 to Appendix 1), identifying the collection sites, medicines, number of batches and number of units per sample to be collected. The target number of samples was set at 60 samples per country (12 samples per product). Detailed instructions for collecting samples, storage and dispatch to testing laboratories were prepared (Annex 2 to Appendix 1), and focal persons arranged for training of collectors with regards to the national sampling plan and instructions.

Collectors were required to be mindful of the stock of sampled products in collection sites so as not to jeopardize the availability to patients. If there was a risk of product shortage after

sampling, they were instructed to either arrange for replacement of the sampled amount or to refrain from collection of that particular product in that facility.

For each sample, collectors assigned a unique code number and completed a standardized Sample Collection Form (Annex 3 to Appendix 1). The following details were recorded at the time of collection: product name, name of active ingredient(s), dosage form, strength per unit dose, package size, type and material of primary container, quantity collected, date of manufacture, batch number, expiry date, name and country of manufacturer, registration status and country and site of sample collection, storage conditions at the site, and date of sample collection. These details were considered essential not only for final data analysis but also to identify each sample and ensure its traceability.

2.6 Testing laboratories

Five quality control laboratories, for which evidence of reliable performance was available, were selected for testing of samples collected within this survey: The laboratories of the Austrian Agency for Health and Food Safety and Luxembourgeois Laboratoire National de Santé together with the laboratory of European Directorate for the Quality of Medicines and Healthcare are members of the European Official Medicines Control Laboratories network and are subject to regular mutual audits. The laboratory of J. W. Goethe University, Institute of Pharmaceutical Technology Biocenter is a long-term WHO Collaborating Centre, specialized in dissolution studies. SGS Life Science Services Lab Simon in Belgium cooperates with The Global Fund and Global Drug Facility in testing of anti-TB medicines. Table 4 shows the division of samples and tests among laboratories.

Table 4 Laboratories performing quality testing

Testing laboratory	Anti-TB medicines tested
Austrian Agency for Health and Food Safety (AGES) PharmMed, Vienna, Austria in cooperation with Laboratoire National de Santé, Luxembourg	Isoniazid tablets Isoniazid injections
European Directorate for the Quality of Medicines and Healthcare (EDQM), Strasbourg, France	Kanamycin Ofloxacin tablets Ofloxacin solution for infusion
J. W. Goethe University, Institute of Pharmaceutical Technology Biocenter, Frankfurt am Main, Germany	Rifampicin capsules Isoniazid/rifampicin tablets [Comparative dissolution study]
SGS Life Science Services Lab Simon SA, Wavre, Belgium	Rifampicin capsules Isoniazid/rifampicin tablets [Identity, assay, related substances, and uniformity of mass tests]

2.7 Quality tests conducted and test methods used

Depending upon the formulation and specifications, samples were tested for the following:

- Appearance
- Identity
- Assay (content of each active ingredient)
- Related substances
- Dissolution (for tablets and capsules)
- Uniformity of mass (for tablets and capsules)
- pH value (for solutions for injection, powders for solution for injection, and solutions for infusion)

- Sterility (for selected samples of solutions for injection, powders for solution for injection, and solutions for infusion)
- Bacterial endotoxins (for selected samples of solutions for infusion)

Test methods and specifications were methods of the respective monographs from the International Pharmacopoeia (Ph. Int.) or United States Pharmacopeia (USP) as detailed in Table 5 and Appendix 1, Annex 4.

Table 5 Specifications and methods used for testing

Product	Method
Isoniazid tablets	US Pharmacopeia monograph
Isoniazid solution for injections	US Pharmacopeia monograph
Rifampicin capsules	International Pharmacopoeia monograph
Isoniazid/rifampicin tablets	International Pharmacopoeia monograph
Kanamycin powder for solution for injection	US Pharmacopeia monograph for kanamycin injection
Ofloxacin tablets and capsules	US Pharmacopeia monograph for ofloxacin tablets
Ofloxacin solution for infusion	US Pharmacopeia monograph for ofloxacin tablets with addition of pH value, sterility, and bacterial endotoxins test

Certain problems with rifampicin bioavailability have been outlined in section 1.2.3. There are further concerns about poor correlation between bioavailability testing and *in vitro* dissolution[50], and about major differences experienced in outcomes of dissolution tests for rifampicin-containing products using conditions according to the Ph. Int. on one hand and USP and the British Pharmacopoeia (BP) on the other.

Given these concerns, it was decided to perform a comparative dissolution study on one sample from each manufacturer with an established comparator. If there was more than one strength from the same manufacturer, all were included in the study. The aim of this was to help clarify the differences in outcomes of dissolution tests performed under different conditions. For rifampicin capsules one set of comparative dissolution was performed using conditions according to the Ph. Int. monograph and the second set using conditions according to the BP monograph. In the case of isoniazid/rifampicin tablets, for which no official dissolution method exists in pharmacopoeias, the laboratory developed the method based on the conditions and acceptance criteria according to the Ph. Int. monograph for rifampicin tablets with slight modification (volume 900 ml instead of 500 ml to ensure sink conditions for both APIs, taking into consideration the different tablet strengths).

2.8 Specifications

The following specifications were used for the different tests:

Appearance

- Tablets should be undamaged, smooth, and usually of uniform colour. Presence of excessive powder and/or pieces of tablets in the container, cracks, chipping in the tablet surfaces or coating, swelling, mottling, discoloration, fusion between tablets, appearance of crystals on the container walls or on the tablets are signs of physical instability
- Capsules should be smooth and undamaged
- Solutions for injection, solutions for infusion, and reconstituted solutions should be clear and free from visible particulate matter

Identity

- Identity was confirmed by matching the retention time of the active ingredient peak in the standard and sample high performance liquid chromatography (HPLC) chromatograms obtained in the assay

Assay (content of each active ingredient)

- The limits for content of the active ingredient(s) applied to the individual products were 90.0 - 110.0% according to the specifications in the pharmacopoeia monographs used

Related substances

- Specifications for testing of related substances applied to the individual products are shown in each table of results in Appendices 4, 5, 7 and 8

Dissolution

- For isoniazid tablets and ofloxacin tablets and capsules the methods of the respective monographs as specified in Table 5 were used for dissolution tests. Dissolution was tested in three stages, with the following acceptance criteria:

Stage	Number of units tested	Acceptance criteria
S1	6 units	Each unit is not <Q*+5%
S2	Another 6 units	Average of 12 units (S1+S2) is ≥ Q, and no unit is <Q-15%
S3	Another 12 units	Average of 24 units (S1+S2+S3) is ≥Q, not more than 2 units are <Q-15%, and no unit is <Q-25%

**Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the content stated on the label. The testing is continued through the three stages unless the results conform at either stage 1 or stage 2*

Specifications applied in terms of Q values and testing time limits are shown in the table of results in Appendices 2 and 7.

Uniformity of mass of dosage units

- The following acceptance criteria were applied:

Pharmaceutical form	Average mass	Acceptable deviation (%)	Number of units (of 20 tested)
Tablets (uncoated and film-coated)	< 80mg	±10.0 ±20.0	Minimum 18 Maximum 2
	80mg - 250mg	±7.5 ±15.0	Minimum 18 Maximum 2
	> 250mg	±5.0 ±10.0	Minimum 18 Maximum 2
Capsules	< 300mg	±10.0 ±20.0	Minimum 18 Maximum 2
	≥300mg	±7.5 ±15.0	Minimum 18 Maximum 2

pH value

- Manufacturers' specifications for pH value, which were provided by NMRAs, were used for liquid dosage forms. Acceptable ranges for pH of solutions, where tested, are shown in the respective tables of results in Appendices 3, 6 and 8.

Sterility

- Test for sterility was performed according to the European Pharmacopoeia (Eur. Ph.) using membrane filtration. Given that sterility testing can never provide 100% certainty about the sterility of the product batch, and is resource-demanding, it was decided to limit the number of tested samples (one sample per manufacturer in case of kanamycin powder for solution for injection and ofloxacin solution for infusion).

Bacterial endotoxins

- Test for bacterial endotoxins was performed according to the Eur. Ph. using the gel-clot method. According to the Ph. Int., all intravenous infusions and those injections and powders for injections where the volume to be injected in a single dose is 15 ml or more must comply with this test. Therefore this test was applied to ofloxacin 0.2% solution for infusion (200ml) only; one sample from each batch and each manufacturer was tested. There was no limit for bacterial endotoxins for this product available as there is no pharmacopoeia monograph for ofloxacin solution for infusion, and manufacturers apply the test for pyrogens. The only information was found in the Brazilian Pharmacopoeia (max.5 E. U. /mg of ofloxacin for ofloxacin injection) and the Chinese Pharmacopoeia (less than 0.5 E. U. /ml for ofloxacin and sodium chloride injection and less than 0.75 E. U. /mg for ofloxacin substance).

2.9 Compliance of samples with standards

The samples were considered to be in compliance with standards if they met the specifications as outlined in the section above and/or listed in the respective tables of results in Appendices 2-8.

All results which were found out-of-specification were investigated and tests were repeated as appropriate, according to a laboratory Standard Operating Procedure on handling out-of-specification results.

In this survey all samples containing the same active ingredient(s) in the same dosage form were tested according to the same specification to enable comparison of samples from different manufacturers. It should be noted that individual manufacturers may use different specifications and different methods for testing of their products, and these specifications and methods may be approved by regulatory authorities in individual countries. Non-compliance with the specification selected for this survey does not necessarily imply non-compliance with the specifications approved in the country.

3. Results

3.1 Overview of samples tested

3.1.1 Products

A total of 291 samples were collected and tested. The nature and numbers of samples are displayed in Table 6.

As regards the strengths of the different products:

- 43/54 (80%) of isoniazid tablets samples were of 300mg, 11/54 (20%) of 100mg strength. The concentration of all solution for injection samples was 10%
- 47/60 (78%) of rifampicin capsules samples were of 150mg, 13/60 (22%) of 300 mg strength
- 38/42 (90%) of isoniazid/rifampicin tablets samples were of 75/150mg strength, only one or two samples were collected for each of the other strengths (150+150mg, 30+60mg, 60+60mg),
- All kanamycin powder for solution for injection samples contained 1g in a vial
- 39/40 (98%) of ofloxacin tablets or capsules samples were of 200mg strength, only one sample consisted of 400mg tablets.

Table 6 Summary of samples by country

Active ingredient	Dosage form	Armenia	Azer-baijan	Belarus	Kazakh-stan	Ukraine	Uzbeki-stan	TOTAL
Isoniazid	Tablets	3	8	8	10	14	11	**54**
	Solution for injection	0	4	4	2	5	0	**15**
Rifampicin	Capsules	12	6	12	12	11	7	**60**
Isoniazid/ rifampicin	Tablets	3	3	12	12	0	12	**42**
Kanamycin	Powder for solution for injection	12	6	12	12	13	12	**67**
Ofloxacin	Tablets	12	4	7	12	0	3	**38**
	Capsules	0	0	2	0	0	0	**2**
	Solution	0	0	3	0	10	0	**13**
Total		**42**	**31**	**60**	**60**	**53**	**45**	**291**

3.1.2 Manufacturers and batches

The 291 samples from 208 different batches originated from 33 manufacturers from the following countries: India (10 manufacturers), Russian Federation (five), Ukraine (five), Kazakhstan (three), Belarus (two), China (two), Cyprus (one), France (one), Palestine (one), Syrian Arab Republic (one), Turkey (one), and Uzbekistan (one).

The number of different manufacturers for the samples collected in individual countries did not vary much: six manufacturers in Ukraine, eight in Belarus, 11 in Azerbaijan and Kazakhstan, and 12 in Armenia and Uzbekistan.

Proportions of samples from domestically produced medicines differed substantially in individual countries: 52/53 (98%) samples collected in Ukraine were produced by domestic manufacturers, 30/60 (50%) in Belarus, 24/60 (40%) in Kazakhstan, 2/45 (4%) in Uzbekistan, and none from Armenia or Azerbaijan. In all countries except Ukraine imported samples included samples produced in NIS (mostly Ukraine, but also Russian Federation and Belarus). There were 20 of 33 manufacturers whose samples were found in one country only. Samples produced by five manufacturers were collected in two countries, samples from three manufacturers were found in three countries, samples from four manufacturers in four countries and finally only one manufacturer's samples were collected in five countries. The number of samples per manufacturer varied from 1 to 30, with a median of 6.

The breakdown of samples by manufacturer with dosage forms, strengths, number of different batches, and countries of collection is shown in Table 7.

Table 7 Samples collected by manufacturer and formulation

Manufacturer	Strength	Number of batches	Number of samples	Country of collection
Isoniazid solution for injection				
Borisovskij zavod medicinskich preparatov, Belarus	10%	2	4	Belarus (4)
Darnica pharmaceutical company, Ukraine	10%	9	11	Azerbaijan (4), Kazakhstan (2), Ukraine (5)
Isoniazid tablets				
Borisovskij zavod medicinskich preparatov, Belarus	300mg	7	8	Belarus (8)
Cadila Pharmaceuticals Ltd, India	100mg	2	2	Kazakhstan (2)
	300mg	5	5	Azerbaijan (2), Uzbekistan (3)
Chimpharm, Kazakhstan	300mg	1	1	Kazakhstan (1)
Darnica pharmaceutical company, Ukraine	300mg	1	1	Ukraine (1)
Luganskij khimiko-farmacevticeskij zavod, Ukraine	100mg	6	6	Kazakhstan (3), Ukraine (2), Uzbekistan (1)
	300mg	16	23	Azerbaijan (4), Kazakhstan (1), Ukraine (11), Uzbekistan (7)
Pavlodarskij farmacevticeskij zavod, Kazakhstan	300mg	3	3	Kazakhstan (3)
Svizera Labs, India	100mg	1	3	Armenia (3)
	300mg	1	1	Azerbaijan (1)
Tyumenskij khimiko-farmacevticeskij zavod, Russian Federation	300mg	1	1	Azerbaijan (1)
Rifampicin capsules				
Belmedpreparaty, Belarus	150mg	12	17	Armenia (5), Belarus (12)
Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	150mg	9	9	Ukraine (9)
Darnica (bulk from Lupin India), Ukraine	150mg	1	1	Ukraine (1)
Lupin Ltd, India	150mg	1	1	Ukraine (1)
	300mg	1	4	Armenia (1), Uzbekistan (3)
Macleods Pharmaceuticals Ltd, India	150mg	7	7	Kazakhstan (7)
Medochemie, Cyprus	300mg	1	2	Armenia (2)
Pavlodarskij farmacevticeskij zavod, Kazakhstan	150mg	5	5	Kazakhstan (5)
Sandoz Private Ltd, India	150mg	2	4	Uzbekistan (4)
Shandong Reyoung Pharmaceutical Co. Ltd, China	150mg	1	3	Azerbaijan (3)
	300mg	1	3	Azerbaijan (3)
Troge Medical, India	300mg	1	4	Armenia (4)
Isoniazid/ rifampicin tablets				
Lupin Ltd, India	75/150mg	12	18	Armenia (3), Azerbaijan (3), Belarus (12)
Macleods Pharmaceuticals Ltd, India	30/60mg	2	2	Kazakhstan (2)
	60/60mg	1	1	Kazakhstan (1)
Pavlodarskij farmacevticeskij zavod, Kazakhstan	75/150mg	1	1	Kazakhstan (1)
	150/150mg	1	1	Kazakhstan (1)
Sandoz Private Ltd, India	75/150mg	11	17	Kazakhstan (7), Uzbekistan (10)
Svizera Labs, India	75/150mg	2	2	Uzbekistan (2)

Manufacturer	Strength	Number of batches	Number of samples	Country of collection
Kanamycin powder for solution for injection				
Chimpharm, Kazakhstan	1g	11	11	Kazakhstan (11)
DHO Nika Pharm, Uzbekistan	1g	1	2	Uzbekistan (2)
Kievmedpreparat, Ukraine	1g	16	29	Armenia (5), Belarus (11), Ukraine (13)
OJSC "Biokhimik" Saransk, Russian Federation	1g	1	1	Uzbekistan (1)
Panpharma SA, France	1g	6	10	Armenia (3), Belarus (1), Kazakhstan (1), Uzbekistan (5)
Shanghai Pharmaceutical Co. Ltd, China	1g	2	4	Uzbekistan (4)
Syntez Kurgan, Russian Federation	1g	6	10	Armenia (4), Azerbaijan (6)
Ofloxacin tablets				
Borisovskij zavod medicinskich preparatov, Belarus	200mg	6	11	Armenia (5), Belarus (6)
Global Pharm RK Almaty, Kazakhstan	200mg	2	2	Kazakhstan (2)
J. Duncan Healthcare Pvt Ltd, India	200mg	1	1	Kazakhstan (1)
Kaspar-Chabani Pharma, Syrian Arab Republic	200mg	1	3	Armenia (3)
Kievmedpreparat, Ukraine	200mg	1	1	Uzbekistan (1)
Macleods Pharmaceuticals Ltd, India	200mg	3	4	Azerbaijan (1), Belarus (1), Kazakhstan (1), Uzbekistan (1)
MU Pharmaceuticals Enibosna, Turkey	200mg	1	1	Azerbaijan (1)
	400mg	1	1	Azerbaijan (1)
OLA Ozon, Russian Federation	200mg	2	3	Armenia (2), Uzbekistan (1)
Pharmacare Int. Co. Jerusalem, Palestine	200mg	1	1	Azerbaijan (1)
Pharmstandart - Lekarstva, Russian Federation	200mg	1	2	Armenia (2)
Plethico Pharmaceuticals Ltd, India	200mg	8	8	Kazakhstan (8)
Ofloxacin capsules				
Holden Medical Laboratories Ltd, India	200mg	1	2	Belarus (2)
Ofloxacin solution for infusion				
Unique Pharmaceutical Laboratories, India	0.2%	3	3	Belarus (3)
Yuria-Pharm, Ukraine	0.2%	6	10	Ukraine (10)
Total		**208**	**291**	

3.1.3 Sites of sample collection

A total of 84 collection sites from the six countries were included in the survey. Most samples (234/291) were collected at public TB treatment delivery sites, such as national TB institutes/centres, clinics/hospitals/polyclinics and TB dispensaries (51 collection sites). Fewer samples (44/291) were collected at pharmacies (29 sites) and this was only in four countries, while just 13 samples were collected at distribution warehouses (four sites) in two countries. The numbers and types of collection sites in individual countries with numbers of collected samples are shown in Table 8.

Table 8 Numbers of collection sites in individual countries with numbers of collected samples

Country	TB treatment delivery sites		Pharmacies		Distribution warehouses	
	Number of sites	Number of samples	Number of sites	Number of samples	Number of sites	Number of samples
Armenia	5	10	18	27	3	5
Azerbaijan	3	27	1	4	-	-
Belarus	8	52	-	-	1	8
Kazakhstan	9	58	2	2	-	-
Ukraine	11	53	-	-	-	-
Uzbekistan	15	34	8	11	-	-
TOTAL	**51**	**234**	**29**	**44**	**4**	**13**

All country teams, except Azerbaijan, collected samples in several regions (Armenia and Belarus 3 regions, Uzbekistan 4 regions, Kazakhstan 5 regions, Ukraine 10 regions). In Azerbaijan, all the samples were collected in four sites in Baku and its outskirts where the widest range of medicines and largest volumes were found.

The types of collection site surveyed in each country together with their location are listed below:

- Armenia (26 sites) - M/XDR-TB polyclinic in Yerevan; National TB Office in Yerevan; three hospital warehouses in Abovyan, Arzni and Gyumri; three distributor warehouses in Yerevan; and 18 private pharmacies (two in Abovyan, two in Gyumri, one in Spitak, two in Vanadzor, and 11 in Yerevan).
- Azerbaijan (four sites) - National Institute of Lung Diseases in Baku; two TB dispensaries in Baku; and a pharmacy in Baku.
- Belarus (nine sites) - Scientific Research Institute on Pulmonology and Phthisiology in Minsk; two city TB dispensaries in Minsk; three regional TB dispensaries in Leskovka - Minsk oblast, Mogilev and Vitebsk; two TB hospitals in Sosnovka - Vitebsk oblast and Volkovichi - Dzerzhinsk region; and a pharmaceutical warehouse in Minsk.
- Kazakhstan (11 sites) - National TB Centre in Almaty; city TB dispensary in Almaty; six regional TB dispensaries in Aktau, Astana, Karaganda, Pavlodar, Petropavlovsk, Taldykurgan; a local TB dispensary in Shymbulak - Talgar region - Almaty oblast; and two private pharmacies in Almaty.
- Ukraine (11 sites) - Central TB clinic in Kiev; 7 regional TB dispensaries in Cherkassy, Chernihiv, Chernivtsi, Ivano-Frankivsk, Nikolaev, Ternopil, and Zhitomir; Regional territorial medical union "Phtiziatrija" in Uzhgorod - Transcarpathia; TB dispensary in Sevastopol; and Republican TB dispensary in Simferopol region - Autonomous Republic of Crimea.
- Uzbekistan (23 sites) - Scientific Research Centre of Phthisiology and Pulmonology in Tashkent; eleven TB dispensaries in regions of Bagdad, Buvayda, Fergana, Kokand, Kuva, Margilan, Rishtan, Tashkent, and Termez; three TB clinics (one in Nukus - Karakalpakstan and two in Tashkent oblast); and eight retail pharmacies (six in Nukus - Karakalpakstan and two in Tashkent).

Even if this sampling method could not ensure a representative set of all anti-TB medicines used in these countries at the time of the survey, the samples collected broadly represented the medicines available to patients.

3.1.4 Storage conditions

Collectors recorded storage conditions at the sites on the Sample Collection Forms. Information on storage conditions was missing on 16% of forms, on 39% of forms only conformity with requirements was stated, and on 45% of forms the temperature at the time of collection was recorded. An inappropriate storage temperature was recorded for only four samples (1.4%). These were samples of isoniazid solution for injection, manufactured by Darnica, collected in three sites in Azerbaijan and stored at 16-18°C despite the manufacturers' requirement for 8±2°C. In general, capsules and tablets were stored at 15-24°C, powders for solution for injection at 5-24°C, solutions for infusion at 18-19°C and solutions for injection (except the four samples mentioned above) at 4-7°C.

During the shipment of samples from one of the countries to the quality control laboratory all ampoules with isoniazid solutions for injection were affected by inappropriate storage conditions during transport (most probably exposed to low temperature) - see Figure 2. All affected samples were replaced by the country team according to the protocol and sent again with guaranteed storage conditions as required by the label. Thus the results were not influenced by this event.

Figure 2
Appearance of isoniazid solution for injection samples delivered to testing laboratory from one of the countries

3.2 Registration status of sampled products

In total, 82.5% of samples were confirmed to be registered by the national authority. Table 9 shows the numbers and proportions of registered and unregistered samples by country. All samples of unregistered products collected in Armenia, Belarus, Kazakhstan and Uzbekistan had been supplied as humanitarian aid by international organizations such as GDF or MSF. In Azerbaijan, apart from unregistered samples supplied through GDF as humanitarian aid, nine samples of unregistered products were found, which were legally supplied under old legislation pre-March 2008.

Table 9 Registration status of samples

Country	Samples	Registered		Unregistered		
		Number	%	Number	%	Note
Armenia	42	30	71.4	12	28.6	Supplied as humanitarian aid (mostly through MSF)
Azerbaijan	31	19	61.3	12	38.7	Supplied as humanitarian aid (through GDF) or under old legislation pre-March 2008
Belarus	60	46	76.7	14	23.3	Supplied as humanitarian aid (through GDF)
Kazakhstan	60	53	88.3	7	11.7	Supplied as humanitarian aid (through GDF)
Ukraine	53	53	100	0	0	-
Uzbekistan	45	39	86.7	6	13.3	Supplied as humanitarian aid (through GDF)
Total	**291**	**240**	**82.5**	**51**	**17.5**	

3.3 WHO prequalification status of sampled products

Of the 291 samples, 38 (13.1%) were from WHO-prequalified products. There are currently 31 anti-TB medicines prequalified and samples from four of these were collected within this survey. All samples of WHO-prequalified products were isoniazid/rifampicin FDCs from three Indian manufacturers (Lupin Ltd, Sandoz Private Ltd, and Macleods Pharmaceuticals Ltd.). The majority of samples were of the strength 75mg/150mg (35 samples), only 3 samples of strengths 30mg/60mg and 60mg/60mg were included. Similar numbers of samples of WHO-prequalified products were collected in Belarus (12), Kazakhstan (10), and Uzbekistan (10), with fewer collected in Armenia (three) and Azerbaijan (three), and none collected from Ukraine.

3.4 Samples supplied through GDF

A list of all samples from products and manufacturers included in the GDF catalogue was sent to the GDF Secretariat for verification with procurement agents and quality control laboratories whether these products and batches had actually been supplied to the country concerned. In this way, 42 of the 291 samples collected in this survey (14.4%) were identified as having been supplied through GDF. These were samples of isoniazid 100mg and 300mg tablets, isoniazid/rifampicin 75mg/150mg, 60mg/60mg, and 30mg/60mg tablets, kanamycin 1g powder for solution for injection and ofloxacin 200mg tablets, supplied to Azerbaijan, Belarus, Kazakhstan and Uzbekistan.

3.5 Compliance with specifications

3.5.1 Overall results

Expiry dates of samples collected in this survey ranged from October 2009 to April 2014 (sample collection took place in June - August 2009). No sample was collected or tested after its expiry date.

In total, 258 (88.7%) samples complied with the specifications set for this survey. The results of laboratory testing are summarized in Table 10.

The proportion of samples which failed the quality tests varied between the countries: Ukraine (3.8%), Belarus (6.7%), Armenia (9.5%), Azerbaijan (9.7%), Uzbekistan (13.3%) and Kazakhstan (23.3%).

No failure was identified for samples of isoniazid solution for injection, kanamycin powder for solution for injection, ofloxacin capsules, and ofloxacin solution for infusion. The highest proportion of non-compliant samples was for rifampicin tablets (28.3%), and relatively high failure rates were also recorded for isoniazid tablets (16.7%) and ofloxacin tablets (15.8%).

