Almaty-Bishkek Economic Corridor

Pharma Testing

Pre-Feasibility Study

Consultant Report

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Abbreviations

ABEC	Almaty–Bishkek Economic Corridor
ADB	Asian Development Bank
AMR	Anti-microbial resistance
API	Active Pharmaceutical Ingredient
DDP	Department of Drug Provision
EAEC	Eurasian Economic Community
GDP	Gross Domestic Product
GDF	Global Drug Facility
GF	The Global Fund
GCLP	Good Quality Control Laboratory Practice (as in GMP)
GLP	Good Laboratory Practice (as in toxicity and clinical studies)
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonization
ILAC	International Laboratory Accreditation Cooperation
JAR	Joint Annual Review
MDR	Multi medicine resistant
NCEM	National Center of Expertise Medicines
NRA	National Medicine Registration Authority
OOP	Out-of-pocket
PIC/s	Pharmaceutical Inspection Convention scheme
PQM	Promoting the Quality of Medicine
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
SRA	Stringent Regulatory Authority
TB	Tuberculosis
TOR	Terms of Reference
USAID	United States Agency for International Development
USP	United States Pharmacopoeia
WB	World Bank
WHO	World Health Organization
YLL	Years of Life Lost

The Almaty–Bishkek Economic Corridor (ABEC)

The Almaty–Bishkek Economic Corridor (ABEC) under the Central Asia Regional Economic Cooperation (CAREC) program aims to integrate the relatively dense economic area in Central Asia and create one economic space without barriers, following a multi-sector approach.

Kazakhstan and Kyrgyz governments envision a corridor as an integrated economic space between the cities of Almaty and Bishkek and their surroundings to foster trade, enhance free movement of labor and capital, and modernize infrastructure. The cross-border corridor will promote greater diversification and competitiveness, allowing businesses to specialize more, operate at a larger scale, and experience agglomeration benefits.

> *"The two cities and four regions can achieve far more together than either can achieve alone".*

The first ABEC Subcommittee meeting was held on 25 September 2017 in Bishkek; the second meeting of ABEC Subcommittee initiative under the Intergovernmental Kazakhstan-Kyrgyz Council was held on 11 June 2018 in Almaty, Kazakhstan.

Two external consultants were contracted by ADB in May 2018 with individual Terms of Reference to do a **pre-feasibility** study on the **practicality of establishing** (1) medical regional reference laboratories) and **(2) testing laboratories on pharmaceutical quality assurance in ABEC**.

This report relates to the Pharmaceutical QA part of the study (ToR provided in annex); it incorporates a review of the relevant supranational regulations including quality control of medicines for a common Eurasian market that are gradually coming into force after ratification in each member state under the Eurasian Union. A single market for medicines enables an automatic recognition of products moving freely across Eurasian Economic Community states in a 'single space' with the identical packaging, same quality standard and same efficacy. A single market for medicines deletes duplication of regulatory activities and creates incentives for manufacturers to market their new products for a larger population under one regulatory system at less costs and a shorter time to market.

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Summary

It is important that all medicines used in a population, irrespective of funding source, are adequately regulated to control the source and to assure the safety, quality and clinical effectiveness.

A technically qualified **Quality Control Laboratory** (**QCL**) that has the capacity to perform independent pharmaceutical analysis in adherence with one or more recognized pharmacopoeias, is a critical element in both phases of the medicine regulatory cycle (pre- and post-market) and in the overall quality assurance of medicines.

Medicine regulation in Kazakhstan and in the Kyrgyz Republic is a centralized government responsibility which is carried out by a designated office in the Ministry of Health as the National Medicine Registration Authority (NRA). In Kazakhstan, this is the Pharmacy Committee that works closely with the Center for Expertise of Medicines (NCEM). In the Kyrgyz Republic, the NRA is the Department for Drug Provision (DDP). In both cases a National Quality Control function is placed in the structure of the Ministry of Health subordinate to the NRA.

There is a reasonable assurance that medicines in the **Kazakhstan** market, for a significant part manufactured by domestic manufacturers, have been assessed by the autonomous NRA and that samples, where required, have been subject to analytical testing in a certified Quality Control Laboratory for compliance with the established normative criteria. Testing criteria are aligned to European standards.

In the **Kyrgyz Republic,** the hospitals and clinics rely on (essential) medicines provided for free to the population under the State Benefits Program and the Additional Medicines program for ambulatory patients. These medicines are regulated by the Department of Drug Provision in the Ministry of Health (semi-autonomous) and for 99% imported through the private pharmacy sector. The Quality Control testing of medicines is sub-optimal and of insufficient capacity mainly limited by its infrastructure. As a result, the quality of medicines provided by the Government is not assured and there are unregistered medicines circulating in the system i.e. without assurance of the manufacturing source and with no control testing at all.

Financial support by the Asian Development Bank in forms or government loans or grants under ABEC to strengthen quality assurance of medicines could be of incremental value for Kazakhstan and of significant value to the Kyrgyz Republic

Substandard quality medicines are incompatible with evidence based practice and they undermine sustainable development goals (SDGs). The issues with quality assurance of medicines in the Kyrgyz Republic have been less visible to the outside world because donors have been supplying critical medicines through external procurement mechanisms as humanitarian aid. This may change in the near future when supplies of the funded health commodities are gradually taken over by domestic funding through the national procurement system oriented to sources in for example Russia (tuberculosis medicines). To detect and avoid import and use of substandard quality medicines it is important that an NRA is autonomous and has access to the expertise of an independent Quality Control laboratory (QCL) of sufficient capacity and that meets an international technical accreditation.

The Eurasian Economic Community (**EAEC**) has its secretariat in Moscow, Russia. It will put common product registrations in place for a single market by ultimately by 2025 with unified databases for information exchange between the national regulatory authorities of the five member states with joint pharmaceutical inspections. Until December 2020, manufacturers may choose between a national registration or already apply for the common EAEC procedure through one of the member states; by December 31, 2025, however all national registrations need to pass re-registration under the regulations of the common market (www.eurasiancommission.org). It is still a ‘young’ system with so far four new common market applications submitted to the NCEM in Kazakhstan and according to the NCEM, zero in other member countries.

Based on the harmonized regulatory systems of the European Medicines Agency (EMA), the EAEC Committee also envisages harmonization of national pharmacopoeias, set up of a pharmaco-vigilance system and a common system for reporting of substandard and falsified medicines detected in member states[1]. The EAEC single market – in principle covering 183 million people - is regarded as an economic integration dominated by Russia with according to some, only limited impact on the global market. From discussions, the impression is that only Kazakhstan and possibly Armenia could be in a position to participate somehow in future decision making, other members (the Kyrgyz Republic, Belarus) would have less or zero voice when it comes to pharmaceuticals in the EAEC.

Stakeholders agree that in a common single EAEC market for medicines there is no need to duplicate regulatory activities. The Association of Southeast Asian Nations (ASEAN) and the Asia-Pacific Economic Cooperation (APEC) are among the regional initiatives in Asia working towards harmonization for medicinal products. In many cases ***reliance*** on assessment reports, test results or inspection work carried out by another trusted regulatory authority can be the best way for countries to cooperate bilaterally in a region, while retaining decision-making responsibilities for each of the NRAs in their country.

Quality control testing can be costly and is a specific area where EAEC members will achieve resource efficiency by harmonizing technical standards and sharing laboratory capacity. One member state QCL specializes in certain products and test methodology and takes those samples from other members while another one reciprocates with expertise in testing of another therapeutic category. For instance, under ABEC the QCL in Almaty could specialize itself in analytical testing of cancer and cardiovascular medicines for the common market while all quality control testing of antibiotics including anti-tuberculosis tablets for the common market could be concentrated in the QCL in Bishkek. Though the Kyrgyz Republic according to interviews scores well among EAEC members with registration of medical devices the lack of a qualified pharmaceutical laboratory will be a barrier for Kyrgyz Ministry to fully participate in the EAEC when it comes to regulation of medicines.

In practice a technical collaboration or mutual 'reliance' will only work if and when the normative quality standards are harmonized and the technical capacities between national QC laboratories are aligned.

To realize the potential of a form of ***regulatory convergence*** between the NRA laboratories in Almaty and in Bishkek under ABEC and for the Kyrgyz Republic to have a say in the future EAEC, it is crucial that the QCL in Bishkek will achieve a sufficient level of technical expertise and develops testing capacity within the next 3 to 5 years. A pre-qualification of the QCL by the World Health Organization (WHO) as a National QC laboratory will need an adequate infrastructure (premises and testing equipment) put in place.