Similar failure rates were found for domestically produced and imported samples (12% and 11% respectively). Due to different proportions of samples from domestically produced and imported medicines collected in individual countries (see section 3.1.2), the failure rates for domestic and imported samples could be compared only for Belarus and Kazakhstan. In Belarus all four non-compliant samples were domestically produced, whilst no imported sample failed. In Kazakhstan seven of 24 samples (29.2%) produced domestically and seven of 36 imported samples (19.4%) failed to comply.

Of the 51 unregistered products (predominantly supplied through humanitarian aid), two samples (3.9%) were found to be non-compliant with specifications set for this survey.

None of the 38 samples from WHO-prequalified products nor any of the 42 samples supplied through GDF failed the quality testing.

Table 10 Summary of results from laboratory tests

Country:		Armenia		Azerbaijan		Belarus		Kazakh-stan		Ukraine		Uzbeki-stan		Total	
Active ingredient	Dosage form	Non-com-pliant	% Fail-ure	Non-com-pliant	% Fail-ure	Non-com-pliant	% Fail-ure	Non-com-pliant	% Fail-ure	Non-com-pliant	% Fail-ure	Non-com-pliant	% Fail-ure	Non-compliant	% Fail-ure
Isoniazid	Tablets *	0/3	0	2/8	25	1/8	12.5	1/10	10	2/14	14.3	3/11	27.3	**9/54**	**16.7**
	Sol. for injection		0	0/4	0	0/4	0	0/2	0	0/5	0		0	**0/15**	**0**
Rifampicin	Capsules *	3/12	25	1/6	16.7	0/12	0	10/12	83.3	0/11	0	3/7	42.9	**17/60**	**28.3**
Isoniazid/ rifampicin	Tablets *	0/3	0	0/3	0	0/12	0	1/12	8.3		0	0/12	0	**1/42**	**2.4**
Kana-mycin	Powder f. sol. f. inj.	0/12	0	0/6	0	0/12	0	0/12	0	0/13	0	0/12	0	**0/67**	**0**
Ofloxacin	Tablets *	1/12	8.3	0/4	0	3/7	42.9	2/12	16.7		0	0/3	0	**6/38**	**15.8**
	Capsules *		0		0	0/2	0		0		0		0	**0/2**	**0**
	Sol. for infusion		0		0	0/3	0		0	0/10	0		0	**0/13**	**0**
TOTAL		4/42	**9.5**	3/31	**9.7**	4/60	**6.7**	14/60	**23.3**	2/53	**3.8**	6/45	**13.3**	**33/291**	**11.3**

*Results for different strengths of the same product are combined in this table

3.5.2 Results of specific quality tests for individual products

The samples from four products (isoniazid solution for injection, kanamycin powder for solution for injection, ofloxacin capsules, and ofloxacin solution for infusion) all complied with the specifications. Results of specific quality tests for the four other products are detailed in Table 11. Details and tests results for each sample are listed in Appendices 2-8, grouped by active ingredients and dosage forms. Samples in each Appendix are sorted according to the countries in which they were collected.

Table 11 Number of samples which failed specific quality tests

(Samples could fail more than one test)

		Isoniazid tablets	Rifampicin capsules	Isoniazid/rifampicin tablets	Ofloxacin tablets
Total samples tested		45	60	42	39
Non-compliant		**9**	**17**	**1**	**6**
Overall failure rate		16.7%	28.3%	2.4%	15.8
Samples that failed in:	Appearance	2	0	0	0
	Assay	0	**12**	0	0
	Related substances test	*	11	**1**	2
	Dissolution test	1	*	*	**3**
	Mass uniformity test	**6**	0	0	2

Cells shaded orange indicate the most frequently failed test for each product type

* Test not included in the respective specifications as a decisive indicator (see 3.5.2.2 and 3.5.2.4 below)

3.5.2.1 *Isoniazid tablets (Appendix 2)*

Fifty-four samples (44 batches) of isoniazid tablets produced by eight manufacturers were tested for appearance, identity, assay, dissolution, and uniformity of mass. Nine samples

(16.7%) from two manufacturers were found to be non-compliant; each sample failed only one specific test.

Eight failing samples were from one manufacturer (six batches):

- Two samples failed in appearance as broken tablets were found in each sample, in one of these samples tablets with brown dots were found (this sample was further tested for friability and did not comply with pharmacopoeial specifications)
- Five samples failed on uniformity of tablet mass (mostly accompanied by the presence of white residual powder in bottles)
- One sample failed the dissolution test, dissolving on average 70% compared to the required 80% of active ingredient (this was the only sample from the respective batch). There were 21 other samples (17 batches) from the same manufacturer which complied in all the tests.

One sample from another manufacturer failed on uniformity of tablet mass; there were seven other samples of six other batches from this manufacturer, which complied in all the tests.

Apart from the samples failing in the mass uniformity test, in a further 13 samples (from four manufacturers) the presence of white residual powder in bottles was noted by the laboratory. As this finding was not accompanied by failure in any test, these samples were evaluated as compliant but the observation might signify problems with adherence to GMP. There were two other samples in which one broken tablet was found in the blister. Cardboard boxes of these two samples (secondary packaging of blisters) were damaged when delivered to the laboratory but no damage had been noted by the collectors in the country. Therefore the defect was considered to have occurred during transportation and this was not classed as non-compliance.

3.5.2.2. Isoniazid solution for injection (Appendix 3)

Fifteen samples (11 batches) of isoniazid solution for injection (10%) produced by two manufacturers were tested for appearance, identity, assay, pH value, and sterility. The limits for pH set by both manufacturers were 6.3-7.3 and for all samples the pH values were between 7.1 and 7.2. The manufacturers' limits were applied in this survey even if the USP monograph sets the range at 6.0-7.0 and therefore the samples were considered compliant in this test. All 15 samples complied in the other tests.

3.5.2.3 Rifampicin capsules (Appendix 4)

Sixty samples (42 batches) of rifampicin capsules produced by ten manufacturers were tested for appearance, identity, assay, rifampicin-related substances and uniformity of mass. Seventeen samples (28.3%) produced by five manufacturers were found to be non-compliant either in the assay or in the related substances test or both.

Content

In 12 samples (nine batches) from four manufacturers the content of rifampicin was found to be below the acceptable limit of 90.0%: the two lowest values were 78.0% and 81.8% of the labelled amount; in the ten remaining samples the content was between 85.1% and 89.6%. In six of these 12 samples failure in assay was accompanied by failure in the related substances test.

Related substances

Eleven samples (10 batches) from four manufacturers failed the related substances test. In all these samples the degradation product 3-formylrifampicin was found at levels of 0.6-0.7%

(marginally above the acceptable limit of 0.5%). In three samples an unknown impurity was found above the acceptable limit of 1.5% (1.6%, 1.9%, and 2.0%). All the non-compliant samples were investigated for the presence of unknown impurities with relative retention times (RRT) 0.29 and 0.45. These peaks were found in all of them, as well as in the non-compliant sample of isoniazid/rifampicin tablets. Therefore it was highly unlikely that these two peaks in samples from different manufacturers and different dosage forms originated from excipients, and they were evaluated as unknown rifampicin-related impurities. In two of three failing samples additionally the total sum of impurities exceeded the acceptable limit of 6.0% (7.5% and 7.6%).

Dissolution

Due to concerns about the conditions to be used for dissolution test of rifampicin capsules (see 2.7), dissolution was not tested for each collected sample. Comparative dissolution of 12 samples (150mg and 300mg) from 10 manufacturers (one sample per strength and manufacturer) and Rifadin, Sanofi Aventis Germany (comparator recommended in the WHO Prequalification of Medicines Programme) was evaluated over a period of 60 minutes under two sets of conditions - according to the Ph. Int. and BP monographs.

BP monograph method:

All 13 samples released more than 70% of labelled amount of rifampicin in 45 min in the acidic medium (mean values from six individual capsules within the range 78-89%) thus conforming to the BP acceptance criteria (each of six tablets not less than (NLT) 70% of the amount declared on the label).

Ph. Int. monograph method:

Samples collected in the survey:

- Two samples released more than 80% of labelled amount of rifampicin in 30 min in 500 ml of dissolution buffer pH 6.8, 0.25% sodium dodecyl sulphate (SDS) medium (mean values 89-91%) and were thus in conformity with Ph. Int. acceptance criteria (each of six tablets NLT 80% of the amount declared on the label)
- Five samples did not fulfil the Ph. Int. acceptance criteria but released in 30 min more than 70% (mean values 72-83%) and in 45 minutes almost or more than 80% (mean values 79-90%) showing thus borderline non-compliance with the Ph. Int. requirements
- Five samples released less than 70% (mean values 39-65%) in 30 minutes and less than 80% in 45 minutes (mean values 48-69%).

For the sample of an established comparator product mean values found were 43% in 30 min and 73% in 45 min.

There may be various reasons for differences in dissolution results when conditions according to the two pharmacopoeias were used. One of them may be discriminating power - low under BP conditions, too high under Ph. Int. conditions. In general, it is known that rifampicin can be almost completely absorbed from the gastrointestinal tract as long as it is dissolved in the upper small intestine. pH 6.8 is widely accepted as a representative pH value for conditions in the upper small intestine, which is consistent from patient to patient. Therefore dissolution medium of pH 6.8 (as in the Ph. Int. method) may be considered more relevant than acidic medium (0.1M HCl) for correlation between bioavailability and dissolution.

However, there are several factors influencing dissolution rates, e.g. dosage form and excipients contained in individual products may influence the wetting of an API during

dissolution test. For instance, if magnesium stearate is included in the formulation it may result in the formation of a hydrophobic film around the particles, preventing wetting and disaggregation, resulting in a slowdown of disintegration/dissolution[51].

The same dissolution medium (buffer pH 6.8, 0.25% SDS) was used for rifampicin capsules and isoniazid/rifampicin tablets produced by the same manufacturers and most likely containing rifampicin of the same provenance (i.e. having the same particle size and crystal form), though in the case of the tablets the volume was increased to 900 ml (see the reason under isoniazid/rifampicin tablets in 3.5.2.4). The dissolution rate was much higher for tablets than for capsules. This suggests that dissolution results under these conditions may not be related to the physical properties of rifampicin, but rather related to the dosage form (the large differences in rate can hardly be ascribed to the difference in the volume of the medium). Capsules containing proquazone, a poorly wettable substance, showed a significantly slower dissolution of the API than tablets containing proquazone, especially for a high content of API, and this is hypothesized to be a characteristic of poorly wettable APIs in general[52].

Taking into account all the above and not having available *in vivo* bioavailability data, the results of dissolution were not included as a decisive quality indicator in the overall evaluation of quality of rifampicin capsules in this survey, though it is acknowledged that some of the products did not comply with the Ph. Int. requirement.

3.5.2.4 Isoniazid/rifampicin tablets (Appendix 5)

Forty-two samples (30 batches) of isoniazid/rifampicin tablets produced by five manufacturers were tested for appearance, identity, assay for each active ingredient, rifampicin-related substances, and uniformity of mass. Forty-one samples complied with specifications in all the tests. One sample failed the rifampicin-related substances test, with one unknown impurity found at a level of 4.9% (above the acceptable limit of 1.5%). As mentioned in 3.5.2.3, this unknown impurity (peak with RRT 0.45) was found also in samples of rifampicin capsules and therefore it was not considered to originate from excipients and was evaluated as unidentified rifampicin-related impurity. The other sample from the same manufacturer but different strength and batch complied in all the tests.

Dissolution

Due to the concerns about conditions to be used for dissolution test of rifampicin containing medicines (see 2.7), dissolution was not tested for each collected sample. Comparative dissolution of seven isoniazid/rifampicin tablets (150/150mg, 75/150mg, 60/60mg or 30/60mg) samples from five manufacturers (one sample per strength and manufacturer) and Rifinah, Grünenthal Germany (comparator recommended within the WHO Prequalification of Medicines Programme) was evaluated over a period of 60 minutes using a validated laboratory method (conditions and the acceptance criteria according to the Ph. Int. monograph for rifampicin tablets with slight modification - volume 900 ml instead 500 ml to ensure sink conditions for both APIs).

All eight samples released more than 80% of the labelled amount of both isoniazid and rifampicin in 30 min in dissolution buffer pH 6.8, 0.25% SDS medium (mean values from 6 individual tablets were 92-99% for isoniazid and 93-99% for rifampicin) and they thus conformed with the acceptance criteria of rifampicin tablets Ph. Int. monograph for dissolution test (each of six tablets NLT 80% of the amount declared on the label).

However, it was observed that for each of the products the dissolution rates of rifampicin – a low soluble substance according to the biopharmaceutical classification system (BCS) and isoniazid – a BCS high soluble substance - in 15 minutes were similar and mostly above

80%, indicating that the presence of SDS may not be suitable to detect differences between the batches in terms of the rifampicin solid state properties, which may play important role in bioavailability.

Some preliminary investigations were done using dissolution conditions according to USP monograph for rifampicin/isoniazid/pyrazinamide/ethambutol HCl combination tablets. This method uses as dissolution medium buffer pH 6.8 without addition of SDS. First tests showed in some samples lower dissolution results for rifampicin compared to dissolution medium with addition of SDS. The lower results may be due to differences in physical properties of rifampicin material used in the batches. For various reasons (availability of samples, expiry dates) the testing could not be finalized and a further study has been considered.

The results of dissolution testing were not considered as a decisive quality indicator and were not included in the overall evaluation of quality of isoniazid/rifampicin tablets samples collected in the survey.

3.5.2.5 Kanamycin powder for solution for injection (Appendix 6)

Sixty-seven samples (43 batches) of kanamycin powder for solution for injection (1g per vial) produced by seven manufacturers were tested for appearance, identity, assay, and pH value. One sample from each manufacturer was tested for sterility. The USP monograph for kanamycin injection sets the range for pH value at 3.5-5.0. However, manufacturers of collected samples set for their powders for injection for solution the pH value range either at 5.5-7.5 or 6.0-7.5 respectively, and all pH values for the samples tested were in the range 6.8-7.4. Therefore all the samples were considered compliant in this test. All 67 samples complied in the other tests.

3.5.2.6 Ofloxacin tablets/capsules (Appendix 7)

Forty samples (29 batches) of ofloxacin solid dosage formulations (38 samples of tablets and 2 samples of capsules) produced by 12 manufacturers were tested for appearance, identity, assay, related substances, dissolution, and uniformity of mass. Six samples from three manufacturers (all tablet form) failed one or two tests.

Two samples from two separate manufacturers failed the related substances test. Both known impurities (A and B) were below the acceptable limit, but there were unknown impurities above the acceptable limit of 0.2% (in one sample two distinct impurities in the amount 0.7% and 0.4%; in the other sample a single impurity at 0.6%). In both these samples the total sum of impurities also exceeded the acceptable limit of 1.0% (1.2% and 1.3% respectively). In the first case there was one more sample from the same manufacturer but different batch, which complied with specifications. In the second case it was the only sample from that manufacturer in the survey.

Three samples failed the dissolution test. Two samples from the same manufacturer and same batch showed very inconsistent dissolution results for individual tablets (24 tablets tested for each sample dissolved in the range 17-99% of the labelled amount of ofloxacin). The average amount of dissolved ofloxacin was 32% and 42% respectively, instead of the specified 80%. The other nine samples from different batches of the same manufacturer were compliant. The third sample which failed the dissolution test was from another manufacturer and, on average, the amount of dissolved ofloxacin was 78% (this sample also failed the related substances test). The other sample from the same manufacturer but a different batch was compliant.

Two samples from different batches of one manufacturer failed in the uniformity of tablet mass test. There were nine other samples from the same batch and other batches from the same manufacturer which complied in this test.

3.5.2.7 Ofloxacin solution for infusion (Appendix 8)

Thirteen samples (nine batches) of ofloxacin solution for infusion produced by two manufacturers were tested for appearance, identity, assay, related substances, and pH value. One sample from each batch was tested for bacterial endotoxins and one sample from each manufacturer was tested for sterility. As there is no pharmacopoeia monograph available for this formulation the limits according to USP monograph for ofloxacin tablets were used and the manufacturers' limits for pH value (see Appendix 8) were applied in this survey. No specification for the limit of bacterial endotoxins was available for this product, however in none of the sample tested were endotoxins detected (limit of detection was 0.06 IU/mg). Therefore bacterial endotoxins were not considered a problem for the collected samples. No sample failed to meet the specifications set for this survey.

4. Discussion

Testing methods and data quality

Standardized laboratory testing methods and specifications according to established pharmacopoeias (Ph. Int. and USP) were used in this survey to define standards of acceptable quality. Testing according to official pharmacopoeial methods enabled the comparison of products from different manufacturers.

The reliability of results was assured by testing at a quality control laboratories for which evidence of reliability was available. Samples were collected, stored and transported in compliance with the survey protocol, which ensured that no quality deterioration occurred before laboratory testing. Two problems occurred during transportation of samples to the laboratories: samples of isoniazid liquid formulation from Azerbaijan were delivered damaged, but they were re-collected and re-sent under the appropriate conditions; two samples of isoniazid tablets (packed in blisters and cardboard box) collected in Kazakhstan were delivered to the laboratory in a damaged cardboard box and in each of them one broken tablet was found in the blister. No damage was noted by the collectors in the country and therefore the defect was considered to have occurred during transportation. These samples were tested and did not fail any test.

Sites of sample collection

This survey aimed to provide a picture on quality of medicines available to patients. Country teams were requested to collect products from different manufacturers and if the same product was found in several sites then to collect different batches. The instruction was to collect a substantial amount of dosage form units per sample (e.g. 100 tablets) while not jeopardizing the availability of products to patients. Therefore the logical choice was to collect samples at public TB treatment delivery sites serving regions or located in bigger cities. Collectors were instructed to collect samples from pharmacies or distribution warehouses only in the event that the planned samples could not be collected in public facilities (in particular in Armenia and Uzbekistan).

Because of limited laboratory capacity for testing of large numbers of samples, and limited funding for testing, the number of samples collected per country was restricted to 60. All these requirements did not allow the use of a randomized procedure for selection of sample collection sites. However, in countries using centralized government procurement and supply of anti-TB medicines it can be assumed that medicines found in the selected facilities are broadly representative of medicines available to patients in that region, even if they may not be representative of all anti-TB medicines used in these countries.

Collectors reported storage conditions at the sites and found in general temperatures below 25°C. An inappropriate storage temperature was recorded for only four samples of isoniazid solution for injection (16-18°C despite the manufacturers' requirement for 8±2°C). In regulatory practice, a storage statement for each particular product should be established for the label based on the stability studies of the product, and there should be a direct link between the storage statement on the label and the stability of the product demonstrated to regulatory authorities. In this survey the approved storage conditions were not reported for each sample collected. However, from the information in pharmacopoeias and WHO procurement requirements it can be derived that in principle solid dosage forms containing rifampicin, isoniazid, isoniazid/rifampicin, ofloxacin and kanamycin should be stored below 25°C. Liquid dosage forms of isoniazid and ofloxacin should also be stored below 25°C but

should not be exposed to low temperatures. Thus, available information did not suggest any damage to samples due to storage conditions at collection sites.

Samples were mostly collected in regional TB dispensaries, and it can be assumed that the relatively straightforward distribution channels had not affected the quality of sampled medicines substantially. Samples collected in pharmacies, where more complex distribution channels can be expected, had similar failure rates as those collected in regional centres; their overall failure rate (3/44) was actually lower than for the other types of sampling sites (30/247). This survey thus did not indicate that distribution was a major factor affecting medicines quality; however, the possible impact of distribution conditions should be further explored.

Overall findings

To our knowledge this is the first large scale survey performed exclusively on the quality of anti-TB medicines. The survey included first-line anti-TB medicines containing rifampicin and isoniazid (both mono-component and FDC) and second-line anti-TB medicines containing kanamycin or ofloxacin. Testing was performed on 291 samples from 208 batches produced by 33 different manufacturers and collected at 84 discrete sites in six NIS. All six countries (Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan) have a high MDR-TB burden. No sample was suspected to be of spurious, falsely-labelled, falsified or counterfeit product. There were no quality problems identified with samples of kanamycin powder for solution for injection, isoniazid solution for injections and ofloxacin solution for infusion. Overall 11.3% samples (33/291) were found to be non-compliant with the specifications set for this survey, although there was considerable variation both between individual products and between countries. The high failure rate for the mono-component first-line anti-TB medicine - rifampicin capsules (28.3%) - is of particular concern.

With full respect to the limitations of the applied approach, an attempt has been made to differentiate between deviations which are likely to impact the health of patients and those which are not. For this purpose, the category of extreme deviations was arbitrarily defined as the content of API deviating by more than 20% from the declared content and/or average dissolution value of tested units below pharmacopoeial Q value minus 25%. This approach has been used in an earlier report on the quality of antimalarials[53]. Focusing only on these extreme deviations, the total failure rate reached 1.0% (3/291). Content of the API below 80% was found in one of failing rifampicin capsules samples only (78.0%) and an average dissolution value below pharmacopoeial Q value minus 25% was found in two ofloxacin tablets samples (32% and 42%).

There were substantial differences in failure rates between the participating countries. Kazakhstan had the highest overall proportion of substandard samples (23.3%), with an especially high failure rate (10 of 12 samples) for rifampicin capsules. Uzbekistan was the other country where the overall failure rate exceeded 10%, and the failures were exclusively with rifampicin capsules (3 of 7 samples) and isoniazid tablets (3 of 11 samples). Overall failure rates in the other four surveyed countries were below 10%. However, the fact that failing samples were still found also in these countries (including in assay or dissolution test) is of concern. Therefore the regulators in all surveyed countries should focus on implementation of GMP in general and specifically on manufacturers whose products failed quality testing in this survey.

Large differences were found in the outcomes of testing of samples produced by individual manufacturers. There were 24 manufacturers (including 12 manufacturers from the countries of the NIS) for which none of the collected samples failed in any test. Even if no general

conclusions on the overall quality of production of a manufacturer can be deduced from testing of several samples (numbers of samples from each manufacturer varied from 1 to 30), this would seem to be a positive observation. For the nine remaining manufacturers (including four manufacturers from the NIS) some of the collected samples failed to comply with the specifications set for this survey. Again, testing results of a few samples collected from the market cannot serve as a measure for the overall quality of production of a manufacturer, but close regulatory supervision should be focused on these manufacturers.

Two manufacturers producing WHO-prequalified products were found among manufacturers with some failing samples of non-prequalified products. This demonstrates a fact which is always emphasized by WHO Prequalification of Medicines Programme, namely that prequalification of a product does not constitute a guarantee for the whole production of a particular manufacturer.

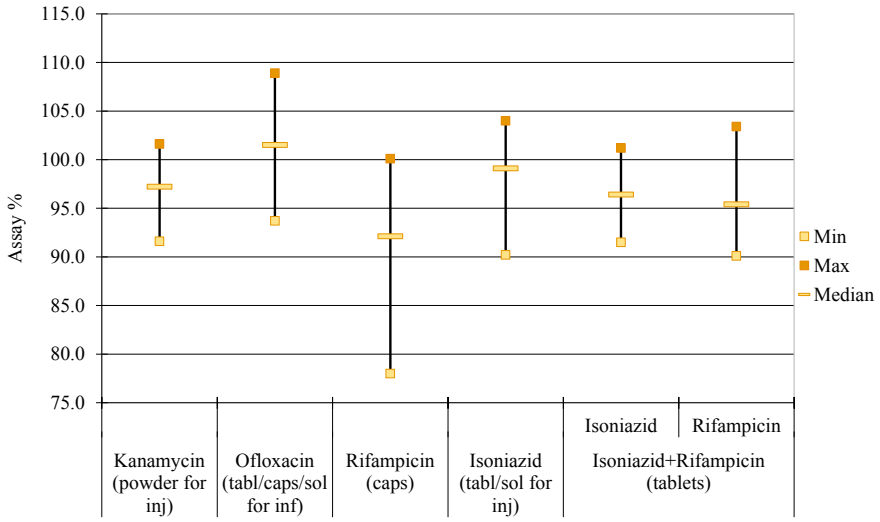
Samples of 13 manufacturers were found in more than one surveyed country and for four of them some failing samples were found. This stresses the need for regulatory supervision and the usefulness of cooperation and communication among NMRAs in market surveillance.

Results of specific quality tests for individual products

The results of individual quality tests show chiefly minor non-compliances, such as failures in appearance, related substances, and uniformity of mass. However, these failures indicate that the manufacturers have problems with Good Manufacturing Practice (GMP) and other international quality standards and that, as a result, the quality of the products is not assured.

Samples of rifampicin capsules were the only samples to fail the assay (Figure 3). Low content of the active ingredient may affect treatment efficacy and may contribute to drug resistance. Rifampicin is known for its potential degradation; therefore presence of related substances as the indicator of possible decrease of the active ingredient content should be followed carefully during production and shelf-life. In this survey the API content was found below standard in 12 samples and in an additional five samples related substances were found above the acceptable limit. This finding is of major concern (even if the extreme deviation in the content of rifampicin - below 80% of the declared content as defined for this report - was found in a single sample only) and regulators should investigate the causes. Specific attention should be paid to the manufacturer of the extremely deviating sample, as none of the five samples produced by this manufacturer was found compliant, and both product design and manufacturing problems may be involved. The content of rifampicin in the majority of failing samples was just below the lower acceptance limit and it was accompanied by no or marginal failure in related substances test. This suggests that manufacturers try to keep the API content close to the lower limit possibly due to competitive pressure on prices.

Figure 3 Assay results for selected medicines within the survey



For the reasons mentioned in section 3.5.2.3, dissolution test results were not included as a decisive quality indicator in the overall evaluation of quality of rifampicin capsules in this survey. The varying dissolution results obtained using the method according to Ph. Int. may indicate some variation in bioavailability of rifampicin. However as no correlation between dissolution and bioavailability has been established in this medium and there is also possible influence of other factors, the results are inconclusive. Based on the outcomes of comparative dissolution study using conditions according to the Ph. Int. monograph and BP monograph, it seems that compliance with pharmacopoeial specifications should be interpreted very carefully in the case of rifampicin capsules.