The most direct path to a WHO pre-qualified QCL is one that is designed and built compliant with ISPE [2] international standards, is equipped with utilities and laboratory instruments for pharmacopoeial testing and that adheres to safety standards. The WHO EURO Region and the United States Pharmacopeia (USP) stand ready to assist with technical support to the Ministry of Health. The route for pre-qualification by the WHO was earlier discussed and in principle agreed (2014) but no tangible steps were taken by the Department under the previous Government.

[1] Formation of Common Markets of Medicines and Medical Products in EAEC
Source: http://www.eurasiancommission.org/ru/act/texnreg/deptexreg/LS1/Pages/orls.aspx

[2] International Society for Pharmaceutical Engineering www.ispe.org (search: good practice guide quality lab facilities)

Quality Control of medicines is a Health System Strengthening component in which ADB can lend the financial support under ABEC to the Government of the Kyrgyz Republic. The output will have an impact in the health sector
and one that will be noted by the Eurasian Committee and Russia.

The KMSA Medical Academy expressed its interest to host a new QCL for the Ministry in Bishkek and possibly make land available for construction. A professional and pre-qualified QCL in Bishkek will also be a realistic way to retain and - possibly- attract more professional QC staff and experts from outside (e.g. from Almaty) so to help with a reverse migration of staff for the Ministry and the Medical Academy.

Review of the HIV/AIDS case is formally not within the scope of this assignment but the geographical proximity of the two ABEC cities offers an opportunity to consolidate resources and efforts to create a tandem of two "*fast track cities*" – which would be unique in Central Asia for PLHIV in the migrant population.

The WHO has supported the Ministry of Health in the Kyrgyz Republic with technical assistance for drafting the fourth-generation health sector strategy and to improve institutional capacity to advance towards Universal Health Coverage (UHC). Recommendations for the Asian Development Bank (ADB) to consider for improving quality assurance between the countries are listed in Section V including support with (funding) the implementation of WHO's Institutional Development Plan for the Drugs Department in the Kyrgyz Ministry of Health, and possibly construction of a tableting factory with financing under ABEC for manufacture of (tuberculosis) medicines that meets international GMP and WHO pre-qualification standards.

Background context

I. Kazakhstan

In 1978 Kazakhstan saw the Declaration of Primary Health Care endorsed in its then capital Alma-Ata, which was a major milestone in the field of Public Health. In 1997, the Republic of Kazakhstan moved its Government capital to Astana. Kazakhstan has seen a steady economic growth since its independence and in 2006 it transitioned from a lower-middle-income to upper-middle income status. Development triggers urbanization and the ratio rural/urban for the population (over 18 million in total) is expected to grow from 47/53 to 30/70 by 2030. In 2015 its Human Development Index scored highest in Commonwealth of Independent States (CIS). Till today the WHO European Centre for Primary Health Care in Almaty is still hosted by the Government of Kazakhstan. The US Government partners with Kazakhstan to support its 'emergence as a regional leader' in Central Asia. In more recent years, external pressures caused sharp drops in both oil prices and the Kazakh national currency; by end 2017 the country's economic exhaustion showing little sign of ending. The president enjoys high popularity, but is increasingly aware of the danger of letting an economic crisis become a protracted phenomenon. There is general popular support for policies that avoid instability as in neighboring Tajikistan and the Kyrgyz Republic but within a context of increasing socioeconomic dissatisfaction and growing protests against a sentiment of gradually losing sovereignty to Russia and China[3].

1. The pharmaceutical market in Kazakhstan has an annual value estimated at one billion US dollars. Kazakhstan established a domestic pharmaceutical base in past years in which the major leading companies are moving towards international GMP standards, some of them in a strategic partnership with foreign companies. Nowadays the Kazakh manufacturers cover about 50% of government needs (of essential medicines) provided to the population under the State Benefit package (free of charge) and under Insurance coverage.

2. Procurement for public sector based on a national tendering process is centralized through a monopoly buyer *Samruk Kazyna Pharmatsiya* (SK Pharma)[4]. A majority of foreign (innovator) products is originating from International Conference on Harmonization (ICH) regions (Europe) with the other (generic branded) products imported from Turkey, Russia, India and other countries.

3. For instance, anti-tuberculosis tablets for patients in the 1st line of treatment are supplied from a Russian source and for second line tuberculosis medicines it is a combination of Indian sources and domestic manufacturers with the new class of tuberculosis medicines (bedaquiline, delamanid) procured through the STOPTB/Global Medicine Facility (GDF) in Geneva. The tuberculosis program in Kazakhstan scores overall good treatment success rates. For its HIV medicines the country uses UNICEF as procurement agency for reasons of quality and price.

4. The Kazakh population is entitled to a package of medicines free of charge[5]. Stakeholders however commented that the Government is spending increasingly less of its Gross Domestic Product (GDP) less on health. Under the Soviet Union spending on health used to be as high as 46% according to the Director of the Medical University (UMC) who nowadays has to cut hospital beds and length of stay. The Government of Kazakhstan with a higher GDP overall still spends far more on health for its larger population compared to the Kyrgyz Republic that receives relative more in donor support and humanitarian aid.

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[3] https://www.bti-project.org/de/berichte/laenderberichte/detail/itc/KAZ/

[4] In January 2016, the Global Fund to Fight AIDS, tuberculosis and Malaria reported that public health officials in Kazakhstan conned the organization out of more than $5 million through a network of "smokescreen companies" used to rig bids and overcharge for goods and services.

[5] Including legal migrant (workers) to treated at no cost to them, for instance for tuberculosis provided that they have an official resident working permit in Kazakhstan. Partners nuanced this to say that in spite of free Government funded tuberculosis medicines, free diagnostics prior to treatment access is not always in place though the primary health care system for migrants. And treatment interruption risks remain when migrants return home during treatment especially a reality with MDR cases.

5. Mortality and disease burden in Kazakhstan is determined predominantly by non-communicable diseases (NCD). Common risk factors for disease and premature death due to NCD are unhealthy diet, smoking and high blood pressure.

II. Kyrgyz Republic

The Kyrgyz Republic, compared to the Republic of Kazakhstan is a young parliamentary republic with an ethnic diverse population of 7 million who live for the larger part (64%) rural and traditionally nomadic. The country's economy was always heavily dependent on export to the Soviet Union. It changed the name of its capital back to Bishkek in 1991 and shortly after that gained independence. Since then it has had a turbulent, disruptive history with the Tulip revolution in 2005 followed by civil unrest and uprisings in 2010, violent clashes and prospects of civil war. A third of its population still lives in poverty while Kyrgyz's GDP depends for 40% on remittances sent back home by (800,000) Kyrgyz working in Russia. the Kyrgyz Republic is currently under a new government elected in 2017; the only 'freely elected democracy in post-Soviet Central Asia' [USAID] and committed to reform and transition to a market economy based on the (traditional) agricultural sector. In recent years, the Kyrgyz Republic has stabilized in both democratic and economic development. In 2016 it joined the UHC partnership to accelerate progress to universal health coverage for its population[6].

6. The pharmaceutical market in the Kyrgyz Republic has an annual value estimated at quarter billion US dollars. The sector is for 99% percent dependent on the importation of medicines[7] which by its history is not surprising. The market is also highly privatized with trade of (generic) medicines as general commodities by hundreds (thousands) of businesses involved in import, distribution and sales of medicines and medical products in retail pharmacies[8].

7. Though its Government spends a higher percentage of its smaller GDP on health compared to Kazakhstan, relative more of that is coming out-of-pocket (OOP), except for the children under 5 years of age for which the State – in principle - covers. According to the WHO (2016) the financial burden of seeking health services was reduced in the early years of reform but the trend appeared to be reversed recently[9]. Overall the Kyrgyz Government compared to its bigger neighbor, has far less resources to spend and is more relying on external donors and NGOs for providing health care to its population and reducing its relative higher level of poverty.

8. With roughly six thousand products registered as a medicine, pharmacy is not surprisingly one of the most dynamic sectors of the national Kyrgyz economy (WHO/META), probably after gold mining. This is evidenced by clusters of multiple similar looking and window-stocked pharmacies around the main hospitals in Bishkek. There are reports of unethical marketing including active promotion and advertisement of medicines, over-prescribing and high levels of self-medication including use of antibiotics without prescriptions.

9. Relevant new pharmaceutical legislation developed under the *"Den Sooluk*" National Health Sector Reform[10] is often found in draft or issued as a government resolution copied from EAEC regulations[11] but inconsistent with existing legislation from past governments or with practice (i.e. "*The Law of the Kyrgyz Republic "On Medicines and technical regulations issued in 2011 on Good Practices*") [12] . According to the estimates (Ministry of Health, 2014), the share of public

[6] http://uhcpartnership.net/country-profile/kyrgyz-republic/

[7] We were informed (Chuy Hospital) that there has been production of local fluids in the country in the past but this production has been closed following reports of fever reactions in patients (endotoxin levels, sub optimal sterilization).

[8] To be noted that in the Kyrgyz National Medicines Program issued in 2014 one specific objective is to: *to recognize medicines as a special kind of products with an impact on health, the quality and efficacy of which can't always be objectively evaluated by either the doctor, prescribing medicines, or by the patient*.

[9] Den Sooluk National Health Reform Program Joint Review Summary Note April 10-14th, 2017

[10] "Den Sooluk" was approved by the Kyrgyz Government's Resolution No 309 dated May 24, 2012 "*in terms of improving health outcomes in priority areas and quality of the key individual services delivery*".

[11] Program of the Government of the Kyrgyz Republic on Development of the area of medicines circulation in the Kyrgyz Republic for 2014-2020 (the Program); Resolution of the Government of the Kyrgyz Republic No 376 as off 8 July 2014.

[12] Ibid (presence of legal conflicts in the legislation already reported in 2014), see § 1. Removing Contradictions and Loopholes in the Legislation.

procurements of medicines and medical devices through the Health Care Organizations (HCO) is about a third of total pharmaceutical sales. The HCOs use government tender procedures in the open market which is known to be rife with products that have not been registered in the Kyrgyz Republic as a medicine. The definition of a “medicine” includes a number of different types of products into the term "medicine" in response to urgent political and regulatory tasks over time which has blurred the responsibilities for following regulations with applying new barriers and bypassing others.

10. The procurement lacks sufficient transparency; there is acknowledgement among stakeholders that the risk of purchasing low quality medicines at excessive prices increases due to the influence of various interest groups on the procurement processes. It is a bit of ‘cold’ comfort knowing that a number of those unregistered medicines will be entering the Kyrgyz Republic from Kazakhstan via regular shuttle import across open border of small quantities. If unsuccessful in procurement, institutions in Bishkek are having to ask patients to purchase their own medication from Almaty and bring it in as personal medication (e.g. verbal information National Oncology Center).

11. The most recent Human Development Index for the Kyrgyz Republic is just above the CIS average with a global ranking of No. 120 out of 188 countries. As in Kazakhstan mortality and disease burden in the Kyrgyz Republic is driven by NCD. Hypertension detection rates remain low (4%) compared with population prevalence levels (43%), failing to put 80% of those with raised blood pressure on medication (Joint Review 2017). Below a similar ‘NCD profile’ at the first look, in comparison to Kazakhstan the burden and mortality due to neonatal conditions and infectious disease including tuberculosis and hepatitis, is twice as high in the Kyrgyz Republic (WHO Global Disease Burden Database[13]).

12. Anti-microbial resistance (AMR) is an additional factor with an undeniable impact on the overall disease burden in the Kyrgyz Republic. AMR levels are driven upwards by continued inappropriate prescribing and use of antibiotics (without a preceding diagnosis or a clinical indication) in an environment where generic quality is not assured/distrusted and where manufacturers of (branded, more expensive and unnecessary) antibiotics can target their marketing at prescribers and users directly. As informed in Chuy there is a general slowness so with far little (zero) activity in the Kyrgyz Republic to address AMR as a priority.

[13] DALYs compared between KAZ and KGZ
Source: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html
YLLs compared between KAZ and KGZ
Source: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html

III. The case of the potential burden in the region caused by **Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS)**

In 2016, more than 160,000 people were newly diagnosed with HIV in the WHO European Region, the highest number of people ever newly diagnosed in one year since HIV case reporting began in the 1980s. The majority (nearly 80%) of people newly diagnosed were from the eastern part of Europe [14]. Annual numbers of new HIV infections continue to increase in eastern Europe and central Asia. There are large gaps along the '90–90–90' cascade in the region. As a result, HIV treatment coverage remains alarmingly low, less than a quarter of people living with HIV have viral suppression and AIDS-related deaths continue to increase[15]. The Republican HIV Center in Bishkek informed that Russia stopped its support in monitoring HIV resistance, while a trend of further receding VL suppression rates is already visible among migrants who fail to take their daily medication. Renewed (political) commitment and more innovative approaches are needed to ensure higher coverage, effective treatment and to promote adherence to recommended protocols in order to contain HIV medicine resistance in the region and to increase the proportion of PLHIV that are virally suppressed to at least 73%.

13. A HIV protocol exists in the CIS countries since 1997. In April 2017, the Ministries of Health in the Commonwealth of Independent States (CIS) re-confirmed their commitment to the 2014 Paris Declaration which aims to end AIDS globally by 2030. The countries agreed to take a Fast-Track approach as recommended by UNAIDS. To do that the countries must achieve the ambitious targets defined by UNAIDS as the "90–90–90" cascade16. The '90' targets herein translate into having at least 81% on antiretroviral treatment and at least 73% of all people living with HIV being virally suppressed so that they become untransmittable. When however, the first steps remain below 90%, the overall target of stopping transmission of the virus in a population quickly falls out of reach.

14. The sooner the '90' targets are reached the sooner it will be possible to reduce future HIV infections to zero. HIV burden is usually concentrated in urban settings so that with a focus on cities feasible progress can be made more quickly. With that 'urban advantage' in mind UNAIDS launched the *"Fast-Track Cities Initiative"*[17]. This ambitious initiative to which 200 cities around the world have since subscribed commits them to achieve the '90' targets at their city level. In 2017 Almaty was the third city in the Eastern Europe/Central Asian region (after Kyiv, and Odessa in Ukraine) that signed this declaration.

15. The Kyrgyz Republic is supported by the United States Agency for International Development (USAID) HIV/AIDS Flagship (UHF) Project[18] to achieve broadly the same goal by 2020 for the whole country. Bishkek as the capital of the Kyrgyz Republic has not signed the Fast Track City declaration yet. At the same time the Kyrgyz Republic will be transitioning from Global Fund support for procurement of their HIV medicines to national republic domestic procurement (starting with 20% in 2019) and it will start procuring Hepatitis medications for HIV/Hepatitis co-infected cases. The use of a UN agency or other specialized international organizations as is described in the Program of the Government of the Kyrgyz Republic on Development of the area of medicines circulation in the Kyrgyz Republic for 2014-2020, will be important to spend budgets efficiently and to make this transition without impacting negatively on the treatment outcomes.

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[14] http://www.euro.who.int

[15] UNAIDS Global_AIDS_update_2017 and UNAIDS HIV Data compared between Kazakhstan and the Kyrgyz Republic Source: http://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf

[16] 90% of people living with HIV know their status, 90% of people living with HIV who know their status are on treatment and 90% of people on treatment are virally suppressed [to become untransmittable]

[17] Urban strategies and actions are central to driving the Fast-Track approach and will, to a large extent, determine success in ending AIDS at the national and global levels (http://www.unaids.org/en/cities).

[18] The USAID funded UHF project is implemented by Population Services International (PSI) country wide through the Republican Center, its AIDS Centers in regions and the Family Medicine Centers. The national program is expanding its treatment sites from 80 to 100 and the government will start paying for HIV medicines from the State budget. The quality and efficacy of HIV medicines remains critical. Kazakhstan took the decision in 2016 to use its domestic funds for procurement through UNICEF. In terms of keeping up with latest recommended treatment protocols and introducing of dolutegravir, the Kyrgyz Republic appears to have been at an advantage with inputs from donors.

IV. **Tuberculosis**, ensuring completion of treatment among migrants

The eastern part of the WHO European Region is most affected by the tuberculosis epidemic: Eighteen high-priority countries[19] among which Kazakhstan and neighboring Kyrgyz Republic, bear 85% of the tuberculosis burden and 99% of the multidrug-resistant tuberculosis (MDR-TB) burden. Although the number of cases in the region as a whole halved in 2006–2015, the number of new tuberculosis cases was almost 8 times higher in these high-priority countries than in the rest of the European region. MDR-TB is one of the key drivers of the tuberculosis epidemic along with social determinants, known tuberculosis risk factors (e.g. HIV), and limited capacity of health systems[20].