One sample of isoniazid tablets failed in dissolution (average value 70%, not considered an extreme deviation as defined for this report) and two samples from another batch from the same manufacturer complied in the dissolution test only at stage two. As isoniazid is a highly soluble substance, it seems to be a production-related problem and should be followed by regulators. Some samples of isoniazid tablets also failed the tests for appearance and uniformity of mass. Even if the failure rate was relatively high - 16.7% (9/45) - the failures found do not suggest a direct threat to patients. Problems with adherence to GMP principles were suggested also by the presence of residual powder in bottles in some samples produced by four manufacturers (even if these samples did not fail any test).

Only one sample of isoniazid/rifampicin FDC tablets failed due to an unidentified impurity above the acceptable limit, but the content of active ingredients was within acceptable limits. For the reasons mentioned in section 3.5.2.4, dissolution results were not included as a decisive quality indicator in the overall evaluation of quality of isoniazid/rifampicin tablets in this survey. Further study is required to help clarify the differences in outcomes of dissolution tests performed under different conditions.

Three of 39 samples of ofloxacin solid dosage forms failed dissolution testing; for two of them the deviation from specifications can be considered extreme as defined for this report (32% and 42%, while the pharmacopoeial Q value is 80%). Such a failure may affect treatment efficacy and even if both compliant and failing samples were found from the two affected manufacturers, the significant inconsistency in tablet production is of major concern and should be followed by the regulatory authorities. Some samples of ofloxacin solid dosage forms also failed the tests for related substances and uniformity of tablet mass; however these deficiencies do not pose a direct threat to patient health.

Registration status

All samples collected in the survey were either registered, or were supplied as humanitarian aid and thus exempt from registration, or (in Azerbaijan) were taken from remaining stock supplied legally under old legislation pre-March 2008. Therefore it can be concluded that all the medicines collected within the survey were placed on the market in line with national legislation.

WHO prequalification status

Although WHO prequalification is an important tool for the assessment of medicines intended to be procured by United Nations agencies, there is a need to verify the quality of procured prequalified medicines by random quality control. Sampling and testing of prequalified medicines at all stages of the supply cycle is therefore an essential part of the WHO Prequalification Programme. Isoniazid/rifampicin FDC was the only medicine of which WHO-prequalified samples were collected in this survey. Of 42 isoniazid/rifampicin FDC samples collected, 38 were of prequalified products and none of those failed to comply with pre-set specifications. Of the four samples of non-prequalified products, one failed the test for rifampicin-related substances. The sample size was too small to compare the quality of WHO-prequalified and non-prequalified samples, but a zero failure rate in 38 WHO-prequalified products would appear to support WHO prequalification as an effective mechanism for assuring product quality.

Samples supplied through GDF

The collection of samples in this survey was not focused specifically on medicines supplied through GDF. Even if only 42 (14% of tested samples) were supplied through GDF, the fact that none of them failed to comply with specifications set for this survey indicates that the GDF quality assurance system is effective. Of the 42 samples, 25 were of WHO-prequalified products. Thirty of the samples supplied through GDF were not registered in the recipient country but their use as humanitarian aid was authorized.

Comparison of the survey outcomes with results of other published studies

Outcomes of this survey indicate somewhat higher failure rates than reported e.g. in studies from India[41], from a multicountry area[18] and from Thailand[39], all of which included anti-TB medicines in wider medicines quality surveys. However any comparison is challenging because different testing methods and specifications were used. For example in the recent survey in India[41] screening of quality was performed using a semi-quantitative TLC method and simple disintegration testing which can identify only extreme deviations in API content, but no failures in dissolution, uniformity of mass or appearance. In the multi-country survey[18] screening using a semi-quantitative TLC method was followed by confirmatory laboratory testing of selected samples, but only content of API was evaluated and acceptable limits were extended to 85-115%. In the survey from Thailand[39] assay and dissolution tests were performed in a laboratory, but failures in related substances, uniformity of mass and appearance tests were not considered. These arrangements led necessarily to lower failure findings than the arrangements used in this survey and therefore it cannot be concluded that the quality of anti-TB medicines in the countries included in this survey is worse than in the abovementioned countries.

Also the comparison with the outcomes of a randomized survey of Nigerian pharmacies[38], where failure rates for rifampicin were similar to those found this survey, is complicated by the fact that the authors applied stricter limits (92.5-107.5%) but evaluated only assay results.

For the future it can be recommended that similar surveys should be organized, following harmonized specifications and testing methods as much as possible.

Anti-TB medicines used in the surveyed countries

Both the pre-survey and the main survey found that relatively few FDCs and WHO-prequalified products were used in the surveyed countries, and that there was greater than expected use of injectable formulations. The reasons for the use of injectable forms of isoniazid and ofloxacin need to be further investigated. There needs to be shift towards more widespread use of FDCs, and there are now twelve WHO-prequalified rifampicin-containing FDCs. Countries should follow the WHO TB treatment guidelines and Essential Medicines List for selection of anti-TB medicines[23,54].

The fact that anti-TB medicines were collected in private pharmacies in four of the countries is concerning. Even if the legal status of anti-TB medicines is prescription only, in practice it may be possible to get them from pharmacies without prescription as well. This supports the findings of a small survey in Georgia that discovered both first-line and second-line anti-TB medicines to be widely available without prescription in pharmacies[55]. This should be addressed by banning sales of anti-TB medicines without prescription.

Recommendations from survey wrap-up meeting

The results of the pre-survey and survey were analysed in a meeting in June 2010 with representatives of participating countries, and the following recommendations were agreed:

Ministries of Health in participating countries:

- To shift towards the use of FDCs, especially for rifampicin-containing products
- To follow the WHO TB treatment guidelines and the WHO Essential Medicines List
- To introduce and reinforce rational use of anti-TB medicines through banning sales of anti-TB medicines without prescription and restricting the use of anti-TB medicines for other diseases
- To conduct investigation of failures with manufacturers and follow-up of corrective actions recommended
- To ensure the compliance of manufacturers with regulatory standards, including GMP
- To identify local manufacturers and encourage their participation in the WHO Prequalification of Medicines Programme
- To continue efforts to ensure proper conditions during distribution and storage of medicines both in pharmaceutical facilities (pharmacies and warehouses) and in health facilities

WHO:

- To publish the results of the survey in an objective and transparent manner (with Russian translation)
- To promote registration of medicines supplied by international organizations/mechanisms
- To further advocate for the participation of manufacturers in the WHO Prequalification of Medicines Programme
- To continue working with NMRAs to improve regulatory systems at country level

NMRAs and WHO:

- To investigate reasons for use of injectable forms of isoniazid, ofloxacin and other anti-TB medicines
- To support resource mobilization for strengthening of medicines regulatory systems, for example from the Global Fund and others

Limitations of methodology

The survey has several methodological limitations which must be acknowledged. For the reasons mentioned on page 40, neither the selection of survey sites nor the selection of samples from each site was done according to a standardized, randomized sampling procedure. It therefore cannot be assumed that the samples collected and tested were representative of all anti-TB medicines used in these countries at the time of the survey. However, in countries using centralized government procurement and supply of anti-TB medicines it can be assumed that collected samples broadly represented the medicines available to patients and that the survey has provided useful baseline data.

This survey has not explored the more complex issue of rifampicin bioavailability. Assuring appropriate bioavailability requires a range of regulatory measures, including assessment of product design, quality specifications for both active ingredients and finished product, compliance of manufacturers with GMP standards, and proof of bioequivalence with a standard comparator. These parameters should be assessed during registration and followed up in the post-registration period. Bioequivalence studies for rifampicin-containing products on their own cannot be applied as a quality control method without proper understanding of GMP compliance and registration conditions, and to measure bioavailability as part of ongoing TB treatment during this study would have had ethical constraints.

5. Conclusions

In conclusion, a survey of quality of selected anti-TB medicines in six NIS identified 11.3% samples failing to meet the specifications set for this survey. Focusing only on extreme deviations as defined in this report, which are likely associated with direct health implications, the failure rate reached 1.0%. No sample was suspected to be of spurious, falsely-labelled, falsified or counterfeit product. This seems to indicate relatively good overall compliance with quality standards, however low content of rifampicin, substantial inconsistencies in ofloxacin dissolution, batch-to-batch as well as intra-batch inconsistencies are of particular concern and need to be addressed.

These findings may be caused by a combination of inconsistent application of Good Manufacturing Practices (GMP) and insufficient regulatory supervision. An impact of inappropriate distribution and storage conditions could not be excluded, but there was not enough information to relate the quality problems identified to specific distribution or storage problems.

The extent to which these faults may contribute to the MDR-TB epidemic in these countries is not known but improvements in the manufacturing, procurement, and supply of medicines are a part of the broader response to the epidemic in this region.

Whilst the failures are of concern, the fact that 88.7% of samples in this survey met the required specifications is encouraging. This, together with the fact that all sampled products had either undergone full registration procedures or were placed on the market in line with national legislation, suggests that the efforts of medicines regulators in the surveyed countries resulted in fairly good control of anti-TB medicines in use. The zero failure rate of samples of WHO-prequalified products and products supplied through GDF suggests that the efforts of WHO to facilitate access to medicines that meet uniform standards of quality, safety, and efficacy through the WHO Prequalification of Medicines Programme and the Global Drug Facility have had some success in this region.

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Appendices

Appendix 1 Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

Version: Final (May 2009)

1. Introduction

WHO estimates that nearly half a million multidrug-resistant tuberculosis (MDR-TB)[1] cases emerge each year, as a result of inadequate or poorly administered treatment regimens, insufficient supply or quality of anti-TB medicine, and transmission of drug-resistant strains. Newly independent states of the former Soviet Union (NIS) have some of the highest prevalence rates of MDR-TB, with proportions of MDR-TB among new and previously treated TB cases have been reported as high as 28.3% and 61.6% respectively[2].

It has been hypothesized that one of the most important factors for the resurgence of TB, and the high rates of MDR-TB, in the NIS, was the socio-economic crisis that followed the disintegration of the Soviet Union in 1991[3,4,5]. This crisis resulted in interruptions in medicines supply and overall deterioration of the health sector, which had an impact on the transmission of and susceptibility to TB and MDR-TB. The lack of standardized treatment regimens in many countries is also likely to have contributed to the development of drug resistance.

Limited research has been conducted into the factors contributing to drug resistance in this region, and to the marked regional and national differences in drug resistance rates. In particular, there has been little consideration of the extent to which substandard, spurious, falsely-labelled, falsified and counterfeit anti-TB medicines might circulate in this region. This survey aims to investigate the quality of anti-TB medicines in use in selected NIS.

2. Definitions

Country code — for the purposes of this project means a 2-digit code used for the country in an email address.

Delivery centre — for the purpose of this project means a point, where a medicine enters the country, central stores and stores, where a medicine is kept during the in country distribution.

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1 MDR-TB is defined as resistance to at least rifampicin and isoniazid, the two most powerful anti-TB medicines.

2 WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. *Anti-tuberculosis drug resistance in the world: fourth global report*. Geneva, World Health Organization, 2008.

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Product abbreviations (for the purposes of coding samples):

Isoniazid = H
Rifampicin = R
Isoniazid + rifampicin = H-R
Kanamycin = Km
Ofloxacin = Ofx

Sample	for the purposes of this project means an item collected from each presentation at the same collection site. That means that a product of the same name, content of APIs, the same dosage form, strength, batch and from the same manufacturer collected in two different sites represents two samples.
Treatment centre	for the purpose of this project means the final site, where a medicine is delivered and where it is provided to a patient.

3. Objectives

The WHO Stop TB and Essential Medicines and Pharmaceutical Policies Departments, and counterparts in the WHO Regional Office for Europe, are collaborating with NMRAs to study the quality of first and second-line anti-TB medicines circulating in the countries with the highest MDR-TB and XDR-TB rates. The project will commence in countries of Eastern Europe and the NIS as indicated in this study protocol, and will subsequently expand to China and India.

The aim of this project is therefore to evaluate the pharmaceutical quality of widely used anti-TB medicines (first and second-line) obtained at public and private sector procurement and treatment centres in selected countries of Eastern Europe and the NIS. The following questions will be addressed:

- Which anti-TB medicines are mostly used?
- What proportion of anti-TB medicines samples, including fixed-dose combination products, collected at approved procurement and treatment centres fail quality testing?
- Which specific quality tests do the samples fail, if any?
- Are any of the deficiencies critical, i.e. could most likely affect treatment efficacy and/or cause harm to the patient?

The results of this study are expected to assist responsible authorities in the countries surveyed to adopt regulatory actions, if necessary, and to develop appropriate quality assurance strategies for anti-TB medicines. They will also provide information for WHO to adapt its prequalification procedures. Finally, they will be of use in awareness and advocacy programmes on quality issues in anti-TB medicines in general.

Limitations of the study

This quality survey cannot completely solve the problem of bioavailability, which may be of special relevance in case of rifampicin.

Appropriate bioavailability must be assured by complex regulatory measures, which include compliance of manufacture with GMP standards, appropriate quality specifications for both active ingredients and finished product and proof of bioequivalence with proper comparator. These parameters should be assessed during registration and followed up in post-registration period.

From anti-TB medicines included in this survey only rifampicin strictly requires bioequivalence testing *in vivo*, for other appropriate bioavailability may be judged upon based on *in vitro* testing. However, organization of bioequivalence studies for rifampicin containing products cannot be applied as quality control method without proper understanding of GMP compliance and registration conditions and as a control method for the given purpose is considered unethical. Instead of that, comparative dissolution is performed to respond at least partially to the issue of bioavailability.

It is obvious that study findings are relevant only to tested samples and extrapolation to individual batches and products is limited.

4. Methodology

4.1 Participating countries

The study should involve some six countries, where anti-TB medicines are not produced or are produced in a small scale.

The following nine countries were approached before the selection of countries was made:

- Armenia
- Azerbaijan
- Belarus
- Estonia
- Kazakhstan
- Moldova
- Latvia
- Ukraine
- Uzbekistan

The countries where samples should be collected were selected as follows:

1. A questionnaire (Annex 1) was sent to the NMRA in the 9 above mentioned countries. The questionnaire asked for first and second-line anti-TB medicines, including FDCs, that were in 2008 used in the country in both public and private sectors, the volumes used, the manufacturers of these medicines and also which institutions were involved in importation and distribution of these medicines (to identify sampling locations).
2. Following the compilation of the results of the questionnaire, six relevant countries were selected, focusing on those where the widest choice of medicines selected for this study was in use.
3. A certain amount of medicines is procured through the Global Drug Facility (GDF), including the Green Light Committee. These medicines should also be tested. However, it is important to select countries using other sources than GDF.
4. An official WHO letter was sent to the Ministries of Health of the six selected countries. The letter described the project and asked for the willingness of the Ministry of Health to collaborate on this project. Without the consent of the Ministry of Health, the country was not included in the project.

Based on the results of the questionnaire and taking into account the above mentioned aspects, the following countries were selected for sampling:

- Armenia
- Azerbaijan

- Belarus
- Kazakhstan
- Uzbekistan
- Ukraine

The Ministries of Health of the above-mentioned six countries also nominated focal persons for this project.

4.2 Anti-tuberculosis medicines surveyed

Based on the information on medicines used in individual countries, the final medicines selection was made. Apart of the availability, volumes and sources of medicines used in individual countries, the susceptibility of medicines to quality deterioration such as low stability was taken into account.

Based on these considerations the following medicines were selected to be surveyed:

- Isoniazid tablets 300mg, 100mg, injection 10% (5ml)
- Rifampicin capsules 300mg, 150mg
- Isoniazid/rifampicin tablets 150mg/300mg, 150/150mg, 75/150mg, 60/60 mg, 30/60mg
- Kanamycin powder for injection 1g
- Ofloxacin tablets/capsules 200 mg, 400mg, solution for injection 0.2% (200ml)

4.3 Study period

The study period should last from summer 2008 to beginning 2010 and as indicated in the below table.

Table 1.Timeframe and responsible officers for the survey of the quality of anti-TB medicines circulating in selected countries of Eastern Europe and the NIS.

Activity	Timeframe	Responsible officers
Anti-TB medicines quality survey questionnaire sent to the 9 countries	June 2008	EURO Pharmaceutical programme
Compilation of results of the questionnaire	October 2008	EURO Pharmaceutical programme
Selection of countries and anti-TB medicines to be surveyed	November 2008	EURO Pharmaceutical programme and HQ TB and EMP/QMS departments
Letters sent to Ministers of Health of six countries for collaboration in this project	December 2008	EURO Pharmaceutical programme
Laboratory/ies selected for the performance of the tests	January 2009	HQ EMP/QMS
Preparations of contracts with NMRA to cover for national expenditures	May 2009	EURO Pharmaceutical programme and HQ TB and EMP/QMS departments
Meeting held with selected countries and pharmaceutical experts	May 2009	EURO Pharmaceutical programme and HQ EMP/QMS
Collection of samples by NMRAs	June - September 2009	NMRAs in close collaboration with WHO country, region and HQ staff
Analysis of medicines quality by selected laboratories	October 2009 - April 2010	HQ EMP/QMS
Compilation of results	April - June 2010	EURO Pharmaceutical programme and HQ TB and EMP/QMS
Meeting held with the participating countries (Ministries of Health and NMRA staff) and WHO pharmaceutical and TB experts to discuss the final results and the actions needed	June 2010	EURO Pharmaceutical programme and HQ TB and EMP/QMS departments

4.4 Selection of sample collection sites

Samples should be collected from the following levels of distribution chain:

- Level 1 - delivery centres (private and/or public); as the aim of the survey is to assess the quality of medicines available to patients, samples should be collected at the manufacturing sites only in case that it is not possible to collect appropriate samples at the other sites
- Level 2 - wholesalers, regulated retailers including dispensing facilities and treatment centres, in both private and public sectors.

A meeting should be held with participation of focal persons from individual countries and WHO representatives from EURO Pharmaceutical Programme and HQ TB and EMP/QMS departments to explain the project, to provide detailed instructions and to identify names and addresses of sample collection sites in each country involved.

Samples will be collected by the staff of the NMRAs in cooperation with the WHO country offices staff in the respective country and with backup support from the EURO Pharmaceutical programme and HQ EMP/QMS department.

4.5 Sample collection

For the purposes of this project, a sample means an item collected from each presentation at the same collection site. That means that a product of the same name, content of APIs, the same dosage form, strength, batch and from the same manufacturer collected in two different sites represents two samples.

A detailed national sampling plan will be prepared for each country by the focal person in the NMRA in cooperation with WHO pharmaceutical experts (Annex 2). The focal person in each country will arrange for training of collectors to be familiar with the national sampling plan and instructions.

In general the following information shall be included in the national sampling plan:

- Identification of the country and the person responsible for sampling
- Names and addresses of the sites, where samples shall be collected
- Identification of medicines to be collected (active ingredients by INNs, dosage form, strength, manufacturer, number of batches to be collected in each site and number of units to be collected per batch of each medicine)
- Maximum number of samples collected per country
- Detailed instructions for collecting samples (see below).

Number of dosage units or multidose packages of selected medicines to be collected should allow for:

- conducting the agreed tests
- possible confirmative testing due to out-of-specification investigations, and
- retention samples.

The following general rules are used, if not justified otherwise:

Dosage form	**Packaging (typical)**	**Number of dosage units or multidose packs per batch**
Tablets &capsules (immediate/modified release, chew, dispersible, etc.)	Blisters, co-blisters, bottles, securitainers	Approx.100 units (e.g.5 packs of 20 units 3 packs of 30 units 3 packs of 40 units 2 packs of 60 units 1 pack of 90 units and above) In case of co-packaged FPPs approx.100 units shall be collected from each medicine.
Multidose oral solutions/suspensions, powder for oral solution/suspension & injections or powders for injections	Multidose bottles and vials	6 containers of 60 ml / 100 ml 3 containers of 240 ml
Single dose powders for oral solution/ suspension & single dose injections or powders for injections	Sachets and single dose bottles, vials & ampoules	Unless otherwise specified, 15 units (20 units if dose is below 50 mg)

Instructions for sample collection:

- The time period, within which samples should be collected in the countries and the deadline for sending the last sample to the testing laboratory, should be clearly indicated and followed.
- The minimum quantity of sample per batch and number of batches to be collected from each collection site for each selected medicine as indicated in the Sampling Plan shall be followed. Note that there should not be a mix-up with batches, all units of one sample must be of the same batch. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.
- Samples collected should have at least six months remaining to expiry.
- Only unopened original packages shall be collected.
- The medicine samples should not be taken out of the original primary packaging and outer containers (though removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened.
- The medicine labels and package leaflets should not be removed or damaged.
- Sampling will be recorded using the Sample Collection Form (Annex 3). Whenever the required information is not available, it should be indicated in the appropriate space on the Sample Collection Form, where also any abnormalities should be recorded.
- In order to avoid confusion, each sample will be identified by a unique Sample Code (for coding system see the Sample Collection Form, Annex 3) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept

together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).

- Manufacturer's batch certificates of analysis will be collected with samples, if available, and kept with the Sample Collection Form.
- The samples should be collected and kept under controlled conditions, as per label requirement. The cold chain should be maintained, where required.

If needed, the appropriate arrangements shall be made with treatment centres to ensure that there is no shortage due to collection of samples (e.g. requesting for replacements of medicines).

4.6 Storage and dispatch of samples

Storage and transport of the sample should be done according to the requirements set out in paragraph 2.3 of WHO's Guidelines for Sampling of Pharmaceutical Products and related materials[6]:

- The samples should be kept in original packaging and under storage conditions specified on the label.
- For transport all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport. Any residual space in the container should be filled with a suitable material. Where required, the cold chain should be retained during storage and transport.
- A covering letter, the copy Sample Collection Form and, if available, copy of Manufacturer's batch certificates of analysis should accompany the samples.
- Samples with the accompanying documents should be sent straightforward to the assigned testing laboratory **by a courier service**. For each shipment it should be clearly indicated that samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. Low price just for customs purposes should be indicated to avoid problems with the customs clearance.
- The laboratory and WHO contact point[7] should be informed about the shipment and the tracking number as provided by the courier service.
- Copies of all Sample Collection Forms and, if available, copies of Manufacturer's batch certificates of analysis should be sent to WHO contact point[7] after dispatch of samples.

4.7 Testing laboratory

An appropriate laboratory has to be selected for testing. Preferably a prequalified laboratory should be used. Should such a laboratory not be available or should it not have sufficient capacity, then another laboratory should be chosen, where evidence of reliability is available.

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[6] WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 4 (WHO Technical Report Series, No.929). http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf#page68

[7] Dr Jitka Sabartova - Phone: +41 22 7913376, Fax: +41 22 7914730, E-mail: sabartovaj@who. int World Health Organization, HSS/EMP/QSM, Prequalification Programme, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland.

The appropriate arrangement with the laboratory has to be made. The request for testing should be in line with WHO's guideline: *Considerations for requesting analysis of drug samples*[8] and no sample will be sent before such an arrangement is made. An agreement for performance of work between WHO and the laboratory should be prepared and agreed upon by both parties.

For this project the following laboratories have been selected:

Name	Address	Products to be tested
AGES - PharmMed - Austrian Agency for Health and Food Safety in cooperation with **Laboratoire National de Santé, Luxembourg** (AGES will be responsible for the logistics and all the mono-component isoniazid samples will be sent to Austria)	Zimmermanngasse 3 A-1090 Vienna AUSTRIA	• Isoniazid tablets, injection
COUNCIL OF EUROPE **European Directorate For The Quality Of Medicines & Healthcare** **(European Pharmacopoeia)**	7 allée Kastner (entrance on rue de la Carpe Haute) - CS 30026 F-67081 Strasbourg FRANCE	• Kanamycin powder for injection • Ofloxacin tablets/capsules, solution for injection
SGS Lab Simon S. A.	Vieux Chemin du Poète 10 B-1301 Wavre BELGIUM	Testing for identity, assay, related substances and uniformity of mass: • Rifampicin capsules • Isoniazid + rifampicin tablets
J. W. Goethe University **Institute of Pharmaceutical Technology** **Biocenter**	Max-von-Laue-Str.9 60438 Frankfurt am Main GERMANY	Comparative dissolution study: • Rifampicin capsules • Isoniazid + rifampicin tablets

4.8 Tests conducted

Laboratory testing of all collected samples will be performed according to the testing protocol agreed with the testing laboratories. In principle the following tests will be included:

- Appearance
- Identity
- Assay
- Related substances test
- Dissolution and Uniformity of mass for tablets and capsules
- pH value for injections and powders for injection
- Sterility, Bacterial endotoxins tests for parenteral products

In the light of known problems with bioavailability of rifampicin, contradictory outcomes of studies evaluating correlation between bioavailability and dissolution *in vitro*, and no clear conclusion on the recommended dissolution methodology in the literature it has been decided to conduct comparative dissolution study of collected products containing rifampicin.

[8] Considerations for requesting analysis of drug samples. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 4 (WHO Technical Report Series, No.902).
http://whqlibdoc. who. int/trs/WHO_TRS_902. pdf#page69

4.9 Test methods and specifications

Tests methods and specifications are in general selected according to the following rules:

- Preferably Ph. Int. monographs should be used, if available.
- If no monograph exists in the Ph. Int., then BP or USP can be used.
- If there is no pharmacopoeial monograph or the existing monographs do not provide for desired tests, a validated method of the laboratory or manufacturer's method, if available, should be used.

Dissolution methodology from various pharmacopoeias and literature was compared and conditions for comparative dissolution study of products containing rifampicin were outlined in cooperation with experts involved in Prequalification Programme and specializing on quality of anti-TB medicines, pharmaceutical technology and waivers of *in vivo* bioequivalence testing.

For the agreed testing protocol for products selected for this survey see Annex 4.