16. Since 2005, significant progress has been achieved with the control of tuberculosis in both post-Soviet republics. The increase in detection and treatment of tuberculosis in the Kyrgyz Republic has been five-fold, and three-fold In Kazakhstan since 2008 and 2009 respectively. According to the WHO (Global Tuberculosis Report 2017) a disparity is still evident between the countries with incidence levels of tuberculosis twice as high in the Kyrgyz population compared to Kazakhstan and ~4 times as much for medicine resistant Multi Medicine Resistant (MDR)/RR forms of the infectious disease (MDR is tuberculosis resistant to first line drugs rifampicin and isoniazid; RR is tuberculosis resistant to the drug rifampicin). Kazakhstan is still listed as one of the 20 highest burden MDR-tuberculosis countries in the world. According to USAID funded NGO Partners-in-Health (PIH) more than 6,000 people in Kazakhstan are diagnosed with MDR-tuberculosis every year. The Kyrgyz Republic is tailing that group with Belarus, and Tajikistan reporting >1000 medicine resistant cases per year.

17. Adjusted for population size in the two ABEC cities both Almaty and Bishkek still experience between 1,000 and 1,500 new tuberculosis (infectious) cases per year with in addition 750 (infectious) medicine resistant tuberculosis cases per year. These cases occur among: i) new cases that became infected by someone else with a drug resistant tuberculosis strain and ii) previously treated patients e.g. carrying a (X)DR strain due to earlier treatment interruptions, and incomplete treatments, defaulting). According to WHO reports the treatment coverage of MDR tuberculosis in Kazakhstan is approaching 90% whereas in the Kyrgyz Republic the coverage and treatment success rate of medicine resistant tuberculosis both lag behind (<30% for the coverage and < 60% for treatment success rate respectively).

> *"After the collapse of the Soviet Union in 1991, many of tuberculosis patients stopped taking their medicines as health systems failed and supplies often ran out. Experts mark this as a main cause of relapse which has subsequently been accelerating the (X)DR tuberculosis epidemic in the region"* (Dr Tamara Voshenkova MOH, KJ Seung PIH).
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> ***"Without addressing the needs of migrants, we cannot end the tuberculosis epidemic"* (Dr. Lucia Ditiu, WHO).**

18. Free movement in a future single market with an increase in numbers of migrant workers finding labor within the Eurasian Economic Community and an increasing number of daily border crossings between cities like Almaty and Bishkek as foreseen under ABEC, will increase risks of i) presumptive cases not being screened timely for detection of tuberculosis, or ii) once enrolled on treatment having higher risks to default and relapse. The first risks to spread the infection while the latter increases the risks of transmitting medicine resistant tuberculosis in public spaces (for instance, queues infecting border guards and passengers infecting train workers) and in households.

19. A common health information system for registering individual tuberculosis cases between the programs on both sides would be a logical step to bridge gaps and enable cross border follow up on tuberculosis patients, irrespective of the national program that initially detected and enrolled a case on treatment. Alignment of standard treatment protocols including the inclusion criteria with standard tuberculosis medicine formulations that are available in both Almaty and Bishkek from a

[19] *Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, **Kazakhstan**, **the Kyrgyz Republic**, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.*

[20] http://www.euro.who.int

source with a short lead time in a same blister presentation that patients can easily recognize, will help to maximize adherence and perhaps be more practical, to mitigate the treatment interruption risks in the first line tuberculosis control among migrants.

20. This could be achieved if and when procurement of the first line tuberculosis medicines (tablets) is harmonized and consolidated at the same manufacturing source (as opposed to having tuberculosis tablets for a patient in Almaty from factory X in Russia, factory Y in India and factory Z in Kazakhstan and the same treatment for a patient in Bishkek from factory Z in Russia, factory Y in India and factory X in Kazakhstan).

21. MDR (XDR) tuberculosis patients in addition depend on initial injections and multiple different tablets to be taken daily for up to 2 years which for the most part will be on an ambulatory basis. With a list of over 20 tuberculosis medicines, there are numerous non-standard regimens often cause terrible side effects and differences between countries which makes harmonization of protocols impossible risking many of the patients to default sooner or later. Both countries are part of the "The EndTB" Project: Expanding New Medicines for tuberculosis that implements a multi-country phase 3 clinical trial[21] managed by PIH and MSF and partners to develop novel, short, all-oral regimens for MDR-tuberculosis patients.

[21] Phase III clinical trial uses bedaquiline and delamanid to find radically shorter (9 months), injection-free, more tolerable treatments for MDR-tuberculosis (http://www.endtuberculosis.org/clinical-trial).

1. Quality Assurance of Medicines

I. Pre- and post-market

22. A product from a particular manufacturer needs to pass the initial quality control testing for a medicine to obtain a marketing authorization. Subsequently, samples of commercial lots taken periodically from the market need to pass the same tests in order for the product to stay in the market. There are thus usually two main, distinct phases for medicines to enter and circulate in a market:

22.1) a **pre-market** phase with a scientific evaluation of the product dossiers, testing of a sample and factory inspections to establish a product specification and to document 'Good Manufacturing Practices' (GMP) compliance of the manufacturing source

22.2) the **post-market** phase during which surveillance of medicines is conducted in the distribution chain. The market is where products are sold (pharmacies and shops), dispensed (hospitals and clinics) or stored (manufacturers, importers and wholesalers). Post-market surveillance often interpreted as having a system for pharmacovigilance [22] in place to retroactively protect future patients from medicines that are found potentially unsafe.

23. A technically qualified Quality Control Laboratory (QCL) that has the capacity to perform independent pharmaceutical analysis in adherence with one or more recognized pharmacopoeias, is a critical element in both phases of the medicine regulatory cycle (pre- and post-market) and in the overall quality assurance of medicines. [23,24]

24. Pre-market testing is often generating a stream of incoming fees whereas the second, post market testing in many countries costs money, so normally the registration and periodic re-registrations fees cover the expenditure for market surveillance. Over time changes in manufacturing are inevitable and the potential pitfall in markets with thousands of existing product registrations, is that the output of a QCL is driven by the pre-market testing of the nth commercial product - which often has zero public health benefit - but does too little to test the basic essential medicines circulating in the market (except when there is a complaint).

Pharmacovigilance is about monitoring medicines safety in a population whereas post-market surveillance is about monitoring the quality of medicines in the system (circulation)

II. Pharmaco-vigilance

25. A system for pharmacovigilance captures clinical events that were not predictable based on earlier information at time of registration. Pharmacovigilance tends to report on medicines that have come onto the market recently and medicines that are potentially more toxic e.g. second line tuberculosis medicines. On its own it doesn't however give much assurance in terms of monitoring quality in the market of the basic essential medicines that have been used (safely) by many in past decades. For a substandard or poor quality medicine to be captured by a pharmacovigilance system

[22] A system to investigate unexpected side effects of medicines and adverse medicine reactions, or lack of clinical efficacy, that are reported to the regulatory office by either health professionals or the public.

[23] Pre**-market** testing is when a pharmaceutical product from a specific manufacturer has not been registered yet and a sample is being tested by a designated quality control laboratory for the purpose of the application. **Post-market** test can refer to two different situations 1) testing of a product after it has been granted registration status for instance as a control at time of importation or release from factory to market or 2) for purpose of monitoring quality, the testing of product samples taken (usually random batches) from the market any time between the product entering the market and its expiration date.

[24] Other regulatory functions are: licensing, import control, inspection of distribution channels including disposal of expired or unused medicines, control of medicine promotion and advertising, price controls, generic substitution and promoting rational medicine use.

it would have to trigger a recognizable adverse event which it often does not. For that reason, post-market surveillance also includes, or should include a (risk based) framework for analytical testing of products prospectively sampled by inspectors from the market at random to detect (and remove) poor quality and substandard products[25].

III. Existing Policies

26. In **Kazakhstan**, the "Pharmacy Committee" in the Ministry of Health is responsible for implementation of the procedures for medicine regulation. The Committee has issued the Kazakh Pharmacopoeia which is fully aligned with the European Pharmacopoeia. The Pharmacy Committee started accession to membership of PIC/s[26] (though this has apparently been delayed since several years with currently no outcome yet).

27. The National Centre of Expertise on Medicines, Medical Supplies and Medical Equipment under the Ministry of Health in short "the National Center" or the "**NCEM**" is a state agency supervised by the Pharmacy Committee that has been given the legal (exclusive) authority to implement the procedures for registration and control of medicines, medical goods and medical equipment in the market.