4.10 Receipt and testing of samples by a testing laboratory

- Inspect each sample to ensure that the labelling is in conformance with the information contained in the Sample Collection Form or test request.
- Store the samples according to the respective medicine requirements. If appropriate, ensure compliance with the cold chain.
- Conduct quality testing in line with this protocol and in compliance with WHO standards recommended for quality control laboratories[9].
- Complete an Analytical Test Report (Annex 5). In the case that non-compliant results are found and confirmed after application of a laboratory out-of-specification procedure, report them immediately to WHO contact point[7].
- Keep records of each sample, accompanying document/s and retention samples for at least six months if the sample complied with the analytical test requirements, or for at least one year or until the expiry date (whichever is longer) if it did not comply.
- An electronic databank (e.g. photos of medicine such as tablets, packaging, package leaflet) is recommended.

5. Data management, analysis and publication

Any non-compliant result found in the survey will be investigated with the respective manufacturer and NMRA.

A data analyst/statistician will be hired to compile and analyse the laboratory test results.

The analytical test reports of the testing laboratories will be provided to all NMRA involved in the project. The outcomes of the project will be discussed by national authorities and WHO in a meeting, and corrective actions, if necessary, will be recommended. To take the relevant measures in countries lies within the responsibility of the NMRA.

Agreed outcomes and report from the project will be published by WHO.

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[9] Good practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010, Annex 1 (WHO Technical Report Series, No.957). http://www.who.int/prequal/info_general/documents/TRS957/GPCL_TRS957_Annex1. pdf

Annex 1 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union
Questionnaire
please fill in ONLY for products, which are actually available in July 2008

Name and address of the site				
Responsible person(s) and contact details (phone, mobile, e-mail)				
Type of the site ***what organization is best to approach for sampling, i.e. which one has the longest list of TB-products available.***		**Hospital pharmacy**	**Warehouse**	**Retail pharmacy**
Please mark with **X** in the box under the right answer				

Finished Pharmaceutical Product and dosage form	**Strength**	**Quantity (Packs)**	**Manufacturer name and manufacturing site address**	**Country of origin**	**Not used in the country**
Single ingredient first-line anti-tuberculosis medicines					
Ethambutol, tablet	400 mg				
Isoniazid, tablet	300 mg				
Pyrazinamide, tablet	400 mg				
Rifampicin, capsule	150 mg; 300 mg				
Streptomycin, powder for injection (vial)	1g				

Other single ingredient anti-tuberculosis medicines used for the first-line treatment (please specify in the same format below)					

Fixed dose combination products of first-line anti-tuberculosis medicines

Isoniazid + rifampicin, tablet	75 mg + 150 mg 150 mg + 150 mg				
Ethambutol + isoniazid, tablet	400 mg + 150 mg				
Ethambutol + isoniazid + rifampicin, tablet	275 mg + 75 mg + 150 mg				
Ethambutol + isoniazid + pyrazinamide + rifampicin, tablet	275 mg + 75 mg + 400 mg + 150 mg				
Other single ingredient anti-tuberculosis medicines used for the first-line treatment (please specify in the same format below)					

Single ingredient second-line anti-tuberculosis medicines

Amikacin, solution for injections (vial 2 ml, 4 ml)	250 mg/ml				
Amikacin, powder for injection (vial)	1g				
Capreomycin, powder for injection (vial)	1g				

Cycloserine, capsule	250 mg				
Ethionamide, coated tablet	125 mg				
Ethionamide, coated tablet	250 mg				
Kanamycin, powder for injection (vial)	1g				
Levofloxacin, tablet	250 mg				
Moxifloxacin, tablet	400 mg				
Ofloxacin, tablet	200 mg				
Ofloxacin, tablet	400 mg				
Prothionamide, coated tablet	250 mg				
P-aminosalicylic acid, granules	4g				
P-aminosalicylic sodium, granules	100 g				
Other single ingredient anti-tuberculosis medicines used for the second-line treatment (please specify in the same format below)					

Scored solid dosage formulations for children, preferably dispersible

Ethambutol, tablet	100 mg				
Isoniazid, tablet	50 mg				

Isoniazid, tablet	100 mg				
Isoniazid + rifampicin, tablet	60 mg + 60 mg				
Isoniazid + rifampicin, tablet	30 mg + 60 mg				
Isoniazid + pyrazinamide + rifampicin, tablet	30 mg + 150 mg + 60 mg				
Pyrazinamide, tablet	150 mg				
Other scored solid dosage formulations for children, preferably dispersible, used for the TB treatment (please specify in the same format below)					

Instructions to fill the questionnaire

1. Before completion of the questionnaire please select the **SITES** which will have products actually available for sampling in July 2008. The site must have the longest list of the medicines and amounts available for sampling.
2. Complete the form only for **PRODUCTS** that would be available at the selected sites for sampling in July 2008.

3. If the site will have more that one product in the line, e.g. Ethambutol, tablet, 400mg, please insert the row below the specified product name and complete it with all requested information.
4. Please complete the form in electronic format (as it is in MS Excel file) and send it by e-mail to Olexandr Polishchuk WHO/EURO at apo@euro. who. int

Annex 2 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

National Sampling Plan

Country: _____

Focal Person: _____

MEDICINES TO BE COLLECTED:

- **Isoniazid tablets 300mg, 100mg, injection 10% (5ml)**
- **Rifampicin capsules 300mg, 150mg**
- **Isoniazid / rifampicin tablets 150/300mg, 150/150mg, 75/150mg, 60/60 mg, 30/60mg**
- **Kanamycin 1g powder for injection**
- **Ofloxacin tablets/capsules 200mg, 400mg, solution for injection 0.2% (200ml)**

NUMBER OF UNITS TO BE COLLECTED PER SAMPLE**:**

- **Approx.100 units for tablets/capsules**
    - In case of rifampicin capsules and isoniazid/rifampicin tablets collect for 1 sample per each strength and each manufacturer at least 24 additional units (in intact original primary packaging) for comparative dissolution study, which will be carried out by the different laboratory than the other tests. Collection of smaller pack-sizes should be preferred to be possible to divide sample for dispatch and not interfere with the primary packaging.
- **5 bottles of 200ml**
- **15 ampoules of 5ml**
- **6 vials for powder for injection**

NUMBER OF BATCHES TO BE COLLECTED PER PRODUCT IN EACH SITE:

- **Maximum 3 batches per product at one collection site**; if the same product (same manufacturer, same dosage from, same strength) is collected in more sites, please select different batches, if possible.

TOTAL NUMBER OF SAMPLES PER COUNTRY:

60 samples (12 samples per product preferably produced by different manufacturers)

NAMES AND ADDRESSES OF THE SITES WHERE SAMPLE SHALL BE COLLECTED:

	Facility name	**Address**	**Facility type** 1. (private/public; 2. level 1/level 2; 3. wholesaler/retailer/ treatment centre/…)
1.			
2.			
3.			
4.			
5.			

SELECTION OF PRODUCTS:

Isoniazid

Strength / Dosage form	**Pack size**	**Manu-facturer**	**Sampling site**	**Batch no**	**Sample code**	**No of units per sample**	**Additional 24 units needed**

Rifampicin

Isoniazid / rifampicin

Kanamycin

Ofloxacin

INSTRUCTIONS FOR COLLECTORS:

- The amount of the selected products defined above will be sampled from the identified sites. All these samples are inclusive of the samples needed for the out-of specifications investigations and retention samples.
- An item collected from each presentation at the same collection site will be called a sample. **All units (tablets, capsules, vials) of one sample must be of the same batch**, there should not be a mix-up with batches. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.
- Samples collected shall have **at least six months remaining to expiry**. Products with shorter period remaining to expiry date are not collected.
- One batch of each product will be collected from each collection site and **only unopened original packages shall be collected**.
- The medicine **samples should not be taken out of the original primary packaging and outer containers** (though removal of blisters from large secondary packs is appropriate). Containers such as **bottles and vials should not be opened**.
- The medicine labels and package leaflets should not be removed or damaged.
- Sampling will be recorded using the Sample Collection Form (Annex 3). Whenever the required information is not available, it should be indicated in the appropriate space on the Sample Collection Form, where also any abnormalities should be recorded.
- In order to avoid confusion, each sample will be identified by a unique Sample Code (for coding system see the Sample Collection Form, Annex 3) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).
- Manufacturer's batch certificates of analysis will be collected with samples, if available, and kept with the Sample Collection Form.
- The **samples should be collected and kept under controlled conditions**, as per label requirement. The cold chain should be maintained, where required.
- Samples should be collected in all the countries involved during June 2009 and the **deadline for sending the last sample to the testing laboratory is 3 July 2009**.

Annex 3 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

Sample Collection Form*

Country: _____ **Sample code:** _____

(Country code/product abbreviation/sequence number/sampling date ddmmyy)**

Name of location/place where sample was taken: _____

_____

Address (with telephone, fax number and email address, if applicable):

_____

_____

Organization and names of people who took samples:

1. _____

2. _____

Product name of the sample: _____

Name of active pharmaceutical ingredient(s) (INN) with strength:

_____

Dosage form (tablet, capsule, powder for injection, etc): _____

Package size, type and packaging material of the container: _____

_____

Batch/lot number: _____

Date of manufacture: _____ Expiry date: _____

Regulatory status in the country, registration number, if applicable: _____

_____

Name and address of the manufacturer: _____

_____

Quantity collected (number of sample units or of multidose containers taken):

_____

Initialize first page

* This Sample Collection Form should always be kept with the sample collected. Proper sampling procedures should be followed.

** Product abbreviations: Isoniazid = H, Rifampicin = R, Isoniazid + rifampicin = H-R, Kanamycin = Km, Ofloxacin = Ofx. Sample code system can be extended to be appropriate for a particular country collection system.

Product name:_____ **Sample code:** _____

Storage/climatic conditions at sampling site/point (temperature and humidity, indication of conditions during daytime only is acceptable, comments on suitability of premises where products are stored at the particular site for the NMRA information):

_____

_____

_____

Abnormalities, remarks or observations that may be considered relevant, if any:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Date:

Signature of person(s) taking samples

Signature of representative of the establishment where sample(s) was taken (optional)

1. .....

2. .....

Note: Samples collected must remain in their original containers, intact and unopened

Annex 4 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

Testing Protocol

	Product	*Tests to be performed and specifications for testing*	*Reference substances*
1.	**Isoniazid tablets 100mg, 300mg**	**USP** • Appearance - package leaflet • Identity - HPLC as for assay • Uniformity of mass • Assay - HPLC • Dissolution - UV	USP: Isoniazid - 1349706, 200mg
2.	**Isoniazid injection 10% (5ml)**	**USP** • Appearance - package leaflet • Visual inspection - clear and free from visible particulate matter • Volume in container/Extractable volume • Identity - HPLC as for assay • Assay - HPLC • pH - 6.0-7.0 • Sterility (to be performed for 1 sample per batch/ manufacturer)	USP: Isoniazid - 1349706, 200mg
3.	**Rifampicin capsules 150mg, 300mg**	**Ph. Int.** • Appearance - package leaflet • Identity - HPLC as for assay • Uniformity of mass • Assay - HPLC • Related substances - HPLC • Comparative dissolution study - 2 sets of comparison - 1 using Ph. Int. conditions, the other USP/BP conditions, 7 points up to 60 min	Ph. Int. : 9930409 - Rifampicin, 300mg 9930410 - Rifampicin quinine, 200mg BP: 627 - 3-formylrifamycin, 25 mg
4.	**Isoniazid / rifampicin tablets 150/300mg, 150/150mg, 75/150mg, 60/60 mg, 30/60mg**	**Ph. Int.** • Appearance - package leaflet • Identity - HPLC as for assay • Uniformity of mass • Assay - 2x HPLC • Related substances - for rifampicin only - HPLC • Comparative dissolution study - 1 set of comparison using laboratory method based on Ph. Int. conditions for Rifampicin tablets, 7 points up to 60 min	Ph. Int. : 9930331 - Isoniazid, 100mg 9930409 - Rifampicin, 300mg 9930410 - Rifampicin quinone, 200mg BP: 627 - 3-formylrifamycin, 25 mg
5.	**Kanamycin powder for injection 1g (vial)**	**USP monograph for kanamycin injection** • Appearance - package leaflet • Identity - HPLC as for assay • Assay - HPLC with amperometric detection • pH - 3.5 - 5.0 • Sterility (to be performed for 1 sample per manufacturer)	USP: Kanamycin Sulfate - 1355006, 200mg Amikacin - 1019508 (for system suitability), 300 mg
6.	**Ofloxacin tablets/capsules 200 mg, 400mg**	**USP monograph for ofloxacin tablets** • Appearance - package leaflet • Identity - HPLC as for assay • Uniformity of mass • Assay - HPLC • Related substances - HPLC • Dissolution - UV	USP: Ofloxacin - 478108, 200mg

	Product	*Tests to be performed and specifications for testing*	*Reference substances*
7.	**Ofloxacin solution for infusion 0.2% (200ml)**	**USP monograph for tablets** • Appearance - manufacturers' specification: clear, light yellow liquid • Visual inspection - clear and free from visible particulate matter • Volume in container/Extractable volume - not less than the nominal volume • Identity - HPLC as for assay • Assay - HPLC with USP limits for tablets 90.0-110.0% • Related substances - HPLC with USP limits for tablets • pH - manufacturers' specification • Bacterial endotoxins (to be performed for 1 sample per batch/manufacturer) *The manufacturer uses test for pyrogens.* *Limits for BE in products containing ofloxacin found in:* ○ *Brazilian pharmacopoeia (max.5 E. U. /mg of ofloxacin for ofloxacin injection) and* ○ *Chinese pharmacopoeia (less than 0.5 E. U. /ml for ofloxacin and sodium chloride injection and less than 0.75 E. U. /mg for ofloxacin substance)* • Sterility (to be performed or 1 sample per manufacturer and in case a positive BE result is found)	USP: Ofloxacin - 478108, 200mg

Annex 5 to Survey protocol

Content of the Analytical Test Report

Analytical test report

> *The report of the results, including the final conclusion of the analysis of a sample which has been submitted by a laboratory in another country or in the field not having appropriate facilities to perform certain tests, and issued by the official pharmaceutical control laboratory that performed the test.* ***This is often in the same style as a certificate of analysis.***

The Analytical Test Report shall in accordance with the Good practices for national pharmaceutical control laboratories provide the following information:

1. Name and address of the laboratory performing the sample testing,
2. Number/code of the Analytical Test Report,
3. Name and address of the originator of the request for testing,
4. Sample code from the Sample Collection Form,
5. Date on which the sample was received,
6. Name of the country where the sample was collected,
7. Sample product name, dosage form, active ingredients, strength, package size, type and packaging material of primary container,
8. Description of the sample (both product and container),
9. Batch number of the sample, expiry date and manufacturing date, if available,
10. Name and address of the manufacturer,
11. Reference to the specifications used for testing the sample, including the limits,
12. Reference to the reference standards used for quantitative determinations,
13. Results of all the tests performed (numerical results, if applicable),
14. Conclusion whether or not the sample was found to be within the limits of the specifications used,
15. Date on which the test was performed, and
16. Signature of the head of the laboratory or authorized person.

Assay: 90.0-110.0%; **Dissolution**: NLT 80% (Q) in 45min ✓= complies; ✖= does not comply

Appendix 2 Isoniazid tablets – test results

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Expiry date	Registered	WHO PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Dissolution	Uniformity of mass	Conclu-sion
AM/H/1/130709	100 mg	28 tabs in blister	Svizera Labs, India	SL45	07 2005	2010 Jun	No Supplied as humanitarian aid	No	Public-2	21°C, protected from light	✓	✓	94.6	Complies at S1 min:97%; max:100%	✓	✓
AM/H/2/140709	100 mg	28 tabs in blister	Svizera Labs, India	SL45	07 2005	2010 Jun	No Supplied as humanitarian aid	No	Public-3	21°C, protected from light	✓	✓	96.8	Complies at S1 min:95%; max:98%	✓	✓
AM/H/3/140709	100 mg	28 tabs in blister	Svizera Labs, India	SL45	07 2005	2010 Jun	No Supplied as humanitarian aid	No	Public-5	21°C, protected from light	✓	✓	93.4	Complies at S1 min:93%; max:98%	✓	✓
AZ/H/6/01.07.09	300 mg	1000 tabs in plastic bottle	Cadila Pharmaceuticals Ltd, India	ITA8006	12 2008	2012 Nov	Yes Supplied through GDF	No	Public-6	Conform, 23°C, 45% humidity	White residual powder in bottle	✓	101.6	Complies at S1 min:101%; max:104%	✓	✓
AZ/H/1/01.07.09	300 mg	28 tabs in blister	Cadila Pharmaceuticals Ltd, India	ITA8004	12 2008	2012 Nov	Yes Supplied through GDF	No	Public-6	Conform, 22°C, 45% humidity	✓	✓	100.7	Complies at S1 min:99%; max:105%	✓	✓
AZ/H/2/01.07.09	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	151108	11 2008	2013 Nov	Yes	No	Public-6	20°C, 40% humidity	White residual powder in bottle	✓	100.1	Complies at S1 min:98%; max:102%	✓	✓
AZ/H/9/03.07.09	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	151108	11 2008	2013 Nov	Yes	No	Public-7	Conform, 22°C, 46% humidity	White residual powder in bottle	✓	99.2	Complies at S1 min:97%; max:101%	✓	✓
AZ/H/10/03.07.09	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	90908	09 2008	2013 Sep	Yes	No	Public-7	✓, 22°C, 46% humidity	White residual powder in bottle	✓	99.0	Complies at S1 min:97%; max:102%	✖ 1	✖
AZ/H/11/03.07.09	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	90908	09 2008	2013 Sep	Yes	No	Public-8	✓, 24°C, 45% humidity	White residual powder in bottle	✓	98.2	Complies at S1 min:88%; max:103%	✖ 2	✖
AZ/H/5/01.07.09	300 mg	1000 tabs in plastic bottle	Svizera Labs, India	SL61	03 2007	2012 Feb	No Supplied through GDF	No	Public-6	✓, 23°C, 45% humidity	White residual powder in bottle	✓	99.7	Complies at S1 min:99%; max:101%	✓	✓
AZ/H/3/01.07.09	300 mg	Pack, 10 blisters x 10 tabs	Tyumenskij khimiko-farmacevticeskij zavod, Russia	010307	03 2007	2013 Apr	No	No	Public-6	✓, 23°C, 42% humidity	✓	✓	97.8	Complies at S1 min:94%; max:100%	✓	✓
BY/H/20/01072009	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	110408	04 2008	2013 May	Yes	No	Public-16	✓	✓	✓	99.3	Complies at S1 min:90%; max:103%	✖ 3	✖

1 **Does not comply:** mean: 328.0mg**,** CV= 4.30%, min: 91.9%; max: 108.0%**, 6 tablets outside ±5%,** no tablets outside ±10%
2 **Does not comply:** mean: 327.8mg**,** CV= 4.09%, min: 86.7%; max: 107.5%**,** 1 tablet outside ±5%**, 1 tablet outside ±10%**
3 **Does not comply:** mean: 326.9mg**,** CV= 3.76%, min: 89.8%; max: 105.4%**,** 2 tablets outside ±5%**, 1 tablet outside ±10%**

Appendix 2: Isoniazid tablets – test results

Assay: 90.0-110.0%; **Dissolution**: NLT 80% (Q) in 45min ✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Expiry date	Registered	WHO PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Dissolution	Uniformity of mass	Conclu-sion
BY/H/01/02 0709	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	060309	03 2009	2014 Apr	Yes	No	Ware-house-4	✓	✓	✓	99.4	Complies at S1 min:98%; max:99%	✓	✓
BY/H/19/01 072009	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	030108	01 2008	2013 Feb	Yes	No	Public-16	✓	✓	✓	99.1	Complies at S1 min:96%; max:100%	✓	✓
BY/H/02/02 0709	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	020108	01 2008	2013 Feb	Yes	No	Ware-house-4	✓	✓	✓	100.0	Complies at S1 min:98%; max:103%	✓	✓
BY/H/10/01 072009	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	291208	01 2009	2014 Jan	Yes	No	Public-15	✓	✓	✓	100.3	Complies at S1 min:97%; max:100%	✓	✓
BY/H/9/010 72009	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	361107	11 2007	2012 Dec	Yes	No	Public-15	✓	✓	✓	99.8	Complies at S1 min:96%; max:100%	✓	✓
BY/H/51/30 0609	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	361107	11 2007	2012 Dec	Yes	No	Public-13	✓	✓	✓	99.1	Complies at S1 min:97%; max:99%	✓	✓
BY/H/35/01 0709	300 mg	Pack, 2 blisters x 10 tabs	Borisovskij zavod medicinskich preparatov, Belarus	210408	04 2008	2013 May	Yes	No	Public-9	✓	✓	✓	100.9	Complies at S1 min:102%; max:104%	✓	✓
KZ/H/1/24.0 7.09	100 mg	Pack, 10 blisters x 10 tabs	Cadila Pharmaceuticals Ltd, India	IST603 8	10 2006	2011 Sep	No Supplied through GDF	No	Public-25	18°C, 64% humidity	4	✓	98.8	Complies at S1 min:94%; max:102%	✓	✓
KZ/H/6/11.0 8.09	100 mg	Pack, 10 blisters x 10 tabs	Cadila Pharmaceuticals Ltd, India	IST800 1	05 2008	2013 Apr	No Supplied through GDF	No	Public-18	18°C, 80% humidity	5	✓	101.0	Complies at S1 min:96%; max:99%	✓	✓
KZ/H/10/06. 08.09	300 mg	Pack, 10 blisters x 10 tabs	Chimpharm, Kazakhstan	61107	11 2007	2012 Dec	Yes	No	Public-24	23°C, 74% humidity	✓	✓	98.8	Complies at S1 min:97%; max:100%	✓	✓
KZ/H/3/27.0 7.09	100 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	80507	05 2007	2012 May	Yes	No	Public-21	20°C, 75% humidity	✓	✓	99.1	Complies at S1 min:96%; max:103%	✓	✓
KZ/H/7/11.0 8.09	100 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	120808	08 2008	2013 Aug	Yes	No	Public-18	18°C, 80% humidity	✓	✓	102.9	Complies at S1 min:98%; max:106%	✓	✓

4 Broken tablet in one blister, *Blisters packed in a damaged cardboard box, to broken tablet not taken as non-compliance*
5 Broken tablet in one blister, *Blisters packed in a damaged cardboard box, so broken tablet not taken as non-compliance*

Appendix 2: Isoniazid tablets – test results

Assay: 90.0-110.0%; **Dissolution**: NLT 80% (Q) in 45min ✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Expiry date	Registered	WHO PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Dissolution	Uniformity of mass	Conclu-sion
KZ/H/9/06.08.09	100 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	140808	08 2008	2013 Aug	Yes	No	Public-24	23°C, 74% humidity	✓	✓	100.2	Complies at S1 min:92%; max:100%	✓	✓
KZ/H/11/06.08.09	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	20506	05 2006	2011 May	Yes	No	Public-24	23°C, 74% humidity	✖ 6	✓	99.2	Complies at S1 min:95%; max:103%	✓	✖
KZ/H/2/24.07.09	300 mg	1000 tabs in jar	Pavlodarskij farmacevticeskij zavod, Kazakhstan	090707	07 2007	2011 Aug	Yes	No	Public-25	18°C, 64% humidity	White residual powder in bottle	✓	99.2	Complies at S1 min:98%; max:101%	✓	✓
KZ/H/4/27.07.09	300 mg	Pack, 10 blisters x 10 tabs	Pavlodarskij farmacevticeskij zavod, Kazakhstan	010408	04 2008	2012 May	Yes	No	Public-21	20°C, 75% humidity	✓	✓	96.5	Complies at S1 min:97%; max:100%	✓	✓
KZ/H/8/11.08.09	300 mg	10 tabs in blister	Pavlodarskij farmacevticeskij zavod, Kazakhstan	031107	11 2007	2011 Dec	Yes	No	Public-18	18°C, 80% humidity	✓	✓	96.3	Complies at S1 min:97%; max:99%	✓	✓
UA/H/6/300609	300 mg	1000 tabs in plastic container	Darnica, Ukraine	71007	10 2007	2012 Nov	Yes	No	Public-37	✓	✓	✓	102.0	Complies at S1 min: 97%; max:101%	✓	✓
UA/H/3/300609	100 mg	7500 tabs in glass jar	Luganskij khimiko-farmacevticeskij zavod, Ukraine	10607	06 2007	2012 Jun	Yes	No	Public-37	✓	✓	✓	98.9	Complies at S1 min:87%; max:101%	✓	✓
UA/H/4/300609	100 mg	100 tabs in glass jar	Luganskij khimiko-farmacevticeskij zavod, Ukraine	10209	02 2009	2014 Feb	Yes	No	Public-37	✓	✓	✓	103.2	Complies at S1 min: 94%; max:104%	✓	✓
UA/H/1/30.06.09	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	30708	07 2008	2013 Jul	Yes	No	Public-33	✓	✓	✓	99.1	Complies at S2 mean (n=12): 93% min:76%; max:100%	✓	✓
UA/H/1/30.06.09	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	30708	07 2008	2013 Jul	Yes	No	Public-26	19°C	✓	✓	96.4	Complies at S2 mean (n=12): 88% min: 62%; max:100%	✓	✓
UA/H/1/300609	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	10209	02 2009	2014 Feb	Yes	No	Public-37	✓	✖ 7	✓	99.0	Complies at S1 min: 96%; max:101%	✓	✖
UA/H/1/30062009	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	60309	03 2009	2014 Mar	Yes	No	Public-31	✓	✓	✓	99.9	Complies at S1 min: 93%; max:98%	✓	✓

6 **Does not comply: Broken tablets** and white residual powder in bottle

7 **Does not comply: Broken tablets, some with brown dots,** Friability test - does not comply (3.6% instead of ≤1.0%)