28. In past years, the NCEM was having its center in Almaty. Since the country capital moved to Astana, the NCEM has its head office in Astana, and a QCL network of eight laboratories. The NCEM is an official observer to the ICH[27] and the United States Pharmacopeia (USP) since 2010. It has an agreement with the British Pharmacopeia since 2014 and adopted the ICH common technical document (CTD) format for applications, for which the template is published on the NCEM website in Russian and English language. NCEM is also the center where all information concerning post market surveillance of medicines including adverse medicine reactions, and safety of medicines is collected, analyzed and assessed.

29. The Pharmacy Committee with the National Center as the drug control agency has access to domestic manufacturing sites which is an advantage to conduct inspections of the manufacturing processes and review quality control systems on a 'batch level'. However, outside Astana and Almaty, Kazakhstan is a very large country having thousands of kilometers' international border with the Russian Federation and with China.

30. In general, the quality assurance emphasis of the Committee and the NCEM appears to be on pre-market registration of medicines and 'series' testing (at import)[28]. The unknown is how active and how effective the Pharmaceutical Inspectorate in the Kazakh Ministry is functioning between the Pharmacy Committee and the NCEM in surveillance of the whole market to control all imports and check: i) storage and distribution practices, ii) registration status of medicines in stock, iii) generic substitution (where it concerns medicine benefit packages) and use of prescriptions for antibiotics, iv) removal and disposal of expired medicines v) removal of unregistered or illegally imported medicines, and lastly vi) to conduct prospective risk-based sampling of random medicine packs for control testing.

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[25] Removing substandard and poor quality products from the market improves quality of service, promotes trust in health care systems and reduces wasting money on ineffective treatments that lead to prolonged disease and increased disability.

[26] www.picscheme.org. A cooperation between regulatory authorities of member countries based on mutual recognition of harmonized GMP inspectorate standards. The list of members is wider than ICH though limited to mostly the developed countries. Russia's Federal State Institution is a pre-applicant as well as Pakistan's DRAP and the SFDA in Saudi Arabia.

[27] www.ich.org. a joint regulatory-industry initiative, set up initially between the EU, USA and Japan (1990) to agree on common guidelines and standards on Safety, Quality and Efficacy of Pharmaceutical products. Globally there are countries that full adopt these guidelines (ICH members) and those that may use or may not use the same technical standards (non-ICH countries).

[28] As in other countries the NDRAs in general have a tendency (and $ incentive) to focus on pre-market registrations and try to ignore post market quality monitoring. It is perceived to be unnecessary, costly and potentially a risk to their reputation as regulator if a product registered by them is subsequently failing in the market.

31. Though NCEM appeared to be familiar with the WHO Guidelines on the Conduct of Surveys of the Quality of Medicines[29], the country has not moved yet to a risk-based post-market testing of random products sampled from pharmacies and stores.

32. The **Kyrgyz Republic** is in comparison is a smaller country, more isolated because of its highly mountainous terrain and is less international oriented due to a different political history. It has nonetheless gained valuable experience in implementing medicine benefit programs for its population and it has recently updated its Essential Medicines list[30]. It is exploring ways to centralize procurement of medicines to increase transparency and implement price controls. On the other hand, the health systems in the Kyrgyz Republic had a relative short time to develop and there is less domestic or external funding available to make quick progress with medicine regulation, implementing market controls or enforcement of required regulations. Aside from a number of local herbal and vitamin preparations, the country is fully dependent on importation of (generic) medicines through the private sector importers and sales through pharmacies.

33. The **Department of Drug Provision** (**DDP**) and Medical Equipment in the Kyrgyz Ministry of Health, was established in 1997 and is the *de facto* Regulatory Authority for medicines. Its goal is to "*ensure accessibility of essential, safe, effective and quality medicines for the citizens of the Kyrgyz Republic and their rational use*". The technical requirements for registration of a medicine in the Kyrgyz Republic are gradually complying with the set of internationally recognized ICH standards for quality, safety and efficacy. A Bishkek based QCL was established by the Kyrgyz Ministry with support of donors in 2010 for the pre-market testing of medicines. The QCL in Bishkek obtained an ISO 17025 certification from the National Accreditation center in June 2017 which is on a voluntary basis.

34. A simplified procedure for the registration of 'generics' applies for medicines of those manufacturers that have already obtained a product registration in a country that falls under the definition of Stringent regulated countries (SRA) or that have been pre-qualified by the WHO.

if the 'simplified procedure' is applied too widely, generic products sourced from outside SRA countries (e.g. Russia, India, China) or procured via agents (e.g. in Turkey) would risk to pass the registration process too easily on a waiver

35. The DDP has a team of experts for issuing routine certifications which similar as in Kazakhstan is equivalent to importation licensing by review of shipping documents and inspection/testing of product batches (serial testing); as in Kazakhstan there was no information on what the testing in each case entails and if it applies to 100% of all batches. Other than that, was clear that also in the Kyrgyz Republic there is no post market surveillance of the market in place. In our meeting the DDP expressed their need for more in depth GMP (manufacturing) and GLP (laboratory) training, and assessing of CMC sections[31] in product dossiers.

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[29] http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidelines-on-medicines-quality-surveys-QAS15-630_30062015.pdf?ua=1

[30] The National List of Life-Saving Medicines and Medical Products was approved by the Evidence-Based Medicine of the Ministry of Health in 2018 (https://24.kg/english/87177/). The national list is approved by the government. It is the main state list for increasing the availability of basic vital medicines for the population and health organizations, used for hospital purchases, medical prescriptions, the State Guarantees Program and other reimbursable budget lists; the list was last revised in 2012. In 2017, a new document was drawn up, 51 medicines were excluded and 95 new ones were added.

[31] The Chemistry and Manufacturing Controls (CMC) section in a product dossier describes the connection in quality between the medicine used in clinical studies and the marketed medicine; typical questions for CMC review are specific to the product/dosage form: How and where is the medicine made? How are raw materials tested and monitored? What control procedures are in place to assure product consistency and quality? Are quality attributes adequately identified and characterized for the product in its specification? Are (sterilization) processes validated? Are the test methods used to monitor product quality appropriate? How long does the product maintain its quality after it is made (shelf life/expiry)? How [for generic products] was interchangeability proven? In each case, the assessors of a dossier should be satisfied that the manufacturer knows which steps and variables in the manufacturing process need to be controlled and why.

36. Though it is expected to be in place by law under the same DDP, there is no effective Pharmaceutical Inspectorate established yet in the Kyrgyz Republic. The Kyrgyz Republic has not yet developed a legislative framework for bilateral cooperation; it is focusing on aligning its draft laws in the area of medicines with the relevant EAEC Council decisions. The Kyrgyz Government is however committed to set up a structural unit in the Department of Medicines (DDP) for the implementation of a Pharmaceutical Inspectorate function. Regulations are in process of being drafted for this new unit, and a surveillance/pharmaco-vigilance unit with assistance from the WHO as part of their support to the Institutional Development Plan (IDP) for the Medicines Department in the Ministry.

IV. Regulatory databases

37. Access to data is critical for regulatory authorities to be able to effectively conduct the product registration, licensing, inspection and surveillance functions.

38. Since cloud-based internet technology with open source software has developed fast, a modernized (on-line) information management system that is effectively integrating regulatory data across different functions has become central to strengthening regulatory capacity and oversight function.

39. Some NRAs have moved to a full online regulatory data management system (e.g. IRIMS in Pakistan, Myanmar and three Latin American countries, Pharmadex in Bangladesh, Ethiopia, Mozambique, and Namibia and a mSupply module in Fiji and PNG). Others have not and continue to rely on cumbersome, paper-based registration applications with manual data entry in either Xcel files or a stand-alone database. Often these registration data bases are static data systems that simply capture the list of registered products and importers (plus whether fees have been paid with an ‘due’ date for renewal). In many NRA’s the software is the SIAMED package developed by WHO/PAHO with MSH in the late nineties, or a customized version. The information may be published on NRA websites or may be made available, for instance on a CDROM.

40. The most straightforward example where an online regulatory data system that allows two way information, creates compelling advantages is that NRA Inspectors equipped with tablets/smart phones to log-in have direct online information about approved medicines, the approved source, and the approved artwork and label information so that they can immediately assess and upload the physical check on the authorization status of medicines being traded and sold (e.g. as OTC or on-prescription) and verify the correct source on the label as well as the approved shelf life between manufacturing and expiry date printed on the label. Additional information in an integrated system could include medicine price controls, and enable access to QC data reported on past samples of specific products or from specific manufacturing sources; the latter could provide automated instructions to inspectors whether a sample is required for post-market testing (e.g. risk-based using import license batch statistics).

41. Both the Kazakh and the Kyrgyz NRAs have registration databases published on their websites that allow to search for registered products and sources. The NCEM in Kazakhstan has moved to an integrated data management system whereas the DDP in the Kyrgyz Republic has a system which is not yet optimally implemented and in process of being upgraded by the State Committee on IT and Communication to integrate with the common database under the EAEC.

42. The NCEM Regulatory database was not accessible for the consultant to review in more detail in Almaty without specific authorization from the NCEM Directorate in Astana (instead we were referred to the NCEM website)

43. The DDP in Bishkek highlighted that their IT system is due for an upgrade and they specifically expressed a request to the ADB for assistance with obtaining an integrated data base system ‘such as the NCEM in Kazakhstan is using’. Additional consulting work on institutionalization of National Drug Database (NDB) and financing is required to make impact on availability of [quality assured] pharmaceuticals. Technical specifications, project plan and budget were developed following 2016 WHO recommendations to expand the regulatory database to a market monitoring

and policy enforcement tool, the current thinking in Bishkek is more in the direction of integration of medicine price controls to make reimbursement decisions rather than e.g. quality assurance through building in post market surveillance activities and data. The DDP estimates that the effort requires 250 – 300 man days of assistance by experts with experience in pharmaceutical markets, global best practices in pharma management (both mature and developing markets), and use of IT solutions.

44. Provided that Ministry of Health in Astana is willing to collaborate, there is an opportunity for starting a process of regulatory convergence, where the ADB under an ABEC pilot can facilitate technical IT assistance needed to align a regulatory information system that works independently for each and can also exchange regulatory information as needed. An alternative option for ADB is to assist the Kyrgyz Ministry with developing an IRIMS that integrates drug registration, inspectorate data, QC laboratory results and importation statistics. Experiences in Myanmar (ADB/WHO-SEARO) showed that building a IRIMS database using open source software takes about a year of work, involves an embedded regulatory consultant and IT experts; overall costs are about USD150,000 (V. Reggi, communication). It could possibly be built for the Kyrgyz Ministry on the model used by ADB with the WHO and CORE/NUS in Myanmar[32] at a lesser overall cost.

V. QC Laboratory infrastructure including equipment (National Center for Expertise (NCEM) and Department of Drug Provision(DDP) Bishkek)

45. In **Kazakhstan**, the NCEM has established a network of (8) laboratories across several cities to tests medicine samples being imported from different border points (series testing of registered medicines). The central laboratories (Almaty and new location in Astana) conduct analytical testing of samples submitted for applications (pre-market testing of samples). The Pharmaceutical committee in Astana has access to infra-red based screening tools to conduct check on medicines during inspections. The QC laboratories of the NCEM have been equipped with ('modern') equipment under a wider sector reform project financed by the World Bank and implemented by the Republican Center for Health Development (RCHD) under the Ministry of Health[33].

46. The NCEM Director of the Almaty branch allowed a general walk-through of the QC laboratory located at Baytursynov str. 40; the Almaty laboratory generally looked appropriately sized, spaced over several floors, rooms having appropriate laboratory furniture, equipped with calibrated instruments and several HPLC systems, dissolution testers, and spectrophotometers. Certification of calibrations, SOPs and lab journals were present on work benches, and areas and offices equipped with computers, that all appeared well maintained.

47. The NCEM has a fully capable internal service and calibration department (8 staff) for routine maintenance of equipment and instruments in the QC laboratories; for its main operations, doesn't depend on outside contracted services. The NCEM deputy Director informed that all NCEM labs are ISO/IEC 17025 certified by the National Center for Accreditation[34] a process that Kazakhstan started in 2008 (which NCEM added, was before Russia did). The Almaty laboratory has in addition obtained a GLP accreditation from Slovak authorities and received an approval from the European Directorate for Quality of Medicines which means it becomes part of the European laboratory network (GEON[35]) as an associate member[36].

48. Across the border, the infrastructure of the main laboratory in **Bishkek, Kyrgyz Republic** is of a sub-optimal design and critical equipment is missing or not well maintained. A scan of available

[32] ADB Briefs No.99 September 2018

[33] USD4.7 million budget over 7 components (report No: ICR00003816 accessed at World Bank DC site); the pharmacy policy review was done in a twining project with EHG, Denmark; and implemented several policy elements, national formulary, therapeutic committees, medicine pricing unit, medicine expertise center, quality control).

[34] www.nca.kz accredited by ILAC (https://ilac.org/) the international organization that operates in accordance with ISO/IEC 17011 for accreditation national bodies.

[35] The Commission of the European Union (EU) and the Council of Europe decided on 26 May 1994 to create a network of official medicines control laboratories (OMCLs). This network (GEON) amounted to a new collaboration in the area of quality control of marketed medicinal products for human and veterinary use.

[36] https://www.edqm.eu/sites/default/files/geon_terms_of_reference_annex_3_list_of_geon_members.pdf.

(and missing) laboratory equipment is summarized in annex which shows that limited range of equipment is actually in a state of use, for most of these one unit only is present without back up, with other equipment broken down, lacking maintenance service, outdated software or being obsolete.

49. Insufficient budget support results in conducting pharmaceutical analysis on samples provided by applicants with uncertified analytical reference standards. ISO/IEC 17025 certification of the QCL was obtained from the National Accreditation Center in 2017. Overall the metrology in place for calibration of instruments is a good basis for a quality control laboratory, but the laboratory is found of insufficiently qualified as a pharmaceutical QLC[37]. This was corroborated by interviews with stakeholders who informed that there is little confidence in what the DDP or the QCL is doing, particularly in the assurance of generic medicine quality (KMSA, Medical Academy, the Center for Dermatology and Venerology).

50. The Medicine Department in the Ministry of Health in the Kyrgyz Republic organized our visit to their National QC laboratory located in Bishkek at 25 Akhunbaev Str. 186. A first general tour of the premises showed that the building is designed for basic laboratory (testing) purpose with different rooms on ground floor and 1st floor for chemistry and instrumentation and storage room in the basement. Areas were manually monitored for temperature levels below 25°C. The set-up of the building seemed workable but is less than ideal in design, lay-out and size to ensure efficient workflows and adequate office and break spaces for analysts.

51. The laboratory infrastructure in Bishkek is not meeting ISPE standards which is regarded as the guiding design standard in the regulated pharmaceutical industry for a QC laboratory that complies with Good Control Laboratory Practice (GCLP). GCLP is the QC laboratory standard as defined in Good Manufacturing Practice (GMP) standards for the manufacturing and control of pharmaceuticals and is used by the WHO for pre-qualification of QCLs. In 2017 the Laboratory however obtained a ISO17025 certification from the National Center for Accreditation (KCA)[38]. Calibration services for instance for weighing balances and pipettes are routinely provided by the "National Center for Standardization & Metrology" that falls under Ministry of Economic Affairs [39]. This Center also advices the laboratory not to use certain instruments in case the calibration fails or cannot be performed with the required accuracy. The KCA is the sole International Laboratory Accreditation Cooperation (ILAC) accredited ISO certification body in the Kyrgyz Republic.

52. The KCA is mainly focusing on calibration of instruments, presence of SOPs and training of staff in the ISO audit of a MOH QC laboratory. Achieving the ISO standard is however not simply equivalent to complying with GCLP[40]. The ISO certification does not cover e.g. maintenance of equipment, method validations or qualification of analytical reference standards when these are not laid down in a formal SOP. A misunderstanding between ISO and GCLP is not uncommon in many countries and in general the route to WHO Pre-qualification based on GCLP is recommended for QCLs that provide testing of pharmaceutical products. If funding can be arranged, the USP (which already has a similar project – Promoting the Quality of Medicine (PQM)- running for years in Kazakhstan) is in principle available to perform a gap analysis and produce a road map for the Bishkek laboratory with more longer term assistance if needed.

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[37] A voluntary *conformity* with the ISO standard for the competency to carry out tests and or calibrations, does not cover a regulatory *compliance* that normally applies to a pharmaceutical test laboratory in a GMP environment. ISO standard is not intended to be used as the [sole] basis for certification of laboratories.