Appendix 2: Isoniazid tablets – test results

Assay: 90.0-110.0%; **Dissolution**: NLT 80% (Q) in 45min ✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Expiry date	Registered	WHO PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Dissolution	Uniformity of mass	Conclu-sion
UA/H/1/30062009	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	90808	08 2008	2013 Aug	Yes	No	Public-30	✓	✓	✓	101.2	Complies at S1 min: 93%; max:100%	✓	✓
UA/H/2/30.06.09	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	60808	08 2008	2013 Aug	Yes	No	Public-26	19°C	✓	✓	102.6	Complies at S1 min: 94%; max:100%	✓	✓
UA/H/2/300609	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	60607	06 2007	2012 Jun	Yes	No	Public-37	✓	✓	✓	99.4	✖ [8]	✓	✖
UA/H/2/30062009	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	80808	08 2008	2013 Aug	Yes	No	Public-31	✓	✓	✓	101.3	Complies at S1 min: 92%; max:103%	✓	✓
UA/H/2/30.06.09	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	20209	02 2009	2014 Feb	Yes	No	Public-32	18°C, 70% humidity, conditions controlled	✓	✓	99.5	Complies at S1 min: 94%; max:101%	✓	✓
UA/H/3/30062009	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	40209	02 2009	2014 Feb	Yes	No	Public-31	✓	✓	✓	101.5	Complies at S1 min: 96%; max:104%	✓	✓
UA/H/3/30.06.09	300 mg	2500 tabs in glass bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	50309	03 2009	2014 Mar	Yes	No	Public-26	19°C	✓	✓	101.9	Complies at S1 min: 84%; max:98%	✓	✓
UZ/H/4/010709	300 mg	100 tabs in bottle	Cadila Pharmaceuticals Ltd, India	267E9001	04 2009	2013 Mar	Yes	No	Pharmacy-28	Protected from light and humidity	White residual powder in bottle	✓	99.9	Complies at S1 min:98%; max:102%	✓	✓
UZ/H/5/010709	300 mg	100 tabs in bottle	Cadila Pharmaceuticals Ltd, India	267E9003	04 2009	2013 Mar	Yes	No	Pharmacy-28	Protected from light and humidity	White residual powder in bottle	✓	104.0	Complies at S1 min:103%; max:105%	✓	✓
UZ/H/6/010709	300 mg	100 tabs in bottle	Cadila Pharmaceuticals Ltd, India	267E9005	04 2009	2013 Mar	Yes	No	Pharmacy-28	Protected from light and humidity	White residual powder in bottle	✓	101.2	Complies at S1 min:100%; max:102%	✓	✓
UZ/H/3/020709	100 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	100607	06 2007	2012 Jun	Yes	No	Public-38	20°C, protected from light and humidity	White residual powder in bottle	✓	100.5	Complies at S1 min:94%; max:110%	✓	✓
UZ/H/1/010709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	101008	10 2008	2013 Oct	Yes	No	Public-40	15-25°C, separate air-conditioned room	White residual powder in bottle	✓	98.1	Complies at S1 min:94%; max:101%	✖ [9]	✖

8 **Does not comply at S1+S2+S3, mean (n=24): 70%, min:52%;** max:86%

9 **Does not comply:** mean: 325.6mg**,** CV= 3.42%, min: 94.1%; max: 107.6%**, 4 tablets outside ±5%,** no tablets outside ±10%

Appendix 2: Isoniazid tablets – test results

Assay: 90.0-110.0%; **Dissolution**: NLT 80% (Q) in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Expiry date	Registered	WHO PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Dissolution	Uniformity of mass	Conclu-sion
UZ/H/7/010 709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	101008	10 2008	2013 Oct	Yes	No	Pharma cy-29	Protected from light and humidity	White residual powder in bottle	✓	102.7	Complies at S1 min:97%; max:100%	✓	✓
UZ/H/8/010 709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	101008	10 2008	2013 Oct	Yes	No	Pharma cy-29	Protected from light and humidity	White residual powder in bottle	✓	98.8	Complies at S1 min:96%; max:101%	✓	✓
UZ/H/9/020 709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	101008	10 2008	2013 Oct	Yes	No	Public-44	No information	White residual powder in bottle	✓	98.3	Complies at S1 min:90%; max:102%	✓	✓
UZ/H/10/02 0709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	101008	10 2008	2013 Oct	Yes	No	Public-42	✓	White residual powder in bottle	✓	100.5	Complies at S1 min:95%; max:103%	✖ 10	✖
UZ/H/2/020 709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	160607	06 2007	2012 Jun	Yes	No	Public-38	16°C, protected from light and humidity	White residual powder in bottle	✓	100.4	Complies at S1 min:97%; max:102%	✓	✓
UZ/H/11/02 0709	300 mg	100 tabs in bottle	Luganskij khimiko-farmacevticeskij zavod, Ukraine	240807	08 2007	2012 Aug	Yes	No	Public-41	No information	White residual powder in bottle	✓	100.4	Complies at S1 min:96%; max:102%	✖ 11	✖

10 **Does not comply:** mean: 322.9mg**,** CV= 4.18%, min: 94.1%; max: 107.6%**,** 1 tablet outside ±5%**, 1 tablet outside ±10%**

11 **Does not comply:** mean: 324.2mg**,** CV= 4.02%, min: 92.7%; max: 110.3%**, 3 tablets outside ±5%, 1 tablet outside ±10%**

Appearance: Clear colourless liquid; **Assay**: 90.0-110.0%; ✓= complies; ✖= does not comply

Appendix 3 Isoniazid solution for injection – test results

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Expiry date	Regist-ered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear-ance	Iden-tity	Assay	pH	Sterility	Conclu-sion
AZ/H/4/010709	10%	5 ml/ amp, 10 amps/ pack	Darnica, Ukraine	30309	03 2009	2011 Apr	Yes	No	Public-6	18°C, 45% humidity - not appropriate temperature	✓	✓	91.5	7.1 (6.3-7.3)	✓	✓
AZ/H/8/03.07.09	10%	5 ml/ amp, 10 amps/ pack	Darnica, Ukraine	30309	03 2009	2011 Apr	Yes	No	Public-7	18°C, 46% humidity - not appropriate temperature	✓	✓	97.1	7.2 (6.3-7.3)	✓	✓
AZ/H/12/03.07.09	10%	5 ml/ amp, 10 amps/ pack	Darnica, Ukraine	30309	03 2009	2011 Apr	Yes	No	Public-8	16°C, 46% humidity - not appropriate temperature	✓	✓	92.1	7.2 (6.3-7.3)	✓	✓
AZ/H/7/03.07.09	10%	5 ml/ amp, 10 amps/ pack	Darnica, Ukraine	131008	10 2008	2010 Nov	Yes	No	Public-6	18°C, 45% humidity - not appropriate temperature	✓	✓	97.1	7.2 (6.3-7.3)	✓	✓
BY/H/21/01072009	10%	5ml/amp, 10 amps in pack	Borisovskij zavod medicinskich preparatov, Belarus	030208	03 2008	2010 Mar	Yes	No	Public-16	Conform to requirements	✓	✓	90.7	7.1 (6.3-7.3)	✓	✓
BY/H/36/010709	10%	5ml/amp, 10 amps in pack	Borisovskij zavod medicinskich preparatov, Belarus	030208	03 2008	2010 Mar	Yes	No	Public-9	Conform to requirements	✓	✓	96.2	7.2 (6.3-7.3)	✓	✓
BY/H/11/01072009	10%	5ml/amp, 10 amps in pack	Borisovskij zavod medicinskich preparatov, Belarus	101107	11 2007	2009 Dec	Yes	No	Public-15	Conform to requirements	✓	✓	94.0	7.1 (6.3-7.3)	✓	✓
BY/H/52/300609	10%	5ml/amp, 10 amps in pack	Borisovskij zavod medicinskich preparatov, Belarus	101107	11 2007	2009 Dec	Yes	No	Public-13	Conform to requirements	✓	✓	95.0	7.1 (6.3-7.3)	✓	✓
KZ/H/12/06.08.09	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	70708	07 2008	2010 Aug	Yes	No	Public-24	5°C	✓	✓	93.7	7.2 (6.3-7.3)	✓	✓
KZ/H/5/27.07.09	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	141008	10 2008	2010 Nov	Yes	No	Public-21	4°C	✓	✓	90.2	7.2 (6.3-7.3)	✓	✓
UA/H/1/30.06.09	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	10309	03 2009	2011 Apr	Yes	No	Public-29	No information	✓	✓	96.6	7.1 (6.3-7.3)	✓	✓
UA/H/7/300609	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	40108	01 2008	2010 Feb	Yes	No	Public-37	Conform to requirements	✓	✓	92.3	7.2 (6.3-7.3)	✓	✓
UA/H/4/30.06.09	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	100708	07 2008	2010 Aug	Yes	No	Public-26	7°C	✓	✓	90.8	7.2 (6.3-7.3)	✓	✓
UA/H/5/300609	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	211108	11 2008	2010 Dec	Yes	No	Public-37	Conform to requirements	✓	✓	91.9	7.1 (6.3-7.3)	✓	✓
UA/H/1/300609	10%	5ml/amp, 10 amps in pack	Darnica, Ukraine	221108	11 2008	2010 Dec	Yes	No	Public-28	5°C	✓	✓	92.2	7.2 (6.3-7.3)	✓	✓

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Appendix 4 Rifampicin capsules

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
AM/R/4/090709	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	080309	03 2009	2011 Apr	Yes	No	Pharmacy -18	Not done	✓	✓	94.4	✓ 1	✓	✓	2	✓ 3
AM/R/5/090709	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	080309	03 2009	2011 Apr	Yes	No	Pharmacy -14	Not done	✓	✓	92.3	✓ 4	✓	✓		
AM/R/7/130709	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	080309	03 2009	2011 Apr	Yes	No	Pharmacy -11	Not done	✓	✓	91.1	✓ 5	✓	✓		
AM/R/11/160709	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	080309	03 2009	2011 Apr	Yes	No	Pharmacy -12	Not done	✓	✓	93.6	✓ 6	✓	✓		
AM/R/12/160709	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	020108	01 2008	2010 Feb	Yes	No	Pharmacy -11	Not done	✓	✓	93.0	✓ 7	✓	✓		
AM/R/8/130709	300 mg	Pack, 10 blisters x 10 caps	Lupin Ltd, India	EA80002	07 2008	2011 Jun	No Supplied through MSF	No	Ware-house-1	21°C, protected from light	✓	✓	✖ **87.1**	✖ 8	✓	✖	9	✓ 10
AM/R/9/140709	300 mg	100 caps	Medochemie, Cyprus	E2D027	04 2008	2011 Apr	No Supplied through MSF	No	Public-1	21°C, protected from light	✓	✓	93.6	✓ 11	✓	✓	12	✓ 13

1 Quinone: 1.1%, 3-Formylrif: 0.3%, Max other: 1.1%, Sum: 3.1%
2 Does not comply (6 cps <80%), individual capsules: 46; 78; 77; 73; 38; 58, mean (n=6): 62%
3 Individual capsules: 83; 84; 87; 85; 84; 82, mean (n=6): 84%
4 Quinone: 1.0%, 3-Formylrif: 0.3%, Max other: 1.1%, Sum: 3.0%
5 Quinone: 1.1%, 3-Formylrif: 0.3%, Max other: 1.1%, Sum: 3.1%
6 Quinone: 1.1%, 3-Formylrif: 0.3%, Max other: 1.2%, Sum: 3.1%
7 Quinone: 1.1%, 3-Formylrif: 0.4%, Max other: 1.2%, Sum: 3.3%
8 Quinone: 3.1%, **3-Formylrif: 0.6%, Max other: RRT 0.29-1.6%**, Sum: 5.9%
9 Does not comply (6 cps <80%), individual capsules: 58; 50; 60; 65; 66; 58, mean (n=6): 60%
10 Individual capsules: 87; 88; 87; 92; 88; 89, mean (n=6): 89%
11 Quinone: 2.2%, 3-Formylrif: 0.4%, Max other: 0.8%, Sum: 4.1%
12 Does not comply (2 cps <80%), individual capsules: 76; 62; 86; 88; 80; 80, mean (n=6): 79%
13 Individual capsules: 88; 91; 91; 89; 87; 90, mean (n=6): 89%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
AM/R/10/140709	300 mg	100 caps	Medochemie, Cyprus	E2D027	04 2008	2011 Apr	No Supplied through MSF	No	Public-4	22°C, protected from light	✓	✓	94.3	✓ 14	✓	✓		
AM/R/6/130709	300 mg	Pack, 10 blisters x 10 caps	Troge Medical, India	1224-01	09 2008	2011 Aug	Yes	No	Pharmacy -16	Not done	✓	✓	91.4	✓ 15	✓	✓	16	✓ 17
AM/R/13/160709	300 mg	Pack, 10 blisters x 10 caps	Troge Medical, India	1224-01	09 2008	2011 Aug	Yes	No	Ware-house-3	Not done	✓	✓	91.3	✓ 18	✓	✓		
AM/R/14/160709	300 mg	Pack, 10 blisters x 10 caps	Troge Medical, India	1224-01	09 2008	2011 Aug	Yes	No	Pharmacy -1	Not done	✓	✓	91.1	✖ 19	✓	✖		
AM/R/15/160709	300 mg	Pack, 10 blisters x 10 caps	Troge Medical, India	1224-01	09 2008	2011 Aug	Yes	No	Pharmacy -2	Not done	✓	✓	91.2	✖ 20	✓	✖		
AZ/R/13/01072009	150 mg	10 x 10 caps in box	Shandong Reyoung Pharm. Co. Ltd, China	6RF1508	08 2007	2010 Aug	No	No	Public-6	Conform, 23°C, 45% humidity	✓	✓	✖ **89.7**	✓ 21	✓	✖		
AZ/R/15/03072009	150 mg	10 x 10 caps in box	Shandong Reyoung Pharm. Co. Ltd, China	6RF1508	08 2007	2010 Aug	No	No	Public-7	Conform, 22°C, 46% humidity	✓	✓	90.2	✓ 22	✓	✓		
AZ/R/17/03072009	150 mg	10 x 10 caps in box	Shandong Reyoung Pharm. Co. Ltd, China	6RF1508	08 2007	2010 Aug	No	No	Public-8	Conform, 24°C, 45% humidity	✓	✓	94.0	✓ 23	✓	✓	✓ 24	✓ 25

14 Quinone: 2.4%, 3-Formylrif: 0.5%, Max other: 0.8%, Sum: 4.3%
15 Quinone: 1.7%, 3-Formylrif: 0.5%, Max other: 1.1%, Sum: 4.9%
16 Does not comply (6 cps <80%), individual capsules: 66; 63; 69; 59; 71; 63, mean (n=6): 65%
17 Individual capsules: 87; 86; 91; 88; 85; 84, mean (n=6): 87%
18 Quinone: 2.0%, 3-Formylrif: 0.5%, Max other: 1.0%, Sum: 5.0%
19 **Does not comply:** Quinone: 2.3%**, 3-Formylrif: 0.6%,** Max other: RRT 0.29-1.1%**,** Sum: 5.6%
20 **Does not comply:** Quinone: 2.1%, **3-Formylrif: 0.6%,** Max other: RRT 0.29- 1.0%, Sum: 5.2%
21 Quinone: 0.9%, 3-Formylrif: 0.3%, Max other: RRT 0.67-1.0%, Sum: 3.0%
22 Quinone: 0.9%, 3-Formylrif: 0.3%, Max other: 1.0%, Sum: 3.0%
23 Quinone: 1.0%, 3-Formylrif: 0.3%, Max other: 1.0%, Sum: 3.1%
24 Individual capsules: 92; 85; 86; 90; 92; 90, mean (n=6): 89%
25 Individual capsules: 84; 86; 75; 75; 71; 80, mean (n=6): 79%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
AZ/R/14/01072009	300 mg	10 x 10 caps in box	Shandong Reyoung Pharm. Co. Ltd, China	6RF3008	08 2007	2010 Aug	No	No	Public-6	Conform, 23°C, 45% humidity	✓	✓	90.4	✓ 26	✓	✓	27	✓ 28
AZ/R/16/03072009	300 mg	10 x 10 caps in box	Shandong Reyoung Pharm. Co. Ltd, China	6RF3008	08 2007	2010 Aug	No	No	Public-7	Conform, 22°C, 46% humidity	✓	✓	91.8	✓ 29	✓	✓		
AZ/R/18/03072009	300 mg	10 x 10 caps in box	Shandong Reyoung Pharm. Co. Ltd, China	6RF3008	08 2007	2010 Aug	No	No	Public-8	Conform, 24°C, 45% humidity	✓	✓	95.8	✓ 30	✓	✓		
BY/R/03/02072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	070309	03 2009	2011 Apr	Yes	No	Ware-house-4	Not done	✓	✓	93.8	✓ 31	✓	✓		
BY/R/12/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	070308	04 2008	2010 Apr	Yes	No	Public-15	Conform	✓	✓	95.1	✓ 32	✓	✓		
BY/R/60/30062009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	601008	11 2008	2010 Nov	Yes	No	Public-10	Conform	✓	✓	97.0	✓ 33	✓	✓		
BY/R/22/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	240608	07 2008	2010 Jul	Yes	No	Public-16	Conform	✓	✓	94.8	✓ 34	✓	✓		
BY/R/38/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	571008	10 2008	2010 Nov	Yes	No	Public-9	Not done	✓	✓	96.5	✓ 35	✓	✓		
BY/R/50/30062009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	571008	10 2008	2010 Nov	Yes	No	Public-13	Not done	✓	✓	100.1	✓ 36	✓	✓		

26 Quinone: 1.0%, 3-Formylrif: 0.4%, Max other: 1.1%, Sum: 3.2%
27 Does not comply (2 cps <80%), individual capsules: 83; 86; 86; 88; 74; 79, mean (n=6): 83%
28 Individual capsules: 84; 88; 85; 88; 82; 97, mean (n=6): 87%
29 Quinone: 1.0%, 3-Formylrif: 0.4%, Max other: 1.0%, Sum: 3.2%
30 Quinone: 1.1%, 3-Formylrif: 0.4%, Max other: 1.1%, Sum: 3.3%
31 Quinone: 0.5%, 3-Formylrif: 0.0%, Max other: 1.1%, Sum: 2.2%
32 Quinone: 0.6%, 3-Formylrif: 0.0%, Max other: 1.2%, Sum: 2.3%
33 Quinone: 0.5%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 1.8%
34 Quinone: 0.6%, 3-Formylrif: 0.0%, Max other: 1.2%, Sum: 2.4%
35 Quinone: 0.4%, 3-Formylrif: 0.0%, Max other: 1.1%, Sum: 2.1%
36 Quinone: 0.7%, 3-Formylrif: 0.1%, Max other: 1.1%, Sum: 2.3%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
BY/R/14/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	130508	05 2008	2010 Jun	Yes	No	Public-15	Conform	✓	✓	93.6	✓ 37	✓	✓		
BY/R/16/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	300708	07 2008	2010 Aug	Yes	No	Public-15	Conform	✓	✓	91.8	✓ 38	✓	✓		
BY/R/15/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	090408	04 2008	2010 May	Yes	No	Public-15	Conform	✓	✓	99.2	✓ 39	✓	✓	✓ 40	✓ 41
BY/R/23/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	320808	08 2008	2010 Sep	Yes	No	Public-16	Conform	✓	✓	95.7	✓ 42	✓	✓		
BY/R/37/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	581008	10 2008	2010 Nov	Yes	No	Public-9	Not done	✓	✓	92.1	✓ 43	✓	✓		
BY/R/13/01072009	150 mg	Box, 2 blisters x 10 caps	Belmedpreparaty, Belarus	581008	10 2008	2010 Nov	Yes	No	Public-15	Conform	✓	✓	98.4	✓ 44	✓	✓		
KZ/R/5/270709	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-864	07 2008	2011 Jun	Yes	No	Public-21	20°C, 75% humidity	✓	✓	92.7	✖ 45	✓	✖		
KZ/R/6/110809	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-844	06 2008	2011 May	Yes	No	Public-18	18°C, 80% humidity	✓	✓	91.3	46	✓	✓	47	✓ 48
KZ/R/7/110809	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-861	07 2008	2011 Jun	Yes	No	Public-18	18°C, 80% humidity	✓	✓	90.5	✖ 49	✓	✖		

37 Quinone: 0.6%, 3-Formylrif: 0.1%, Max other: 1.2%, Sum: 2.4%
38 Quinone: 0.5%, 3-Formylrif: 0.1%, Max other: 1.2%, Sum: 2.3%
39 Quinone: 0.6%, 3-Formylrif: 0.1%, Max other: 1.2%, Sum: 2.3%
40 Individual capsules: 91; 100; 91; 86; 85; 95, mean (n=6): 91%
41 Individual capsules: 83; 89; 84; 83; 82; 79, mean (n=6)= 83%
42 Quinone: 0.5%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 1.9%
43 Quinone: 0.6%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 2.1%
44 Quinone: 0.6%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 2.1%
45 **Does not comply:** Quinone: 1.4%, **Formylrif: 0.6%,** Max other: RRT 0.67-1.3%, Sum: 5.0%
46 Complies, Quinone: 1.8%, 3-Formylrif: 0.5%, Max other: 1.0%, Sum: 4.9%
47 Does not comply (5 cps <80%), individual capsules: 74; 57; 74; 66; 73; 86, mean (n=6): 72
48 Individual capsules: 81; 83; 81; 84; 82; 83, mean (n=6): 82%
49 **Does not comply:** Quinone: 1.5%, **Formylrif: 0.6%,** Max other: RRT 0.67-1.3%, Sum: 4.6%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
KZ/R/8/110809	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-866	07 2008	2011 Jun	Yes	No	Public-18	18°C, 80% humidity	✓	✓	94.5	✓ 50	✓	✓		
KZ/R/9/060809	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-846	06 2008	2011 May	Yes	No	Public-24	23°C, 74% humidity	✓	✓	✖ **89.4**	✓ 51	✓	✖		
KZ/R/10/060809	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-869	07 2008	2011 Jun	Yes	No	Public-24	23°C, 74% humidity	✓	✓	✖ **89.6**	✖ 52	✓	✖		
KZ/R/11/110809	150 mg	1000 caps in jar	Macleods Pharmaceuticals Ltd, India	M15-862	07 2008	2011 Jun	Yes	No	Public-17	18°C, 64% humidity	✓	✓	91.2	✖ 53	✓	✖		
KZ/R/1/240709	150 mg	1000 caps in jar	Pavlodarskij farmacevticeskij zavod, Kazakhstan	270707	07 2007	2010 Aug	Yes	No	Public-25	18°C, 64% humidity	✓	✓	✖ **86.8**	✖ 54	✓	✖	55	✓ 56
KZ/R/2/240709	150 mg	1000 caps in jar	Pavlodarskij farmacevticeskij zavod, Kazakhstan	010508	05 2008	2011 Jun	Yes	No	Public-25	18°C, 64% humidity	✓	✓	✖ **78.0**	✖ 57	✓	✖		
KZ/R/3/270709	150 mg	1000 caps in jar	Pavlodarskij farmacevticeskij zavod, Kazakhstan	110707	07 2007	2010 Aug	Yes	No	Public-21	20°C, 75% humidity	✓	✓	✖ **81.8**	✖ 58	✓	✖		
KZ/R/4/270709	150 mg	1000 caps in jar	Pavlodarskij farmacevticeskij zavod, Kazakhstan	030508	05 2008	2011 Jun	Yes	No	Public-21	20°C, 75% humidity	✓	✓	✖ **85.1**	✖ 59	✓	✖		

50 Quinone: 1.1%, 3-Formylrif: 0.5%, Max other: 1.3%, Sum: 4.4%
51 Quinone: 1.7%, Formylrif: 0.5%, Max other: RRT 0.67 or 0.29- 1.1%, Sum: 5.0%
52 **Does not comply:** Quinone: 0.9%, **Formylrif: 0.6%,** Max other: RRT 0.67-1.2%, Sum: 4.3%
53 **Does not comply:** Quinone: 0.7%, **Formylrif: 0.6%,** Max other: RRT 0.67-1.3%, Sum: 3.9%
54 **Does not comply:** Quinone: 3.4%, **3-Formylrif: 0.7%, Max other: RRT 0.29-2.0%**, **Sum: 7.6%**
55 Does not comply (6 cps <80%), individual capsules: 51; 57; 67; 65; 53; 74, mean (n=6): 61%
56 Individual capsules: 87; 85; 81; 82; 85; 85, mean (n=6): 84%
57 **Does not comply:** Quinone: 2.2%, **3-Formylrif: 0.7%,** Max other: RRT 0.29-1.5%, Sum: 5.8%
58 **Does not comply:** Quinone: 3.3%, **3-Formylrif: 0.7%, Max other: RRT 0.29-1.9%, Sum: 7.5%**
59 **Does not comply:** Quinone: 2.6%, **Formylrif: 0.6%,** Max other: RRT 0.29-1.3%, Sum: 5.6%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
KZ/R/12/110809	150 mg	1000 caps in jar	Pavlodarskij farmacevticeskij zavod, Kazakhstan	090509	05 2009	2012 Jun	Yes	No	Public-17	18°C, 64% humidity	✓	✓	✖ **89.4**	✓ 60	✓	✖		
UA/R/2/300609	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	40209	02 2009	2011 Mar	Yes	No	Public-28	18°C	✓	✓	95.9	✓ 61	✓	✓		
UA/R/2/30062009	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	60209	02 2009	2011 Mar	Yes	No	Public-30	Conform	✓	✓	92.1	✓ 62	✓	✓		
UA/R/2/30.06.09	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	280608	06 2008	2011 Jul	Yes	No	Public-33	Conform	✓	✓	90.7	✓ 63	✓	✓	64	✓ 65
UA/R/2/300609	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	100309	03 2009	2011 Apr	Yes	No	Public-29	Not done	✓	✓	91.7	✓ 66	✓	✓		
UA/R/1/300609	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	730808	08 2008	2011 Sep	Yes	No	Public-32	18°C, 70% humidity, conditions controlled	✓	✓	95.2	✓ 67	✓	✓		
UA/R/1/30.06.2009	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	70309	03 2009	2011 Apr	Yes	No	Public-27	Conform	✓	✓	90.0	✓ 68	✓	✓		