[38] www.kca.gov.kg accredited by ILAC (https://ilac.org/) the international organization that operates in accordance with ISO/IEC 17011 for accreditation national bodies.

[39] The World Bank supported Kyrgyz with the acquisition of two Metrology labs and establishing the National Accreditation Center (FY07; Reducing Technical Barriers for Entrepreneurship and Trade). Source CPS the Kyrgyz Republic FY14-FY17 Report No. 78500-KG, Annex 2 CAS FY07-10 and Interim Strategy Note, FY12-13.

[40] The WHO guideline for Pharmaceutical QC laboratories provide detailed guidance performing quality control of medicines that are consistent with the requirements of the WHO guidelines for good manufacturing practices and with the requirements of the International Standard ISO/IEC 17025 http://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodpracticesPharmaceuticalQualityControlLaboratoriesTRS957Annex1.pdf):

VII. QC Laboratory Capacity (NCEM and DDP Bishkek)

53. **National Center of Expertise Medicines (NCEM) Kazakhstan**. According to verbal information the NCEM handles thousands of samples per year to test medicines for conformance with the Kazakh Pharmacopoeia. The analytical testing is based on official analytical reference standards procured by NCEM from the European Directorate for Quality of Medicines and the United States Pharmacopoeia (USP). Of these around 5% to 10% are samples that have been tested as result of medical complaints or adverse medicine reactions reported to the NCEM[41]. The bulk of testing is for pre-market registration work and 'series' (i.e. batch) testing at importation. The testing done for post-market surveillance by prospective sampling and testing of medicines in the market, is relatively small which to some extent weakens the overall quality assurance of medicines.

54. **Department of Drug Provision and Medical Equipment (DDP) Kyrgyz Republic.** As result of the weaker laboratory infrastructure and limited staff numbers a sub-optimal QC capacity is reflected by a backlog in testing of pre-market samples. Delay in testing[42] causes a delay in the registration process which for some products can become an access barrier. For other less essential products it means a delay to market (sales) which could be equally disputed by applicants on commercial grounds. The inefficiency is seen in the reporting of test failures over the past years which are for the most part described as visual of a pH value only i.e. non-analytical failures for which an expensive laboratory set up is not necessarily required[43].

55. There are twenty employees in the Bishkek QC laboratory among them sixteen chemical analysts; only two of them are qualified to work on High Pressure Liquid Chromatography (HPLC) and two are qualified in microbiology. The DDP needs to develop more effective procedures in procurement of equipment including maintenance contracts to avoid protracted downtime of critical equipment like HPLCs which directly affects the testing capacity/output. Procurement should include exploring options to lease equipment from vendors which in principle would solve the issues of maintenance and spare parts and reduce downtime of equipment to zero. Vendors may however be reluctant to offer lease agreements if there is no financial back up. Under ABEC, the ADB could coordinate such back-up with Government as part of a larger financing package for the QC laboratory.

56. To implement the 'Medicines Program' the DDP has published a **Plan of Action** (POA) on its website[44] which proposes major updating of all pharmaceutical policies including establishing a State Pharmacopoeia of the Kyrgyz Republic that contains the basic quality standards of medicines aligned with world's leading pharmacopoeias. The WHO office in Bishkek is assisting the DDP to find ways for getting a better grip on policy implementation based on the, rather overwhelming, action plan. An Institutional Development Plan is being finalized by the WHO with the DDP and MOH (expected by late 2018 or early 2019) in which an Inspectorate, Post-market Surveillance and Quality Control are expected to be highlighted as key QA elements for which adequate capacity in the DDP needs to be realized over the next years.

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[41] The Committee has set up website and hot line purposely to encourage the medical profession and public to make reports on unexpected or severe side effects, or experiencing ineffective medicine. For instance, NCEM informed verbally that it evaluated and tested 45 samples as result of side effects/ADRs in past 6 months.

[42] In the first half of 2018, a total of 1597 samples were registered (1170 for import certification, 413 for new applications, and 14 for purpose of re-registration). Of the total, 1444 sample tests were completed (350 samples among these were carried over from 2017), and 419 tests were still ongoing (which included 50% of the new applications).

[43] QC failures in 2017: 25 test failures in total of which 3 were products originating from Russia (1 riboxinum rr / in 20mg / ml and 2 salbutamol inhalers) were rejected on basis of not being registered in the Kyrgyz Republic; 14 other products were rejected based on defects in the 'marking' some with also a wrong pH measurement in case of glucose solutions, one product was rejected based on shelf life and one injection was rejected based on density. QC failures in n 2018 (first half): 25 test failures: three were samples of an identical batch of one product Nohshaverin ""OZ"" rr d / and 20mg / ml 2 ml; origin Ukraine), that was rejected because it was found not registered. Another product was rejected due to short remaining shelf life (3 months); another 15 samples failed due to either packaging, visible damage or label information including products from Abbott, Pfizer and Sanofi. One sample of Viferon rectal (source Feron, Russia) failed on low assay of ascorbic acid, /Nicotine-ta' (source Khimfarm, Kazakhstan) failed on a mismatch of the pH value.

[44] PLAN OF ACTIVITIES [ACTION] on the implementation of the Program of the Government of the Kyrgyz Republic on the development of the circulation of medicines in the Kyrgyz Republic for 2014-2020. The Program and Plan of Actions for its implementation will contribute to implementation of the objectives of the National Health Sector Reform Program "Den Sooluk".

2. **Development partner support** (for Quality Assurance of Medicines)

57. A Joint Annual Review (JAR)[45] was carried out in the Kyrgyz Republic in 2017 to assess the main achievements and implementation of the Action plan of the Den Sooluk Program for 2016; and agree on priorities for the remaining two years 2017-2018. The JAR was jointly conducted by teams from the Government of the Kyrgyz Republic and development partners (DPs), most notably the Ministry, MHIF, Ministry of Health, KfW, GIZ, Swiss/SDC, GFATM, GAVI, UNFPA, UNICEF, UNAIDS, USAID, WHO, and the World Bank.

58. The World Bank has supported QCLs in Kazakhstan with laboratory equipment which has now been closed. The WHO (in the Kyrgyz Republic) and the USP (Kazakhstan PQM project) are currently involved in strengthening medicine quality assurance.

I. World Bank (WB)

59. The World Bank has been supporting the **Kazakhstan** Government with a loan to implement a Pharmaceutical Policy Reform process that covered a period 6 years. The project has resulted among others in the implementation of an online Kazakh National Formulary (KNF), a system for pharmacovigilance (reporting yellow cards) and support to procure and install modern analytical equipment in the main NCEM laboratories[46]. There is no current WB support in the area of Pharmaceutical Quality Assurance.

II. World Health Organization (WHO)

60. In the **Kyrgyz Republic,** the WHO supported the drafting and revision of the health technology (medicines and medical devices) regulatory framework. This update of the legislation is a critical point which will significantly improve the regulatory environment and ensure the quality and safety of medicines circulating throughout the country. A self-evaluation of the National Regulatory Authority, with support from international experts, was conducted in 2017 (using WHO Global Benchmarking tool) followed by development of an Institutional Development Plan (being finalized, expected by end of 2018). According to verbal information the functioning of a competent and adequately equipped Quality Control laboratory will be a priority to implement effective medicine regulation.

III. United States Pharmacopoeia (USP/USAID)

61. The United States Pharmacopoeia is assisting NCEM QC laboratories in **Kazakhstan** to achieve WHO Pre-qualification and (selected) Pharmaceutical Manufacturers to achieve international (WHO) GMP levels. PQM is a time bound project (2019).

IV. The Global Fund

62. Global Fund grants that fund health products, and particularly pharmaceuticals will as per the Global Fund QA policy, include budget lines for performing quality control activities on pharmaceutical supplies post-marketing. The past grants were similar in size (USD7 million) which under pharmaceuticals, included mainly second line medicines for treatment of MDR tuberculosis for both countries and all ARVs for the Kyrgyz Republic (equal to a QA budget annually of USD50,000 in Kazakhstan and around USD100,000 in the Kyrgyz Republic). It was not clear from program nor from Global Fund team in Geneva whether these budget lines were actually used for the purpose of quality assurance.