60 Quinone: 1.2%, Formylrif: 0.4%, Max other: RRT 0.67-1.0%, Sum: 3.6%
61 Quinone: 0.7%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 1.6%
62 Quinone: 0.8%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 1.7%
63 Quinone: 1.6%, 3-Formylrif: 0.2%, Max other: 0.9%, Sum: 3.7%
64 Does not comply (6 cps <80%), Individual capsules: 48; 42; 36; 38; 36; 31, mean (n=6): 39%, *Compact mass of excipient-drug mixture remained at the bottom of each vessel*
65 Individual capsules: 83; 90; 74; 80; 81; 82, mean (n=6): 82%
66 Quinone: 1.7%, 3-Formylrif: 0.3%, Max other: 1.0%, Sum: 4.0%
67 Quinone: 1.7%, 3-Formylrif: 0.2%, Max other: 1.1%, Sum: 4.0%
68 Quinone: 1.8%, 3-Formylrif: 0.3%, Max other: 1.0%, Sum: 4.3%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
UA/R/8/30.06.09	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	690808	08 2008	2010 Sep	Yes	No	Public-26	19°C	✓	✓	97.5	✓ 69	✓	✓		
UA/R/6/30062009	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	670808	08 2008	2010 Sep	Yes	No	Public-26	19°C	✓	✓	97.0	✓ 70	✓	✓		
UA/R/7/30062009	150 mg	1000 caps in plastic container	Borshagovskij khimiko-farmacevticeskij zavod, Ukraine	10209	02 2009	2011 Mar	Yes	No	Public-26	19°C	✓	✓	95.4	✓ 71	✓	✓		
UA/R/8/300609	150 mg	1000 caps in plastic container	Darnica, Ukraine	30907	09 2007	2010 Jun	Yes	No	Public-37	Conform	✓	✓	90.8	✓ 72	✓	✓	73	✓ 74
UA/R/2/30.06.2009	150 mg	1000 caps in plastic container	Lupin Ltd, India	ED90013	03 2009	2012 Feb	Yes	No	Public-27	Conform	✓	✓	96.4	✓ 75	✓	✓	76	✓ 77
UZ/R/17/02072009	300 mg	Box, 20 blisters x 4 caps	Lupin Ltd, India	EA80002	07 2008	2011 Jun	Yes	No	Public-47	Not done	✓	✓	✖ **89.0**	✓ 78	✓	✖		
UZ/R/12/02072009	300 mg	Box, 20 blisters x 4 caps	Lupin Ltd, India	EA80002	07 2008	2011 Jun	Yes	No	Public-40	Conform	✓	✓	✖ **87.2**	✓ 79	✓	✖		
UZ/R/18/02072009	300 mg	Box, 20 blisters x 4 caps	Lupin Ltd, India	EA80002	07 2008	2011 Jun	Yes	No	Public-46	Conform	✓	✓	✖ **88.0**	✓ 80	✓	✖	81	✓ 82

69 Quinone: 0.7%, 3-Formylrif: 0.2%, Max other: 0.8%, Sum: 2.0%
70 Quinone: 0.9%, 3-Formylrif: 0.1%, Max other: 0.8%, Sum: 2.2%
71 Quinone: 0.8%, 3-Formylrif: 0.1%, Max other: 0.9%, Sum: 2.2%
72 Quinone: 2.0%, 3-Formylrif: 0.4%, Max other: 1.1%, Sum: 3.9%
73 Does not comply (6 cps <80%), individual capsules: 57; 57; 62;63; 54; 65, mean (n=6): 60%
74 Individual capsules: 83; 83; 83; 81; 81; 78, mean (n=6): 82%
75 Quinone: 1.5%, 3-Formylrif: 0.1%, Max other: 0.7%, Sum: 2.2%
76 Does not comply (5 cps <80%), individual capsules: 74; 76; 81; 76; 74; 74, mean (n=6): 76%
77 Individual capsules: 83; 80; 84; 83; 79; 87, mean (n=6): 83%
78 Quinone: 2.6%, 3-Formylrif: 0.5%, Max other: RRT 0.29-1.4%, Sum: 5.1%
79 Quinone: 2.4%, 3-Formylrif: 0.5%, Max other: RRT 0.29- 1.3%, Sum: 4.8%
80 Quinone: 2.6%, 3-Formylrif: 0.5%, Max other: RRT 0.29- 1.3%, Sum: 5.1%
81 Does not comply (6 cps <80%), individual capsules: 66; 61; 60; 70; 61; 64, mean (n=6): 64%
82 Individual capsules: 88; 84; 84; 89; 88; 90, mean (n=6): 87%

Appendix 4: Rifampicin capsules – test results

Assay: 90.0-110.0%
Related substances: Rifampicin quinone ≤ 4.0% , 3-formylrifamycin ≤ 0.5% , Any other peak ≤ 1.5% , Sum ≤ 6.0%;
Dissolution, Ph. Int: NLT 80% in 30min**; BP:** NLT 70% in 45min ✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manufacturer	Batch No.	Manu-facture date	Ex-piry date	Registered	WHO -PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear ance	Iden-tity	Assay	Rel. substances	Uniform-ity of mass	Conclu-sion	Dis-solution Ph. Int.	Dis-solution BP
UZ/R/16/02072009	150 mg	Box, 10 blisters x 10 caps	Sandoz Private Ltd, India	RL01 H8L	08 2008	2010 Jul	Yes	No	Public-40	Conform	✓	✓	96.6	✓ [83]	✓	✓	[84]	✓ [85]
UZ/R/14/02072009	150 mg	Box, 10 blisters x 10 caps	Sandoz Private Ltd, India	RL01 H8L	08 2008	2010 Jul	Yes	No	Public-38	Protected from light and humidity	✓	✓	92.9	✓ [86]	✓	✓		
UZ/R/13/02072009	150 mg	Box, 10 blisters x 10 caps	Sandoz Private Ltd, India	RL01 H8L	08 2008	2010 Jul	Yes	No	Public-50	Protected from light and humidity	✓	✓	91.6	✓ [87]	✓	✓		
UZ/R/15/02072009	150 mg	Box, 10 blisters x 10 caps	Sandoz Private Ltd, India	RL02 H8L	08 2008	2010 Jul	Yes	No	Public-43	Not done	✓	✓	97.5	✓ [88]	✓	✓		
Comparator for dissolution study	300 mg		Sanofi Aventis, Germany														[89]	✓ [90]

[83] Quinone: 2.1%, 3-Formylrif: 0.5%, Max other: 0.8%, Sum: 3.4%
[84] Does not comply (4 cps <80%), Individual capsules: 77; 76; 80; 71; 83; 73, mean (n=6): 77%
[85] Individual capsules: 85; 81; 82; 84; 89; 78, mean (n=6): 83%
[86] Quinone: 2.1%, 3-Formylrif: 0.5%, Max other: 0.9%, Sum: 3.5%
[87] Quinone: 2.1%, 3-Formylrif: 0.5%, Max other: 1.0%, Sum: 3.5%
[88] Quinone: 1.8%, 3-Formylrif: 0.5%, Max other: 0.8%, Sum: 3.1%
[89] Does not comply (6 cps <80%), Individual capsules: 48; 44; 36; 42; 41; 46, mean (n=6): 43%
[90] Individual capsules: 90; 87; 87; 89; 91; 89, mean (n=6): 89%

Assay: 90.0-110.0%
Related substances: Hydrazone impurity ≤ 5.0% , Rifampicin quinone ≤ 4.0% , Any other peak ≤ 1.5% , Sum ≤ 10.0%
Dissolution: NLT 80% at 30min

✓= complies; ✖= does not comply

Appendix 5 Isoniazid / rifampicin tablets – test results

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No	Manu-facture date	Ex-piry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay		Related sub-stances	Unifor mity of mass	Con-clu-sion	Dissolution	
													Isonia-zid	Rifamp icin				Isoniazid	Rif-ampicin
AM/R/16/130709	75+150 mg	Pack 24 x 28	Lupin Ltd, India	GA78 043	07 2007	2010 Jun	No Supplied through MSF	Yes TB 068 (2003)	Public-2	21°C, protected from light	✓	✓	93.8	93.7	✓ 1	✓	✓		
AM/R/17/140709	75+150 mg	Pack 24 x 28	Lupin Ltd, India	GA78 043	07 2007	2010 Jun	No Supplied through MSF	Yes TB 068 (2003)	Public-3	21°C, protected from light	✓	✓	93.5	92.3	✓ 2	✓	✓		
AM/R/18/160709	75+150 mg	Pack 24 x 28	Lupin Ltd, India	GA78 043	07 2007	2010 Jun	No Supplied through MSF	Yes TB 068 (2003)	Public-5	21°C, protected from light	✓	✓	91.5	92.5	✓ 3	✓	✓		
AZ/H-R/21/010709	75+150 mg	Plastic bottle 1000	Lupin Ltd, India	GA78 025	03 2007	2010 Feb	Not registered	Yes TB 068 (2003)	Public-6	Conform, 23°C, 45% humidity	✓	✓	97.0	94.5	✓ 4	✓	✓		
AZ/H-R/20/010709	75+150 mg	Plastic bottle 1000	Lupin Ltd, India	GA88 122	11 2008	2011 Oct	No Supplied through GDF	Yes TB 068 (2003)	Public-6	Conform, 23°C, 45% humidity	✓	✓	97.0	95.3	✓ 5	✓	✓		
AZ/H-R/19/010709	75+150 mg	28	Lupin Ltd, India	GA88 135	12 2008	2011 Nov	No Supplied through GDF	Yes TB 068 (2003)	Public-6	Conform, 23°C, 45% humidity	✓	✓	100.3	93.3	✓ 6	✓	✓		
BY/H-R/30/300609	75+150 mg	Box 24x28	Lupin Ltd, India	GA88 062	05 2008	2011 Apr	No Supplied through GDF	Yes TB 068 (2003)	Public-10	Conform	✓	✓	96.5	93.5	✓ 7	✓	✓		
BY/H-R/24/010709	75+150 mg	Box 24x28	Lupin Ltd, India	GA88 063	05 2008	2011 Apr	No Supplied through GDF	Yes TB 068 (2003)	Public-16	Conform	✓	✓	93.8	90.1	✓ 8	✓	✓		
BY/H-R/40/010709	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 064	06 2008	2011 May	No Supplied through GDF	Yes TB 068 (2003)	Public-9	Conform	✓	✓	94.0	96.3	✓ 9	✓	✓		

1 Hydrazone: 0.8%, Quinone: 0.5%, Max other: 0.9%, Sum: 3.7%
2 Hydrazone: 0.6%, Quinone: 0.4%, Max other: 0.9%, Sum: 3.5%
3 Hydrazone: 0.7%, Quinone: 0.4%, Max other: 0.9%, Sum: 3.6%
4 Hydrazone: 0.7%, Quinone: 0.1%, Max other: 1.2%, Sum: 4.6%
5 Hydrazone: 0.9%, Quinone: 0.1%, Max other: 1.0%, Sum: 4.2%
6 Hydrazone: 1.2%, Quinone: 0.2%, Max other: 0.7%, Sum: 3.9%
7 Hydrazone: 1.0%, Quinone: 0.1%, Max other: 0.9%, Sum: 4.2%
8 Hydrazone: 1.3%, Quinone: 0.1%, Max other: 0.8%, Sum: 4.1%
9 Hydrazone: 1.5%, Quinone: 0.1%, Max other: 0.9%, Sum: 4.5%

Appendix 5: Isoniazid / rifampicin tablets – test results

Assay: 90.0-110.0%
Related substances: Hydrazone impurity ≤ 5.0% , Rifampicin quinone ≤ 4.0% , Any other peak ≤ 1.5% , Sum ≤ 10.0%
Dissolution: NLT 80% at 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No	Manu-facture date	Ex-piry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay		Related sub-stances	Unifor mity of mass	Con-clu-sion	Dissolution	
													Isonia-zid	Rifamp icin				Isoniazid	Rif-ampicin
BY/H-R/59/010709	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 064	06 2008	2011 May	No Supplied through GDF	Yes TB 068 (2003)	Public-14	Conform	✓	✓	98.4	92.2	✓ 10	✓	✓		
BY/H-R/43/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 064	06 2008	2011 May	No Supplied through GDF	Yes TB 068 (2003)	Public-11	Conform	✓	✓	96.3	93.9	✓ 11	✓	✓		
BY/H-R/27/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 064	06 2008	2011 May	No Supplied through GDF	Yes TB 068 (2003)	Public-12	Conform	✓	✓	96.9	90.4	✓ 12	✓	✓		
BY/H-R/47/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 065	06 2008	2011 May	No Supplied through GDF	Yes TB 068 (2003)	Public-13	Conform	✓	✓	94.2	92.6	✓ 13	✓	✓		
BY/H-R/46/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 172	12 2008	2011 Nov	No Supplied through GDF	Yes TB 068 (2003)	Public-13	Conform	✓	✓	97.0	98.5	✓ 14	✓	✓		
BY/H-R/31/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 173	12 2008	2011 Nov	No Supplied through GDF	Yes TB 068 (2003)	Public-10	Conform	✓	✓	96.8	91.0	✓ 15	✓	✓		
BY/H-R/49/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 173	12 2008	2011 Nov	No Supplied through GDF	Yes TB 068 (2003)	Public-13	Conform	✓	✓	98.3	103.4	✓ 16	✓	✓		
BY/H-R/39/010709	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA88 174	12 2008	2011 Nov	No Supplied through GDF	Yes TB 068 (2003)	Public-9	Conform	✓	✓	96.6	95.2	✓ 17	✓	✓		
BY/H-R/48/300609	75+150 mg	Box, 24 blisters x 28 tabs	Lupin Ltd, India	GA98 006	01 2009	2011 Dec	No Supplied through GDF	Yes TB 068 (2003)	Public-13	Conform	✓	✓	95.3	96.6	✓ 18	✓	✓	✓ 19	✓ 20

10 Hydrazone: 1.5%, Quinone: 0.1%, Max other: 0.9%, Sum: 4.5%
11 Hydrazone: 1.5%, Quinone: 0.1%, Max other: 0.8%, Sum: 4.4%
12 Hydrazone: 1.3%, Quinone: 0.1%, Max other: 0.9%, Sum: 4.1%
13 Hydrazone: 1.0%, Quinone: 0.1%, Max other: 0.9%, Sum: 4.0%
14 Hydrazone: 1.0%, Quinone: 0.2%, Max other: 1.0%, Sum: 3.9%
15 Hydrazone: 1.0%, Quinone: 0.3%, Max other: 0.9%, Sum: 3.7%
16 Hydrazone: 1.2%, Quinone: 0.2%, Max other: 0.9%, Sum: 4.2%
17 Hydrazone: 0.7%, Quinone: 0.2%, Max other: 0.9%, Sum: 3.1%
18 Hydrazone: 0.7%, Quinone: 0.2%, Max other: 0.7%, Sum: 3.1%
19 Individual tablets: 104; 100; 104; 90; 96; 95, mean (n=6): 98%
20 Individual tablets:100; 101; 103; 94; 97; 97, mean (n=6): 99%

Appendix 5: Isoniazid / rifampicin tablets – test results

Assay: 90.0-110.0%
Related substances: Hydrazone impurity ≤ 5.0% , Rifampicin quinone ≤ 4.0% , Any other peak ≤ 1.5% , Sum ≤ 10.0%
Dissolution: NLT 80% at 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No	Manu-facture date	Ex-piry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay		Related sub-stances	Unifor mity of mass	Con-clu-sion	Dissolution	
													Isonia-zid	Rifamp icin				Isoniazid	Rif-ampicin
KZ/H-R/2/240709	30+60 mg	1000 tabs in jar	Macleods Pharm Ltd, India	RM808	10 2008	2010 Sep	No Supplied through GDF	Yes TB 181 (3/2009)	Public-25	18°C, 64% humidity	✓	✓	96.4	94.1	✓ [21]	✓	✓		
KZ/H-R/1/240709	30+60 mg	1000 tabs in jar	Macleods Pharm Ltd, India	RM809	10 2008	2010 Sep	No Supplied through GDF	Yes TB 181 (3/ 2009)	Public-25	18°C, 64% humidity	✓	✓	94.0	95.0	✓ [22]	✓	✓	✓ [23]	✓ [24]
KZ/H-R/6/110809	60+60 mg	1000 tabs in jar	Macleods Pharm Ltd, India	RP802	10 2008	2010 Sep	No Supplied through GDF	Yes TB 182 (11/ 2009)	Public-18	18°C, 80% humidity	✓	✓	96.0	92.8	✓ [25]	✓	✓	✓ [26]	✓ [27]
KZ/H-R/12/190809	75+150 mg	100 tabs in jar	Pavlodarskij farm. zavod, Kazakhstan	010308	03 2008	2010 Apr	Yes	No	Public-20	24°C, 51% humidity	✓	✓	99.9	93.3	✓ [28]	✓	✓	✓ [29]	✓ [30]
KZ/H-R/11/190809	150+150 mg	100 tabs in jar	Pavlodarskij farm. zavod, Kazakhstan	031008	10 2008	2010 Nov	Yes	No	Public-20	24°C, 51% humidity	✓	✓	92.0	91.5	✖ [31]	✓	✖	✓ [32]	✓ [33]
KZ/H-R/7/060809	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	7206087	06 2008	2010 May	Yes	Yes TB 085 (2004)	Public-24	23°C, 74% humidity	✓	✓	96.6	97.6	✓ [34]	✓	✓		
KZ/H-R/4/110809	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	7206088	06 2008	2010 May	Yes	Yes TB 085 (2004)	Public-18	18°C, 80% humidity	✓	✓	94.7	97.3	✓ [35]	✓	✓		

21 Hydrazone: 0.2%, Quinone: 0.3%, Max other: 0.8%, Sum: 2.0%
22 Hydrazone: 0.2%, Quinone: 0.6%, Max other: 0.8%, Sum: 2.6%
23 Individual tablets: 88; 99; 90; 98; 95; 89, mean (n=6): 93%
24 Individual tablets: 97; 100; 95; 99; 101; 99, mean (n=6): 99%
25 Hydrazone: 0.4%, Quinone: 0.5%, Max other: 0.7%, Sum: 2.6%
26 Individual tablets: 95; 97; 102; 97; 97; 96, mean (n=6): 97%
27 Individual tablets: 99; 98; 100; 97; 102; 99, mean (n=6): 99%
28 Hydrazone: 0.5%, Quinone: 0.6%, Max other: 1.5%, Sum: 5.0%
29 Individual tablets:96; 102; 98; 101; 90; 106, mean (n=6): 99%
30 Individual tablets: 100; 98; 98; 97; 98; 92, mean (n=6): 97%
31 **Does not comply:** Hydrazone: 0.5%, Quinone: 0.2%, **Max other: RRT 0.45-4.9%,** Sum: 8.6%
32 Individual tablets: 93; 94; 90; 94; 92; 91, mean (n=6): 92%
33 Individual tablets: 100; 97; 95; 98; 93; 98, mean (n=6): 97%
34 Hydrazone: 0.6%, Quinone: 0.8%, Max other: 0.9%, Sum: 3.4%
35 Hydrazone: 0.7%, Quinone: 0.6%, Max other: 0.9%, Sum: 3.5%

Appendix 5: Isoniazid / rifampicin tablets – test results

Assay: 90.0-110.0%
Related substances: Hydrazone impurity ≤ 5.0% , Rifampicin quinone ≤ 4.0% , Any other peak ≤ 1.5% , Sum ≤ 10.0%
Dissolution: NLT 80% at 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No	Manu-facture date	Ex-piry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay		Related sub-stances	Unifor mity of mass	Con-clu-sion	Dissolution	
													Isonia-zid	Rifamp icin				Isoniazid	Rif-ampicin
KZ/H-R/5/110809	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	7206089	06 2008	2010 May	Yes	Yes TB 085 (2004)	Public-18	18°C, 80% humidity	✓	✓	93.3	99.5	✓ 36	✓	✓		
KZ/H-R/9/120809	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	K08C015	03 2008	2010 Feb	Yes	Yes TB 085 (2004)	Public-19	23°C, 82% humidity	✓	✓	97.2	100.5	✓ 37	✓	✓		
KZ/H-R/10/120809	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	K08C016	03 2008	2010 Feb	Yes	Yes TB 085 (2004)	Public-19	23°C, 82% humidity	✓	✓	94.4	97.7	✓ 38	✓	✓		
KZ/H-R/8/060809	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	K08D021	04 2008	2010 Mar	Yes	Yes TB 085 (2004)	Public-24	23°C, 74% humidity	✓	✓	95.0	102.5	✓ 39	✓	✓		
KZ/H-R/3/270709	75+150 mg	Pack, 10 blisters x 10 tabs	Sandoz Private Ltd, India	K08D024	04 2008	2010 Mar	Yes	Yes TB 085 (2004)	Public-21	23°C, 80% humidity	✓	✓	97.0	100.5	✓ 40	✓	✓		
UZ/H-R/25/01072009	75+150 mg	Box, 10 blisters x 10 tabs	Sandoz Private Ltd, India	K08D025A	04 2008	2010 Mar	Yes	Yes TB 085 (2004)	Public-41	Conform	✓	✓	101.2	99.0	✓ 41	✓	✓		
UZ/H/R/30/01072009	75+150 mg	Box, 10 blisters x 10 tabs	Sandoz Private Ltd, India	K08D025A	04 2008	2010 Mar	Yes	Yes TB 085 (2004)	Public-43	Conform	✓	✓	99.8	98.3	✓ 42	✓	✓		
UZ/H-R/28/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF14E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-51	Conform	✓	✓	93.5	98.9	✓ 43	✓	✓		
UZ/H-R/22/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF14E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-44	No information	✓	✓	94.2	101.4	✓ 44	✓	✓		

36 Hydrazone: 0.7%, Quinone: 0.7%, Max other: 0.9%, Sum: 3.4%
37 Hydrazone: 0.3%, Quinone: 0.4%, Max other: 0.8%, Sum: 2.6%
38 Hydrazone: 0.4%, Quinone: 0.5%, Max other: 0.8%, Sum: 2.7%
39 Hydrazone: 0.3%, Quinone: 0.5%, Max other: 0.9%, Sum: 2.7%
40 Hydrazone: 0.5%, Quinone: 0.4%, Max other: 1.0%, Sum: 2.9%
41 Hydrazone: 0.6%, Quinone: 0.6%, Max other: 1.1%, Sum: 3.3%
42 Hydrazone: 0.6%, Quinone: 0.5%, Max other: 1.2%, Sum: 3.7%
43 Hydrazone: 1.3%, Quinone: 0.4%, Max other: 1.1%, Sum: 3.7%
44 Hydrazone: 1.4%, Quinone: 0.7%, Max other: 1.1%, Sum: 4.0%

Appendix 5: Isoniazid / rifampicin tablets – test results

Assay: 90.0-110.0%
Related substances: Hydrazone impurity ≤ 5.0% , Rifampicin quinone ≤ 4.0% , Any other peak ≤ 1.5% , Sum ≤ 10.0%
Dissolution: NLT 80% at 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No	Manu-facture date	Ex-piry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay		Related sub-stances	Unifor mity of mass	Con-clu-sion	Dissolution	
													Isonia-zid	Rifamp icin				Isoniazid	Rif-ampicin
UZ/H-R/29/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF14 E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-46	No information	✓	✓	95.5	101.6	✓ 45	✓	✓		
UZ/H-R/21/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF14 E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-45	Conform	✓	✓	94.3	99.2	✓ 46	✓	✓		
UZ/H-R/19/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF14 E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-40	Conform	✓	✓	94.1	96.5	✓ 47	✓	✓		
UZ/H-R/24/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF15 E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-41	Conform	✓	✓	97.2	95.4	✓ 48	✓	✓		
UZ/H-R/20/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF15 E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-45	Conform	✓	✓	96.7	99.4	✓ 49	✓	✓		
UZ/H-R/23/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Sandoz Private Ltd, India	WF16 E8B	05 2008	2010 Apr	Yes, Supplied through GDF	Yes TB 085 (2004)	Public-47	No information	✓	✓	95.4	99.7	✓ 50	✓	✓	✓ 51	✓ 52
UZ/H-R/26/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Svizera Labs, India	SL350	03 2007	2010 Feb	Yes, Supplied through GDF	No	Public-42	Conform	✓	✓	98.1	91.0	✓ 53	✓	✓		
UZ/H-R/27/01072009	75+150 mg	Box, 12 blisters x 28 tabs	Svizera Labs, India	SL351	05 2007	2010 Apr	Yes, Supplied through GDF	No	Public-42	Conform	✓	✓	98.5	93.9	✓ 54	✓	✓	✓ 55	✓ 56
Comparator	150+300 mg		Gruenenthal, Germany															✓ 57	✓ 58

45 Hydrazone: 1.5%, Quinone: 0.5%, Max other: 1.0%, Sum: 3.9%
46 Hydrazone: 1.5%, Quinone: 0.5%, Max other: 1.0%, Sum: 3.9%
47 Hydrazone: 1.3%, Quinone: 0.6%, Max other: 1.0%, Sum: 3.9%
48 Hydrazone: 1.5%, Quinone: 0.7%, Max other: 1.0%, Sum: 4.1%
49 Hydrazone: 1.2%, Quinone: 0.6%, Max other: 1.0%, Sum: 3.7%
50 Hydrazone: 1.1%, Quinone: 0.5%, Max other: 1.1%, Sum: 3.6%
51 Individual tablets: 103; 98; 100; 81; 83; 85, mean (n=6): 92%
52 Individual tablets: 106; 103; 103; 87; 85; 87, mean (n=6): 95%
53 Hydrazone: 0.6%, Quinone: 0.4%, Max other: 0.6%, Sum: 3.2%
54 Hydrazone: 0.4%, Quinone: 0.4%, Max other: 0.6%, Sum: 2.7%
55 Individual tablets: 90; 89; 94; 95; 94; 97, mean (n=6): 93%
56 Individual tablets: 94; 95; 97; 100; 95; 96, mean (n=6): 96%
57 Individual tablets: 93; 88; 88; 91; 95; 96, mean (n=6): 92%
58 Individual tablets: 93; 90; 91; 92; 95; 96, mean (n=6): 93%

Appearance: White powder; **Assay**: 90.0-110.0%

✓= complies; ✖= does not comply

Appendix 6 Kanamycin powder for solution for injection

Country (see App. 9)/ sample code	Pack size	Manufacturer	Batch number	Manu-facture date	Expiry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay	Mass (g)	pH	Steri-lity	Con-clu-sion
AM/KM/20/0 60709	1 g in glass bottle	Kievmedprepar at, Ukraine	10308	No information	2011 Apr	Yes	No	Pharmacy -10	22°C	✓	✓	95.4	1.48	6.9 (5.5-7.5)	Not done	✓
AM/KM/30/1 60709	1 g in glass bottle	Kievmedprepar at, Ukraine	330908	No information	2011 Oct	Yes	No	Pharmacy -15	No information	✓	✓	98.5	1.50	7.0 (5.5-7.5)	Not done	✓
AM/KM/29/1 50709	1 g in glass bottle	Kievmedprepar at, Ukraine	330908	No information	2011 Oct	Yes	No	Pharmacy -3	No information	✓	✓	97.3	1.50	7.0 (5.5-7.5)	Not done	✓
AM/KM/21/0 60709	1 g in glass bottle	Kievmedprepar at, Ukraine	330908	No information	2011 Oct	Yes	No	Pharmacy -6	No information	✓	✓	101.3	1.53	7.0 (5.5-7.5)	Not done	✓
AM/KM/22/0 80709	1 g in glass bottle	Kievmedprepar at, Ukraine	381107	No information	2012 Oct	Yes	No	Pharmacy -14	No information	✓	✓	97.9	1.51	7.0 (5.5-7.5)	Not done	✓
AM/KM/28/1 40709	1 g in glass bottle	Panpharma SA, France	F70401	04 2007	2010 Apr	No, supplied through MSF	No	Public-1	21°C, protected from light	✓	✓	95.4	1.43	7.0 (6.0-7.5)	Not done	✓
AM/KM/27/1 40709	1 g in glass bottle	Panpharma SA, France	F70401	04 2007	2010 Apr	No, supplied through MSF	No	Public-4	22°C, protected from light	✓	✓	96.0	1.43	7.0 (6.0-7.5)	Not done	✓
AM/KM/26/1 30709	1 g in glass bottle	Panpharma SA, France	F70401	04 2007	2010 Apr	No, supplied through MSF	No	Ware-house-1	21°C, protected from light	✓	✓	97.6	1.43	7.0 (6.0-7.5)	Not done	✓
AM/KM/24/1 20709	1 g in glass bottle	Syntez Kurgan, Russia	140209	02 2009	2013 Mar	Yes	No	Pharmacy -5	No information	✓	✓	99.4	1.44	7.3 (6.0-7.5)	Not done	✓
AM/KM/25/1 30709	1 g in glass bottle	Syntez Kurgan, Russia	380708	07 2008	2012 Aug	Yes	No	Pharmacy -11	No information	✓	✓	98.1	1.47	7.4 (6.0-7.5)	✓	✓
AM/KM/23/1 10709	1 g in glass bottle	Syntez Kurgan, Russia	380708	07 2008	2012 Aug	Yes	No	Pharmacy -13	No information	✓	✓	99.0	1.48	7.3 (6.0-7.5)	Not done	✓
AM/KM/19/0 6072009	1 g in glass bottle	Syntez Kurgan, Russia	380708	07 2008	2012 Aug	Yes	No	Pharmacy -9	21°C	✓	✓	97.8	1.46	7.3 (6.0-7.5)	Not done	✓
AZ/KM/25/0 30709	1 g in glass bottle	Syntez Kurgan, Russia	220308	03 2008	2012 Apr	Yes	No	Public-8	Conform, 24°C, 45% humidity	✓	✓	98.5	1.49	7.2 (6.0-7.5)	Not done	✓
AZ/KM/22/0 10709	1 g in glass bottle	Syntez Kurgan, Russia	561108	11 2008	2012 Dec	Yes	No	Public-6	Conform, 23°C, 45% humidity	✓	✓	95.3	1.46	7.4 (6.0-7.5)	Not done	✓
AZ/KM/23/0 30709	1 g in glass bottle	Syntez Kurgan, Russia	561108	11 2008	2012 Dec	Yes	No	Public-7	Conform, 22°C, 46% humidity	✓	✓	97.2	1.46	7.4 (6.0-7.5)	Not done	✓
AZ/KM/26/0 30709	1 g in glass bottle	Syntez Kurgan, Russia	561108	11 2008	2012 Dec	Yes	No	Public-8	Conform, 24°C, 45% humidity	✓	✓	96.3	1.48	7.4 (6.0-7.5)	Not done	✓
AZ/KM/24/0 30709	1 g in glass bottle	Syntez Kurgan, Russia	571108	11 2008	2012 Dec	Yes	No	Public-7	Conform, 22°C, 46% humidity	✓	✓	97.0	1.47	7.4 (6.0-7.5)	✓	✓
AZ/KM/27/0 30709	1 g in glass bottle	Syntez Kurgan, Russia	591108	11 2008	2012 Dec	Yes	No	Pharmacy -19	No information	✓	✓	97.0	1.48	7.4 (6.0-7.5)	Not done	✓
BY/Km/17/0 1072009	1 g in glass bottle	Kievmedprepar at, Ukraine	80209	04 2009	2012 Mar	Yes	No	Public-15	Conform	✓	✓	95.3	1.50	7.0 (5.5-7.5)	Not done	✓
BY/Km/41/0 10709	1 g in glass bottle	Kievmedprepar at, Ukraine	80209	04 2009	2012 Mar	Yes	No	Public-9	Conform	✓	✓	96.0	1.52	7.1 (5.5-7.5)	Not done	✓

Appendix 6: Kanamycin powder for solution for injection

Appearance: White powder; **Assay**: 90.0-110.0%

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Pack size	Manufacturer	Batch number	Manu-facture date	Expiry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay	Mass (g)	pH	Steri-lity	Con-clu-sion
BY/Km/55/3 00609	1 g in glass bottle	Kievmedprepar at, Ukraine	80209	04 2009	2012 Mar	Yes	No	Public-13	Conform	✓	✓	96.1	1.52	7.0 (5.5-7.5)	Not done	✓
BY/Km/28/3 00609	1 g in glass bottle	Kievmedprepar at, Ukraine	80209	04 2009	2012 Mar	Yes	No	Public-12	Conform	✓	✓	95.2	1.49	7.1 (5.5-7.5)	Not done	✓
BY/Km/04/0 20709	1 g in glass bottle	Kievmedprepar at, Ukraine	80209	04 2009	2012 Mar	Yes	No	Ware-house-4	Conform	✓	✓	94.5	1.53	7.1 (5.5-7.5)	Not done	✓
BY/KM/32/3 00609	1 g in glass bottle	Kievmedprepar at, Ukraine	260708	08 2008	2011 Aug	Yes	No	Public-10	Conform	✓	✓	100.3	1.48	7.1 (5.5-7.5)	Not done	✓
BY/Km/25/0 1072009	1 g in glass bottle	Kievmedprepar at, Ukraine	260708	08 2008	2011 Aug	Yes	No	Public-16	Conform	✓	✓	99.7	1.49	7.1 (5.5-7.5)	Not done	✓
BY/Km/05/0 20709	1 g in glass bottle	Kievmedprepar at, Ukraine	260708	08 2008	2011 Aug	Yes	No	Ware-house-4	Conform	✓	✓	98.5	1.51	7.1 (5.5-7.5)	Not done	✓
BY/Km/18/0 1072009	1 g in glass bottle	Kievmedprepar at, Ukraine	260708	08 2008	2011 Aug	Yes	No	Public-15	Conform	✓	✓	98.2	1.47	7.1 (5.5-7.5)	Not done	✓
BY/Km/45/3 00609	1 g in glass bottle	Kievmedprepar at, Ukraine	260708	08 2008	2011 Aug	Yes	No	Public-11	Conform	✓	✓	94.0	1.49	7.1 (5.5-7.5)	Not done	✓
BY/KM/58/0 10709	1 g in glass bottle	Kievmedprepar at, Ukraine	260708	08 2008	2011 Aug	Yes	No	Public-14	Conform	✓	✓	100.5	1.48	7.1 (5.5-7.5)	Not done	✓
BY/KM/56/3 00609	1 g in glass bottle	Panpharma SA, France	F80113	01 2008	2011 Jan	No, supplied through GDF	No	Public-13	Conform	✓	✓	98.1	1.41	7.1 (5.5-7.5)	✓	✓
KZ/K/8/12.0 8.09	1 g in glass bottle	Chimpharm, Kazakhstan	10109	01 2009	2013 Feb	Yes	No	Public-19	23°C, 82% humidity	✓	✓	93.9	1.39	7.0 (5.5-7.5)	Not done	✓
KZ/K/7/11.0 8.09	1 g in glass bottle	Chimpharm, Kazakhstan	30407	04 2007	2011 May	Yes	No	Public-17	18°C, 64% humidity	✓	✓	96.0	1.48	6.9 (5.5-7.5)	Not done	✓
KZ/K/5/11.0 8.09	1 g in glass bottle	Chimpharm, Kazakhstan	40408	04 2008	2012 May	Yes	No	Public-18	19°C, 59% humidity	✓	✓	96.9	1.46	7.0 (5.5-7.5)	Not done	✓
KZ/K/4/27.0 7.09	1 g in glass bottle	Chimpharm, Kazakhstan	50806	08 2006	2010 Sep	Yes	No	Public-21	20°C, 67% humidity	✓	✓	91.6	1.40	6.8 (5.5-7.5)	Not done	✓
KZ/K/10/06. 08.09	1 g in glass bottle	Chimpharm, Kazakhstan	60808	08 2008	2012 Sep	Yes	No	Public-24	23°C, 70% humidity	✓	✓	94.8	1.44	7.0 (5.5-7.5)	Not done	✓
KZ/K/2/27.0 7.09	1 g in glass bottle	Chimpharm, Kazakhstan	70806	08 2006	2010 Sep	Yes	No	Public-21	20°C, 67% humidity	✓	✓	94.6	1.43	6.9 (5.5-7.5)	Not done	✓
KZ/K/3/27.0 7.09	1 g in glass bottle	Chimpharm, Kazakhstan	70808	08 2008	2012 Sep	Yes	No	Public-21	20°C, 67% humidity	✓	✓	96.5	1.43	7.0 (5.5-7.5)	Not done	✓
KZ/K/1/24.0 7.09	1 g in glass bottle	Chimpharm, Kazakhstan	91007	10 2007	2011 Nov	Yes	No	Public-25	19°C, 66% humidity	✓	✓	98.0	1.51	7.0 (5.5-7.5)	✓	✓
KZ/K/9/11.0 8.09	1 g in glass bottle	Chimpharm, Kazakhstan	91108	11 2008	2012 Dec	Yes	No	Public-22	19°C, 66% humidity	✓	✓	97.1	1.43	7.0 (5.5-7.5)	Not done	✓
KZ/K/11/19. 08.09	1 g in glass bottle	Chimpharm, Kazakhstan	101108	11 2008	2012 Dec	Yes	No	Pharmacy -20	5°C	✓	✓	98.0	1.43	7.0 (5.5-7.5)	Not done	✓
KZ/K/12/19. 08.09	1 g in glass bottle	Chimpharm, Kazakhstan	141208	12 2008	2013 Jan	Yes	No	Pharmacy -21	21°C, 72% humidity	✓	✓	93.2	1.40	7.0 (5.5-7.5)	Not done	✓

Appendix 6: Kanamycin powder for solution for injection

Appearance: White powder; **Assay**: 90.0-110.0%

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Pack size	Manufacturer	Batch number	Manu-facture date	Expiry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay	Mass (g)	pH	Steri-lity	Con-clu-sion
KZ/K/6/11.08.09	1 g in glass bottle	Panpharma SA, France	F81113	11 2008	2011 Nov	No, supplied through GDF	No	Public-18	19°C, 59% humidity	✓	✓	97.8	1.45	7.0 (5.5-7.5)	Not done	✓
UA/KM/3/300609	1 g in glass bottle	Kievmedpreparat, Ukraine	20209	03 2009	2012 Mar	Yes	No	Public-29	No information	✓	✓	101.6	1.54	7.0 (5.5-7.5)	Not done	✓
UA/Km/4/30.06.2009	1 g in glass bottle	Kievmedpreparat, Ukraine	50309	04 2009	2012 Apr	Yes	No	Public-27	Conform	✓	✓	97.4	1.48	7.0 (5.5-7.5)	Not done	✓
UA/Km/1/300 62009	1 g in glass bottle	Kievmedpreparat, Ukraine	50309	04 2009	2012 Apr	Yes	No	Public-36	No information	✓	✓	98.7	1.49	6.9 (5.5-7.5)	Not done	✓
UA/Km/10/300609	1 g in glass bottle	Kievmedpreparat, Ukraine	90309	03 2009	2012 Apr	Yes	No	Public-37	Conform	✓	✓	99.2	1.52	7.1 (5.5-7.5)	Not done	✓
UA/Km/4/30.06.09	1 g in glass bottle	Kievmedpreparat, Ukraine	90309	03 2009	2012 Apr	Yes	No	Public-32	18°C, 70% humidity, conditions controlled	✓	✓	97.4	1.51	7.0 (5.5-7.5)	Not done	✓
UA/KM/4/300609	1 g in glass bottle	Kievmedpreparat, Ukraine	90508	05 2008	2011 Jun	Yes	No	Public-28	18°C	✓	✓	93.7	1.50	6.9 (5.5-7.5)	Not done	✓
UA/Km/3/30.06.2009	1 g in glass bottle	Kievmedpreparat, Ukraine	100409	04 2009	2012 May	Yes	No	Public-27	Conform	✓	✓	97.8	1.46	7.0 (5.5-7.5)	Not done	✓
UA/Km/9/300609	1 g in glass bottle	Kievmedpreparat, Ukraine	190708	07 2008	2011 Aug	Yes	No	Public-37	Conform	✓	✓	98.0	1.50	7.0 (5.5-7.5)	Not done	✓
UA/Km/3/300 62009	1 g in glass bottle	Kievmedpreparat, Ukraine	190708	08 2008	2011 Aug	Yes	No	Public-30	Conform	✓	✓	94.3	1.49	7.0 (5.5-7.5)	Not done	✓
UA/Km/3/30.06.09	1 g in glass bottle	Kievmedpreparat, Ukraine	210708	08 2008	2011 Aug	Yes	No	Public-33	Conform	✓	✓	98.0	1.48	7.1 (5.5-7.5)	Not done	✓
UA/Km/7/300 62009	1 g in glass bottle	Kievmedpreparat, Ukraine	250907	08 2007	2010 Oct	Yes	No	Public-34	Conform	✓	✓	96.1	1.45	7.0 (5.5-7.5)	✓	✓
UA/KM/02/300609	1 g in glass bottle	Kievmedpreparat, Ukraine	260907	09 2007	2010 Oct	Yes	No	Public-35	No information	✓	✓	97.2	1.48	7.0 (5.5-7.5)	Not done	✓
UA/Km/6/300 62009	1 g in glass bottle	Kievmedpreparat, Ukraine	341107	11 2007	2010 Dec	Yes	No	Public-34	Conform	✓	✓	96.8	1.52	6.9 (5.5-7.5)	Not done	✓
UZ/KM/35/010709	1 g in glass bottle	DHO Nika Pharm, Uzbekistan	040908	03 2008	2012 Apr	Yes	No	Pharmacy-24	Protected from light and humidity	✓	✓	98.4	1.53	7.1 (6.0-7.5)	✓	✓
UZ/KM/40/010709	1 g in glass bottle	DHO Nika Pharm, Uzbekistan	040908	03 2008	2012 Apr	Yes	No	Public-38	20°C, protected from light and humidity	✓	✓	99.0	1.50	7.2 (6.0-7.5)	Not done	✓
UZ/KM/36/010709	1 g in glass bottle	OJSC "Biokhimik" Saransk, Russia	261206	12 2006	2011 Jan	Yes	No	Pharmacy-23	Protected from light and humidity	✓	✓	97.3	1.44	7.1 (6.0-7.5)	✓	✓
UZ/KM/31/010709	1 g in glass bottle	Panpharma SA, France	F80403	04 2008	2011 Apr	No, supplied through GDF	No	Public-39	20°C, protected from light and humidity	✓	✓	97.2	1.45	7.1 (5.5-7.5)	Not done	✓

Appendix 6: Kanamycin powder for solution for injection

Appearance: White powder; **Assay**: 90.0-110.0% ✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Pack size	Manufacturer	Batch number	Manu-facture date	Expiry date	Registered	WHO-PQ'd	Site (see App. 9)	Storage conditions at collection site	Appear-ance	Iden-tity	Assay	Mass (g)	pH	Steri-lity	Con-clu-sion
UZ/KM/34/0 10709	1 g in glass bottle	Panpharma SA, France	F80408	04 2008	2011 Apr	No, supplied through GDF	No	Public-39	20°C, protected from light and humidity	✓	✓	95.3	1.38	7.1 (5.5-7.5)	Not done	✓
UZ/KM/32/0 10709	1 g in glass bottle	Panpharma SA, France	F80616	06 2008	2011 Jun	No, supplied through GDF	No	Public-39	20°C, protected from light and humidity	✓	✓	97.4	1.44	7.1 (5.5-7.5)	Not done	✓
UZ/KM/33/0 10709	1 g in glass bottle	Panpharma SA, France	F81113	11 2008	2011 Nov	No, supplied through GDF	No	Public-48	21°C, protected from light and humidity	✓	✓	96.5	1.46	7.1 (5.5-7.5)	Not done	✓
UZ/KM/38/0 10709	1 g in glass bottle	Panpharma SA, France	F81113	11 2008	2011 Nov	No, supplied through GDF	No	Public-39	20°C, protected from light and humidity	✓	✓	97.0	1.47	7.1 (5.5-7.5)	Not done	✓
UZ/KM/37/0 10709	1 g in glass bottle	Shanghai Pharmaceutical Co. Ltd, China	061002	10 2006	2009 Oct	Yes	No	Pharmacy -27	Protected from light and humidity	✓	✓	97.0	1.46	7.1 (5.5-7.5)	Not done	✓
UZ/KM/39/0 10709	1 g in glass bottle	Shanghai Pharm. Co. Ltd, China	081105	11 2008	2011 Nov	Yes	No	Pharmacy -26	19°C, protected from light and humidity	✓	✓	95.5	1.44	7.0 (5.5-7.5)	Not done	✓
UZ/KM/41/0 10709	1 g in glass bottle	Shanghai Pharm. Co. Ltd, China	081105	11 2008	2011 Nov	Yes	No	Public-38	Protected from light and humidity	✓	✓	95.3	1.47	7.0 (5.5-7.5)	Not done	✓
UZ/KM/42/0 10709	1 g in glass bottle	Shanghai Pharmaceutical Co. Ltd, China	081105	11 2008	2011 Nov	Yes	No	Public-49	19°C, protected from light and humidity	✓	✓	96.1	1.51	7.0 (5.5-7.5)	✓	✓

Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%
Dissolution:NLT 80% (Q) in 30min

✓= complies; ✖= does not comply

Appendix 7 Ofloxacin tablets/capsules

Country (see App. 9)/ sample code	Dosage form, strength	Pack size	Manufacturer	Batch number	Manu-facture date	Ex-piry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear-ance	Iden-tity	Assay	Related sub-stances	Dissolution	Uniformity of mass	Con-clusion
AM/OFX/34/100 709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	010808	No informa-tion	2010 Sep	Yes	No	Pharmacy-17	No information	✓	✓	100.0	✓ 1	Complies at S1 min:88%; max:98%	✓	✓
AM/OFX/35/130 709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	010808	No informa-tion	2010 Sep	Yes	No	Pharmacy-16	No information	✓	✓	100.9	✓ 2	Complies at S1 min:92%; max:104%	✓	✓
AM/OFX/37/160 709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	031108	No informa-tion	2010 Dec	Yes	No	Pharmacy-17	No information	✓	✓	95.2	✓ 3	Complies at S1 min:97%; max:102%	✓	✓
AM/OFX/39/160 709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	031108	No informa-tion	2010 Dec	Yes	No	Ware-house-2	No information	✓	✓	97.5	✓ 4	Complies at S1 min:96%; max:101%	✓	✓
AM/OFX/41/160 709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	031108	No informa-tion	2010 Dec	Yes	No	Pharmacy-15	No information	✓	✓	97.2	✓ 5	Complies at S1 min:96%; max:101%	✖ 6	✖
AM/OFX/33/090 709	Tab 200 mg	10 tab	Kaspar-Chabani Pharma, Syrian Arab Republic	12023	01 2009	2012 Jan	Yes	No	Pharmacy-18	No information	✓	✓	106.6	✓ 7	Complies at S1 min:103%; max:106%	✓	✓
AM/OFX/40/160 709	Tab 200 mg	10 tab	Kaspar-Chabani Pharma, Syrian Arab Republic	12023	01 2009	2012 Jan	Yes	No	Ware-house-2	No information	✓	✓	106.8	✓ 8	Complies at S1 min:101%; max:104%	✓	✓
AM/OFX/42/160 709	Tab 200 mg	10 tab	Kaspar-Chabani Pharma, Syrian Arab Republic	12023	01 2009	2012 Jan	Yes	No	Pharmacy-15	No information	✓	✓	103.3	✓ 9	Complies at S1 min:99%; max:105%	✓	✓

1 A: below DL, B: 0.13%, Any other: below DL, Sum: 0.13%
2 A: below DL, B: 0.12%, Any other: below DL, Sum: 0.12%
3 A: below DL, B: 0.22%, RRT 4.7: 0.05%, Sum: 0.27%
4 A: below DL, B: 0.09%, Any other: below DL, Sum: 0.09%
5 A: below DL, B: 0.10%, Any other: below DL, Sum: 0.10%
6 **Does not comply,** mean: 315.6mg**,** CV= 2.7%, min: 89.4%; max: 106.1%**,** 1 tablet outside ±5%**, 1 tablet outside ±10%**
7 A: below DL, B: 0.21%, RRT 3.5: 0.05%, Sum: 0.26%
8 A: below DL, B: 0.10%, Any other: below DL, Sum: 0.10%
9 A: below DL, B: 0.09%, Any other: below DL, Sum: 0.09%

Appendix 7: Ofloxacin tablets / capsules

Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%
Dissolution:NLT 80% (Q) in 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Dosage form, strength	Pack size	Manufacturer	Batch number	Manu-facture date	Ex-piry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear-ance	Iden-tity	Assay	Related sub-stances	Dissolution	Unifor-mity of mass	Con-clusion
AM/OFX/38/160709	Tab 200 mg	10 tab	OLA Ozon, Russia	040808	08 2008	2010 Sep	Yes	No	Pharmacy-7	No information	✓	✓	95.2	✓ 10	Complies at S1 min:95%; max:96%	✓	✓
AM/OFX/32/090709	Tab 200 mg	10 tab	OLA Ozon, Russia	040808	08 2008	2010 Sep	Yes	No	Pharmacy-4	No information	✓	✓	94.0	✓ 11	Complies at S1 min:94%; max98%	✓	✓
AM/OFX/36/150709	Tab 200 mg	10 tab	Pharmstandart - Lekarstva, Russia	41207	No informa-tion	2010 Jan	Yes	No	Pharmacy-8	No information	✓	✓	96.0	✓ 12	Complies at S1 min:95%; max:99%	✓	✓
AM/OFX/31/090709	Tab 200 mg	10 tab	Pharmstandart - Lekarstva, Russia	41207	No informa-tion	2010 Jan	Yes	No	Pharmacy-14	No information	✓	✓	96.5	✓ 13	Complies at S1 min:95%; max:101%	✓	✓
AZ/OF/28/010709	Tab 200 mg	100 tab in plastic bottle	Macleods Pharmaceuticals Ltd, India	OF805	04 2008	2011 Mar	Yes	No	Public-6	Conform, 23°C, 45% humidity	✓	✓	95.4	✓ 14	Complies at S1 min:95%; max:101%	✓	✓
AZ/OF/29/030709	Tab 200 mg	10 tab	MU Pharmaceuticals Enibosna, Turkey	8M12A3A	12 2008	2010 Dec	Yes	No	Pharmacy-19	Conform, 22°C, 41% humidity	✓	✓	102.4	✓ 15	Complies at S1 min:98%; max:104%	✓	✓
AZ/OF/30/030709	Tab 400 mg	5 tab	MU Pharmaceuticals Enibosna, Turkey	8M15A3A	12 2008	2010 Dec	Yes	No	Pharmacy-19	Conform, 22°C, 41% humidity	✓	✓	99.6	✓ 16	Complies at S1 min:97%; max:104%	✓	✓
AZ/OF/31/030709	Tab 200 mg	10 tab	Pharmacare Int. Co. Jerusalem, Palestine	080195	03 2008	2011 Mar	No	No	Pharmacy-19	Conform, 22°C, 46% humidity	✓	✓	95.9	✓ 17	Complies at S1 min:94%; max:100%	✓	✓
BY/Ofx/26/0107 2009	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	030309	03 2009	2011 Apr	Yes	No	Public-16	Conform	✓	✓	103.2	✓ 18	Complies at S1 min:96%; max:100%	✖ 19	✖

10 A: below DL, B: 0.26%, RRT 3.6: 0.06%, Sum: 0.32%
11 A: below DL, B: 0.25%, RRT 3.6: 0.07%, Sum: 0.32%
12 A: below DL, B: 0.07%, Any other: below DL, Sum: 0.07%
13 A: below DL, B: 0.19%, RRT 3.7: 0.06%, Sum: 0.25%
14 A: below DL, B: 0.24%, RRT 4.3: 0.10%, Sum: 0.34%
15 A: below DL, B: 0.12%, Any other: below DL, Sum: 0.12%
16 A: below DL, B: 0.08%, Any other: below DL, Sum: 0.08%
17 A: below DL, B: 0.28%, RRT 4.3: 0.10%, Sum: 0.38%
18 A: below DL, B: 0.24%, RRT 4.1: 0.09%, Sum: 0.33%
19 **Does not comply,** mean: 329.4mg**,** CV= 3.3%, min: 96.9%; max: 107.3%**, 3 tablets outside ±5%,** no tablets outside ±10%

Appendix 7: Ofloxacin tablets / capsules

Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%
Dissolution:NLT 80% (Q) in 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Dosage form, strength	Pack size	Manufacturer	Batch number	Manu-facture date	Ex-piry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear-ance	Iden-tity	Assay	Related sub-stances	Dissolution	Unifor-mity of mass	Con-clusion
BY/Ofx/53/300609	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	030309	03 2009	2011 Apr	Yes	No	Public-13	Conform	✓	✓	101.5	✓ [20]	Complies at S1 min:101%; max:109%	✓	✓
BY/Ofx/29/300609	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	040309	03 2009	2011 Apr	Yes	No	Public-12	Conform	✓	✓	101.9	✓ [21]	Complies at S1 min:99%; max:105%	✓	✓
BY/Ofx/33/300609	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	050409	04 2009	2011 May	Yes	No	Public-10	Conform	✓	✓	103.3	✓ [22]	Complies at S1 min:97%; max:104%	✓	✓
BY/Ofx/06/020709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	060509	05 2009	2011 Jun	Yes	No	Ware-house-4	Conform	✓	✓	103.3	✓ [23]	✖ [24]	✓	✖
BY/Ofx/42/010709	Tab 200 mg	10 tab in blister	Borisovskij zavod medicinskich preparatov, Belarus	060509	05 2009	2011 Jun	Yes	No	Public-9	Conform	✓	✓	108.9	✓ [25]	✖ [26]	✓	✖
BY/OFX/44/300609	Capsules 200 mg	14 caps in plastic container	Holden Medical B. V. /Holden Medical Laboratories Pvt Ltd, India	020409	01 2009	2011 Dec	Yes	No	Public-11	Conform	✓	✓	99.2	✓ [27]	Complies at S1 min:95%; max:99%	✓	✓
BY/Ofx/07/020709	Capsules 200 mg	14 caps in plastic container	Holden Medical B. V. /Holden Medical Laboratories Pvt Ltd, India	020409	01 2009	2011 Dec	Yes	No	Ware-house-4	Conform	✓	✓	99.1	✓ [28]	Complies at S1 min:98%; max:104%	✓	✓
BY/Ofx/54/300609	Tab 200 mg	6 tab in blister	Macleods Pharmaceuticals Ltd, India	OF804	04 2008	2011 Feb	No Supplied through GDF	No	Public-13	Conform	✓	✓	98.1	✓ [29]	Complies at S1 min:95%; max:100%	✓	✓

20 A: below DL, B: 0.14%, Any other: below DL, Sum: 0.14%
21 A: below DL, B: 0.06%, Any other: below DL, Sum: 0.06%
22 A: below DL, B: 0.14%, Any other: below DL, Sum: 0.14%
23 A: below DL, B: 0.19%, RRT 4.6: 0.05%, Sum: 0.24%
24 **Does not comply at S1+S2+S3, mean (n=24): 42%, min:19%; max:99%**, *(After dissolution tablets were not disintegrated)*
25 A: below DL, B: 0.19%, RRT 4.6: 0.05%, Sum: 0.24%
26 **Does not comply at S1+S2+S3, mean (n=24): 32%, min:17%; max:89%**, *(After dissolution tablets were not disintegrated)*
27 A: below DL, B: 0.18%, RRT 3.9: 0.05%, Sum: 0.23%
28 A: below DL, B: 0.17%, RRT 3.9: 0.05%, Sum: 0.23%
29 A: below DL, B: 0.24%, RRT 4.1: 0.09%, Sum: 0.33%

Appendix 7: Ofloxacin tablets / capsules

Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%
Dissolution:NLT 80% (Q) in 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Dosage form, strength	Pack size	Manufacturer	Batch number	Manu-facture date	Ex-piry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear-ance	Iden-tity	Assay	Related sub-stances	Dissolution	Unifor-mity of mass	Con-clusion
KZ/Ofx/11/11.08.09	Tab 200 mg	100 tab in jar	Global Pharm RK Almaty, Kazakhstan	20509	05 2009	2012 Jun	Yes	No	Public-17	18°C, 64% humidity	✓	✓	104.4	✓ [30]	Complies at S2 mean (n=12): 87% min:75%; max:101%	✓	✓
KZ/Ofx/8/06.08.09	Tab 200 mg	100 tab in jar	Global Pharm RK Almaty, Kazakhstan	50509	05 2009	2012 Jun	Yes	No	Public-24	22°C	✓	✓	95.6	✖ [31]	✖ [32]	✓	✖
KZ/Ofx/3/27.07.09	Tab 200 mg	Pack, 10 blisters x 10 tab	J. Duncan Healthcare Pvt Ltd, India	G046	05 2007	2010 Apr	Yes	No	Public-21	23°C, 80% humidity	✓	✓	98.3	✖ [33]	Complies at S1 min:94%; max:98%	✓	✖
KZ/Ofx/5/11.08.09	Tab 200 mg	Pack, 6blisters x 10 tab	Macleods Pharmaceuticals Ltd, India	OF804	04 2008	2011 Mar	No, supplied through GDF	No	Public-18	19°C, 59% humidity	✓	✓	101.5	✓ [34]	Complies at S1 min:95%; max:99%	✓	✓
KZ/Ofx/12/12.08.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80431	05 2008	2011 Apr	Yes	No	Public-23	21°C, 72% humidity	✓	✓	101.9	✓ [35]	Complies at S1 min:97%; max:102%	✓	✓
KZ/Ofx/4/27.07.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80432	05 2008	2011 Apr	Yes	No	Public-21	23°C, 80% humidity	✓	✓	101.0	✓ [36]	Complies at S1 min:96%; max:100%	✓	✓
KZ/Ofx/2/24.07.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80433	05 2008	2011 Apr	Yes	No	Public-25	19°C, 66% humidity	✓	✓	100.7	✓ [37]	Complies at S1 min:97%; max:102%	✓	✓
KZ/Ofx/1/24.07.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80434	05 2008	2011 Apr	Yes	No	Public-25	19°C, 66% humidity	✓	✓	100.7	✓ [38]	Complies at S1 min:96%; max:103%	✓	✓
KZ/Ofx/6/11.08.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80440	05 2008	2011 Apr	Yes	No	Public-18	19°C, 59% humidity	✓	✓	103.5	✓ [39]	Complies at S1 min:98%; max:102%	✓	✓

30 A: below DL, B: 0.08%, RRT 2.4: 0.17%, Sum: 0.25%
31 **Does not comply:** A: below DL, B: below DL, RRT 0.3: 0.08%, RRT 0.8: 0.05%, **RRT0.9: 0.67%**, **RRT 2.4: 0.36%, Sum: 1.16%**
32 **Does not comply at S1+S2+S3, mean (n=24): 78%, min:68%; max:86%**
33 **Does not comply:** A: below DL, B: 0.20%, RRT 0.2: 0.11%, RRT 0.3: 0.08%, RRT 0.8: 0.06%, RRT 0.9: 0.16%, **RRT 2.5: 0.64%, Sum: 1.25%**
34 A: below DL, B: below DL, RRT 2.3: 0.07%, Sum: 0.07%
35 A: below DL, B: 0.08%, RRT 2.3: 0.14%, Sum: 0.22%
36 A: below DL, B: below DL, RRT 2.4: 0.18%, Sum: 0.18%
37 A: below DL, B: below DL, RRT 2.4: 0.19%, Sum: 0.19%
38 A: below DL, B: below DL, RRT 2.3: 0.19%, Sum: 0.19%
39 A: below DL, B: below DL, RRT 2.3: 0.17%, Sum: 0.17%

Appendix 7: Ofloxacin tablets / capsules

Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%
Dissolution:NLT 80% (Q) in 30min

✓= complies; ✖= does not comply

Country (see App. 9)/ sample code	Dosage form, strength	Pack size	Manufacturer	Batch number	Manu-facture date	Ex-piry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appear-ance	Iden-tity	Assay	Related sub-stances	Dissolution	Unifor-mity of mass	Con-clusion
KZ/Ofx/7/11.08.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80441	05 2008	2011 Apr	Yes	No	Public-18	19°C, 59% humidity	✓	✓	100.2	✓ 40	Complies at S1 min:99%; max:104%	✓	✓
KZ/Ofx/9/11.08.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80552	06 2008	2011 May	Yes	No	Public-17	18°C, 64% humidity	✓	✓	101.8	✓ 41	Complies at S1 min:96%; max:99%	✓	✓
KZ/Ofx/10/11.08.09	Tab 200 mg	Pack, 10 blisters x 10 tab	Plethico Pharmaceuticals Ltd, India	80553	06 2008	2011 May	Yes	No	Public-17	18°C, 64% humidity	✓	✓	104.4	✓ 42	Complies at S1 min:96%; max:97%	✓	✓
UZ/OFX/45/010709	Tab 200 mg	10 tab in blister	Kievmedpreparat, Ukraine	81008	No informa-tion	2010 Nov	Yes	No	Pharmacy-25	Protected from light and humidity	✓	✓	103.7	✓ 43	Complies at S1 min:101%; max:104%	✓	✓
UZ/OFX/43/010709	Tab 200 mg	100 tab in plastic container	Macleods Pharmaceuticals Ltd, India	OF807	07 2008	2011 Jun	No, supplied through GDF	No	Public-48	No information	✓	✓	101.7	✓ 44	Complies at S1 min:95%; max:104%	✓	✓
UZ/OFX/44/010709	Tab 200 mg	10 tab in blister	OLA Ozon, Russia	010508	05 2008	2010 Jun	Yes	No	Pharmacy-22	Protected from light and humidity	✓	✓	100.4	✓ 45	Complies at S1 min:70%; max:100%	✓	✓

40 A: below DL, B: below DL, RRT 2.4: 0.18%, Sum: 0.18%
41 A: below DL, B: below DL, RRT 2.4: 0.14%, Sum: 0.14%
42 A: below DL, B: below DL, RRT 2.3: 0.07%, Sum: 0.07%
43 A: below DL, B: 0.13%, Any other: below DL, Sum: 0.13%
44 A: below DL, B: 0.26%, RRT 5.2: 0.11%, Sum: 0.37%
45 A: below DL, B: 0.15%, Any other: below DL, Sum: 0.15%

Appearance: Clear, yellowish liquid
Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%

✓= complies

Appendix 8 Ofloxacin solution for infusion

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No.	MF date	Expiry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Related substances	pH	Bacterial endotoxins	Steri-lity	Conclu-sion
BY/Ofx/57/300609	0.2%	100 ml in plastic bottle	Unique Pharm. Labs, India	P8012	02 2008	2011 Jan	Yes	No	Public-13	Conform	✓	✓	93.7	✓ 1	6.7 (5.0-8.0)	Below 0.06 IU/mg	Not done	✓
BY/Ofx/34/300609	0.2%	100 ml in plastic bottle	Unique Pharm. Labs, India	P8016	05 2008	2011 Apr	Yes	No	Public-10	Conform	✓	✓	95.4	✓ 2	6.7 (5.0-8.0)	Below 0.06 IU/mg	✓	✓
BY/Ofx/08/020709	0.2%	100 ml in plastic bottle	Unique Pharm. Labs, India	P8017	05 2008	2011 Apr	Yes	No	Ware-house-4	Conform	✓	✓	95.1	✓ 3	6.7 (5.0-8.0)	Below 0.06 IU/mg	Not done	✓
UA/OFX/6/30.06.2009	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	040309	03 2009	2011 Mar	Yes	No	Public-27	Conform	✓	✓	106.4	✓ 4	4.5 (3.5-5.5)	Below 0.06 IU/mg	Not done	✓
UA/OFX/5/30.06.09	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	040309	03 2009	2011 Mar	Yes	No	Public-26	19°C	✓	✓	105.2	✓ 5	4.5 (3.5-5.5)	Not done	Not done	✓
UA/OFX/11/300609	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	050309	03 2009	2011 Mar	Yes	No	Public-37	Conform	✓	✓	104.9	✓ 6	4.7 (3.5-5.5)	Below 0.06 IU/mg	Not done	✓
UA/OFX/03/300609	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	050309	03 2009	2011 Mar	Yes	No	Public-35	No information	✓	✓	106.1	✓ 7	4.6 (3.5-5.5)	Not done	Not done	✓
UA/OFX/5/30.06.2009	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	080608	06 2008	2010 Jun	Yes	No	Public-27	Conform	✓	✓	105.1	✓ 8	4.7 (3.5-5.5)	Below 0.06 IU/mg	Not done	✓
UA/OFX/3/300609	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	090608	06 2008	2010 Jun	Yes	No	Public-32	18°C, 70% humidity, conditions controlled	✓	✓	107.1	✓ 9	5.0 (3.5-5.5)	Below 0.06 IU/mg	Not done	✓

1 A: below DL, B: 0.14%, RRT 0.9: 0.07%, RRT 1.9: 0.12%, Sum: 0.33%
2 A: below DL, B: 0.15%, RRT 0.9: 0.07%, RRT 1.9: 0.08%, Sum: 0.30%
3 A: below DL, B: 0.13%, RRT 0.9: 0.06%, RRT 1.9: 0.08%, Sum: 0.27%
4 A: below DL, B: 0.14%, Any other: below DL, Sum: 0.14%
5 A: below DL, B: 0.13%, Any other: below DL, Sum: 0.13%
6 A: below DL, B: 0.14%, Any other: below DL, Sum: 0.14%
7 A: below DL, B: 0.12%, Any other: below DL, Sum: 0.12%
8 A: below DL, B: 0.06%, RRT 3.8: 0.12%, Sum: 0.18%
9 A: below DL, B: 0.14%, RRT 0.9: 0.05%, Sum: 0.19%

Appendix 8: Ofloxacin solution for infusion

Appearance: Clear, yellowish liquid
Assay: 90.0-110.0%
Related substances: Impurity A ≤ 0.3% , Impurity B ≤ 0.3% , Any other impurity ≤ 0.2% , Sum ≤ 1.0%

✓= complies

Country (see App. 9)/ sample code	Strength	Pack size	Manu-facturer	Batch No.	MF date	Expiry date	Regist-ered	WHO-PQ'd	Site (see App. 9)	Storage cond. at collection site	Appearance	Identity	Assay	Related substances	pH	Bacterial endotoxins	Steri-lity	Conclu-sion
UA/OFX/4/30.06.09	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	090608	06 2008	2010 Jun	Yes	No	Public-29	No information	✓	✓	105.2	✓ 10	4.9 (3.5-5.5)	Not done	✓	✓
UA/OFX/4/30062009	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	090608	06 2008	2010 Jun	Yes	No	Public-30	Conform	✓	✓	106.1	✓ 11	4.9 (3.5-5.5)	Not done	Not done	✓
UA/OFX/3/300609	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	100608	06 2008	2010 Jun	Yes	No	Public-28	18°C	✓	✓	106.8	✓ 12	4.7 (3.5-5.5)	Below 0.06 IU/mg	Not done	✓
UA/OFX/5/30062009	0.2%	200 ml in glass bottle	Yuria-Pharm, Ukraine	120608	06 2008	2010 Jun	Yes	No	Public-31	Conform	✓	✓	107.6	✓ 13	4.5 (3.5-5.5)	Below 0.06 IU/mg	Not done	✓

10 A: below DL, B: 0.14%, Any other: below DL, Sum: 0.14%
11 A: below DL, B: 0.15%, Any other: below DL, Sum: 0.15%
12 A: below DL, B: 0.15%, Any other: below DL, Sum: 0.15%
13 A: below DL, B: 0.14%, Any other: below DL, Sum: 0.14%

Appendix 9 Country codes and site codes

Country Code	Sample Collection Site	Site codes in Appendices 2-8			Number of samples collected
Armenia					
AM	Pharmacy "ALFA-Farm", Bagkatuvyais st, Abovyan		Pharmacy-1		1
AM	Pharmacy "ALFA-Farm", Pioneer st, Abovyan		Pharmacy-2		1
AM	Pharmacy "Arevir Navasardyan", Yerevan		Pharmacy-3		1
AM	Pharmacy "Arm Pharm", Yerevan		Pharmacy-4		1
AM	Pharmacy "Gurgen Pharm", Yerevan		Pharmacy-5		1
AM	Pharmacy "Kameryan and son", Vanadzor		Pharmacy-6		1
AM	Pharmacy "Latagi", Yerevan		Pharmacy-7		1
AM	Pharmacy "Livafarm", Yerevan		Pharmacy-8		1
AM	Pharmacy "Qrigri", Avetisya st, Spitak		Pharmacy-9		1
AM	Pharmacy "Tarmia", Vanadzor		Pharmacy-10		1
AM	Pharmacy "A. IGITYAN", Gyumri		Pharmacy-11		3
AM	Pharmacy "Viola and Zwashyn", Yerevan		Pharmacy-12		1
AM	Pharmacy located in supermarket "STAR", Avan, Yerevan		Pharmacy-13		1
AM	Pharmacy "Esculap", Nalbandyan st, Yerevan		Pharmacy-14		3
AM	Pharmacy "Natali Pharm", Yerevan		Pharmacy-15		3
AM	Pharmacy "ALFA-Farm" CSSC, Gyumri		Pharmacy-16		2
AM	Pharmacy "ALFA-Farm" CSSC, Yerevan		Pharmacy-17		2
AM	Pharmacy "Tovmasyan", Yerevan		Pharmacy-18		2
AM	Hospital Warehouse of MDR/XDR department, Abovyan, Kotayk region	Public-1			2
AM	Hospital Warehouse, Gyumri Infectious and TB diseases, Gyumri	Public-2			2
AM	Hospital Warehouse, Republic TB dispensary, Arzni, Kotayk region	Public-3			2
AM	Polyclinic, MDR/XDR department no 12, Yerevan	Public-4			2
AM	Warehouse of National Office for Tuberculosis, Yerevan	Public-5			2
AM	MSF Warehouse MSF France representative office, Yerevan			Warehouse-1	2
AM	Warehouse of distributor "Natali Pharm", Yerevan			Warehouse-2	2
AM	Warehouse of distributor "ALFA-FARM", Yerevan			Warehouse-3	1
Azerbaijan					
AZ	Drug-store "Ulvi", Baku		Pharmacy-19		4
AZ	ARMH Institute of Lung Diseases, Baku	Public-6			14
AZ	ARMH TB Dispensary N°1, Alatava	Public-7			7
AZ	ARMH TB Dispensary N°4, Baku	Public-8			6
Belarus					
BY	Health Institution "Mogilev regional TB dispensary", Mogilev	Public-9			8
BY	Vitebsk regional clinical TB dispensary, Vitebsk	Public-10			6
BY	2nd Minsk City Phthisiology Dispensary, Minsk	Public-11			3
BY	Republican tuberculosis hospital "Sosnovka", Sosnovka, Vitebsk oblast	Public-12			3
BY	State Institution "Scientific research institute of pulmonology and phthisiology", Minsk	Public-13			12
BY	1st Minsk City Phthisiology Dispensary, Minsk	Public-14			2
BY	Republican tuberculosis hospital "Volkovichi", Dzerzhinsk region	Public-15			10
BY	Health Institution "Minsk regional TB dispensary" Leskovka, Minsk oblast	Public-16			8
BY	Pharmaceutical Warehouse of the trade and manufacturing unitary enterprise "Belpharmacia", Minsk			Warehouse-4	8
Kazachstan					
KZ	Private pharmacy N4, Almaty		Pharmacy-20		1
KZ	Private pharmacy, Almaty town		Pharmacy-21		1
KZ	Regional TB dispensary, Karaganda	Public-17			6
KZ	Almaty city TB-dispensary, Almaty	Public-18			14
KZ	Regional TB dispensary, Astana	Public-19			3
KZ	Local TB dispensary, Shymbulak village, Talgar region, Almaty oblast	Public-20			2
KZ	Regional TB dispensary, Petropavlovsk	Public-21			12
KZ	Regional TB dispensary, Aktau, Mangystau region	Public-22			1
KZ	Regional TB dispensary, Pavlodar	Public-23			1
KZ	Regional TB dispensary, Taldykurgan	Public-24			10
KZ	National Centre Problems of TB, Almaty	Public-25			9

Appendix 9: Country codes and site codes

Country Code	Sample Collection Site	Site codes in Appendices 2-8			Number of samples collected
Ukraine					
UA	Republican TB dispensary, Pionersky village, Simferopol, Crimea	Public-26			8
UA	Regional TB dispensary, Chernihiv	Public-27			6
UA	Regional Phthiziopulmonology centre, Ivano-Frankivsk	Public-28			4
UA	Regional TB dispensary, Cherkassy	Public-29			4
UA	Regional TB dispensary, Nikolaev	Public-30			4
UA	Regional TB dispensary, Ternopil	Public-31			4
UA	Regional territorial medical union "Phtiziatrija", Uzhgorod	Public-32			4
UA	Kiev Central anti-TB clinic, Kiev	Public-33			3
UA	Regional TB dispensary, Ternopil	Public-34			2
UA	Regional TB dispensary, Chernivtsi	Public-35			2
UA	TB dispensary, Sevastopol	Public-36			1
UA	Regional TB dispensary, Zhitomir	Public-37			11
Uzbekistan					
UZ	"Asnal" pharmacy, Nukus, Karakalpakstan Republic		Pharmacy-22		1
UZ	"Bayr-Bak" pharmacy, Nukus, Karakalpakstan Republic		Pharmacy-23		1
UZ	Chernobyltsev rep. Association pharmacy, Nukus, Karakalpakstan Republic		Pharmacy-24		1
UZ	JSC "Elite Service" pharmacy, Nukus, Karakalpakstan Republic		Pharmacy-25		1
UZ	JV Grand Farm Medical Pharmacy, Tashkent		Pharmacy-26		1
UZ	PFC "Dinur Pharmaceuticals" pharmacy, Nukus, Karakalpakstan Republic		Pharmacy-27		1
UZ	"Shayana Farm" pharmacy, Tashkent		Pharmacy-28		3
UZ	"Bayshinur" pharmacy, Nukus, Karakalpakstan Republic		Pharmacy-29		2
UZ	Antituberculosis dispensary, Termez	Public-38			5
UZ	2-antituberculosis clinic, Nukus, Karakalpakstan Republic	Public-39			4
UZ	Antituberculosis dispensary, Fergana, M. Salil st.	Public-40			4
UZ	Antituberculosis dispensary, Kuva	Public-41			3
UZ	Antituberculosis dispensary, Rishtan	Public-42			3
UZ	Antituberculosis clinic, Urta-Chirchik, Tashkent area	Public-43			2
UZ	Antituberculosis dispensary, Bagdad	Public-44			2
UZ	Antituberculosis dispensary, Kokand	Public-45			2
UZ	Antituberculosis dispensary, Margilan	Public-46			2
UZ	Antituberculosis dispensary, Yangikurgan village, Buvayda region	Public-47			2
UZ	Republican scientific research centre of phthisiology and pulmonology, Tashkent	Public-48			2
UZ	Antituberculosis dispensary, Kuvasay, Fergana area	Public-49			1
UZ	Antituberculosis dispensary, Tashkent area	Public-50			1
UZ	Antituberculosis dispensary, Vodil village, Fergana area	Public-51			1

WHO estimates that nearly half a million multidrug-resistant tuberculosis (MDR-TB) cases emerge worldwide each year due to inadequate or poorly-administered treatment regimens, insufficient supply or quality of anti-TB medicines, and transmission of drug-resistant strains. Newly independent states of the former Soviet Union (NIS) have the highest prevalence rates of MDR-TB. Limited research has been conducted into the factors contributing to drug resistance in this region, and into the marked regional and national differences in drug resistance rates. The survey reported here aimed to explore the quality of anti-TB medicines in use in six NIS (Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan) as one of the potential factors contributing to the development of drug resistance. First-line medicines containing rifampicin and/or isoniazid, and second-line medicines containing kanamycin and ofloxacin, were collected from public- and private-sector procurement and treatment centres.

The survey was conducted by WHO in cooperation with the ministries of health and national medicines regulatory authorities of each participating country. A total of 291 samples produced by 33 manufacturers were collected from 84 collection sites and tested by preselected reliable laboratories.

No sample was suspected to be of a spurious, falsely-labelled, falsified or counterfeit product. No quality problems were identified for the samples of kanamycin powder for solution for injection, isoniazid solution for injections or ofloxacin solution for infusion. Overall, 33 samples (11.3%) failed to meet the specifications set for the survey. The highest failure rate was found for mono-component products containing rifampicin — more than a quarter of rifampicin samples (28.3%) failed to meet the specifications, the predominant reason being that the content of active ingredient was below the acceptable limit. The total failure rate with respect to extreme deviations from specifications (as defined in this report), was 1.0%.

The fact that 88.7% of samples in this survey met required specifications is encouraging. The zero failure rate among WHO-prequalified samples and those supplied through the Global Drug Facility (GDF) indicates that WHO prequalification and GDF's quality assurance policy are effective in ensuring the quality of anti-TB medicines. However, survey results demonstrating low content of rifampicin, substantial inconsistencies in ofloxacin dissolution, as well as batch-to-batch and intra-batch inconsistencies, are of concern. They may be the result of inconsistent application of Good Manufacturing Practices combined with insufficient regulatory supervision. The results of the survey cannot be generalized to the overall anti-TB medicines market in the surveyed countries because of the limitations in the sampling, and - although the results are encouraging - they also indicate that further efforts are required to facilitate access to medicines that meet international quality standards in order to ensure the provision of quality anti-TB medicines to TB patients in the region.

For further information contact:

Quality Assurance and Safety: Medicines

Department of Essential Medicines and Pharmaceutical Policies

World Health Organization
20 Avenue Appia
CH-1211 Geneva 27