63. The Global Fund furthermore supports tuberculosis diagnostics for the NRL in Bishkek and some minor HIV laboratory supplies in Kazakhstan. Kazakhstan already funds its own ARVs and is not dependent for HIV treatment on outside donors. It was not 100% sure (GF team) whether Kazakhstan will also start to cover second line tuberculosis medicines from its State budget. the Kyrgyz Republic government has committed to start funding first line tuberculosis medicines as well

[45] JAR accessed at: http://www.nationalplanningcycles.org/sites/default/files/planning_cycle_repository/the Kyrgyz Republic/krygzstan_jar.pdf

[46] Reference: HEALTH SECTOR TECHNOLOGY TRANSFER AND INSTITUTIONAL REFORM (P101928) Implementation Completion Report No: ICR00003816, December 2017.

as (part of) ARVs in the next years; (procurement of 1st line tuberculosis medicines started already), it will maintain GF funding for second line tuberculosis medicines procured via the GDF in Geneva.

V. Centre for Disease Control (CDC/USAID)

64. CDC is assisting with the Road Map for Introduction of the International Health Regulations (IHR) and Global Health Security Agenda in the Republic of Kazakhstan for 2018-2022 (among other topics: National Laboratory service, biosafety and biosecurity, and Antimicrobial resistance and Information systems). In the Kyrgyz Republic USAID is funding the HIV Flagship 5 years' project ending November 2020 with a budget of USD21 million) to help the country achieving its ambitious 90's targets by 2020. USAID is supporting Project HOPE in both countries to improve tuberculosis control and treatment of tuberculosis and MDR tuberculosis in migrant populations.

3. Funding of Quality Control activities

65. Normally government funding of a NRA needs to be adequate to complement budgets to a sufficient level for carrying out the duties in a transparent, timely and professional/responsible manner. The fees charged for registration and testing are often lower than the real costs so that the financial sustainability [of a NRA] is not entirely dependent on the fees charged for services. Regulatory offices and QC laboratories under a Ministry of Health are thus expected to be funded for a substantial part by Government budgets (building, utilities, salaries) which is not directly linked to fees In the Kyrgyz Republic, the QCL is financed only against the extra-budget funds (residual budget) which is a weak point to bring QC standards and QC capacity up to the level that is required for effective quality assurance. The recommendations in next section (4) of the report therefore focus on bridging that financial gap particularly to help the Kyrgyz Republic to be at par for medicine regulation with Kazakhstan and other EAEC members by 2025.

I. Fees registration

66. In **Kazakhstan**, the NCEM published the price list for product registration and QC testing (quality/safety) for foreign products and domestic manufactured medicines between USD4,500 and USD2,500 depending on whether the formulation contains one or multiple active ingredients. The fees for domestic manufactured medicines are between 4 to 6 times lower compared to the fees paid by foreign applicants which is to promote a domestic preference. Registration of additional dosage forms of the same product are costed at 80% of the initial fee, and additional pack presentations at a marginal 2%. In the **Kyrgyz Republic** registration fee is USD1,500 per product, comparable to the fees in Kazakhstan adjusted for a 3 to 4 times smaller market. Re-registrations cost USD500.

67. Fees have been capped by the Government in both countries for a number of years. Pricing is currently being reviewed by both to align with the common market under the EAEC.

II. Fees testing

68. Quality control i.e. testing of samples in **Kazakhstan** appears to cost between $157 and $204 depending on whether the formulation contains one or multiple active ingredients. The official fees are not covering the real costs, and indeed quite low compared to what commercial laboratories would charge. At this level of fees for QC testing, it could mean the actual testing is limited to e.g. only an Identification or an assay. It seemed though that NCEM in Kazakhstan is supported with budget through the Pharmaceutical Committee in MOH generated through registration fees or otherwise. In addition, capital investments for all equipment of past years have been funded by a WB loan to the Government. In the **Kyrgyz Republic**, the fee for analytical tests is a blanket USD23 which is even more low. Without government funding (except for salaries of staff) it is not sustainable for full compliant QC testing with a sufficient level of GLP (or GCLP) i.e. qualified and maintained equipment, trained personnel, validated methods, and use of certified analytical standards, timely replacement of equipment, updating technology, purchase of pharmacopoeia subscriptions… etc.)

III. Inspection fees

69. According to NCEM website the assessment of the ‘conditions of production’ in Kazakhstan costs only 101,165 tenge (which is less than USD300), domestic plants only for local GMP (mandatory since 2018). KGZ has no active inspection unit.

4. Recommendations to improve quality assurance

I. Policy making and institutional strengthening

70. Create value for money, make use of each other and showcase a model of collaboration between QC laboratories that can be replicated by other members in the EAEC. Kazakhstan specializes in QC of cancer medicines, heart and cardiovascular medicines while Bishkek specializes in testing of antibiotics, anti-tuberculosis medicines and medicines to treat parasitic infections and maternal conditions. The QC testing is intended to be supporting pre-market testing of product samples, 'serial' testing at import (risk based) and post-market surveillance (risk based)

> Condition: establish MOUs and create compatible databases for exchanging information to be put in place between NCEM and the Kyrgyz DDP. Assist the Ministry of Health in the Kyrgyz Republic to implement an IRIMS (Regulatory data information management system), preferably in cooperation with the NCEM in Kazakhstan to align systems, alternatively as a system based using open source software (Myanmar FDA model).
> Condition: Bishkek needs financial support to establish QC capacity (see under infrastructure)

71. Addressing HIV/AIDS at the city level under UNAIDS "Fast Track Cities Initiative". Consolidate resources and efforts (through block grants for NGOs) to create a tandem of two fast track cities – unique in Central Asia – using the 'joint urban advantage'. ADB financial support could be a catalyzer; experience from Kiev in Ukraine shows that a clear actionable policy to meet the '90 targets' by 2020, will interest global partners to participate and provide support the cities with for instance funding for procurement of tests and anti-retroviral medicines though UNICEF.

> Condition: Like Almaty already did, Bishkek would have to sign the Fast Track City Declaration and work with partners and NGO's (in a Fast Track City consortium) to align procurement and supply of HIV commodities, and with ABD financial support, create a common supportive nondiscriminatory environment and safe space in both cities to accelerate meeting the '90 targets' by 2020.
> Condition: Governments of the two cities have to be willing to use new approaches and innovative tools to increase testing among key populations.
> Condition: USAID has to be on board as they are active in both countries in are of HIV.

72. A concern is emerging globally around the transitioning of countries away from Global Fund funding to government led procurement systems for TB medicines (MSF Press release November 2018). The first-line tuberculosis medicines in Kazakhstan are procured through the national system (SK Pharma) with tablets supplied from typically non-GDF sources i.e. that are not WHO pre-qualified (domestic manufacturers and imported from Russian factories). The Kyrgyz Republic was receiving their tuberculosis medicines through the GDF from only WHO pre-qualified sources under the Global Fund grants. Whereas the tuberculosis medicines procurement has already shifted to become a Kyrgyz government responsibility there is a potential opportunity to establish a GMP production facility in the Bishkek area; this would be based on using GMP knowledge from a Kazakh manufacturer (and other potential partners) that can manufacture rifampicin based tuberculosis combination tablets and non-rifampicin tablets for both (and other EAEC member states) in the recommended adult and pediatric dosage strengths and in standardized packaging.

> Condition: one of the leading Kazakh tablet manufacturers that has already achieved an acceptable level of GMP has to be willing, with financial support from ADB under ABEC and if needed a technical joint venture with a company that already manufacturers WHO pre-qualified tuberculosis tablets e.g. in India), to establish a new GMP facility in Bishkek, the Kyrgyz Republic. Once certified for GMP by the WHO with pre-qualified products the Kyrgyz/Kazakh venture would have a CIS and global market.

73. Support the Kyrgyz Ministry with the (financial) means to complete the implementation of its Plan of Action and the Institutional Development Plan (IDP) developed with the WHO for updating legislation and strengthening regulatory capacity of Medicine Department in the Ministry of Health,

including set up of Pharmaceutical Inspectorate (budget to finance the NRA is to be discussed with WHO office when the IDP is finalized, expected end 2018 or early 2019). The Kyrgyz Pharmaceutical Inspectorate which will be a new unit in the Medicine Department could be equipped with modern (hand held) IR/RAMAN screening devices, financed with support from the ADB to start qualitative/semi-quantitative screening of medicine packs at import and randomly from the circulating in the Bishkek market to detect fake and or counterfeited products being sold. Subsequently these can be safely disposed of just like expired or otherwise unused medicines. Investment in an industry scale incinerator to be installed at a selected location, will be part of the financing package.

Condition: the Kyrgyz Ministry of Health must make progress with passing updated legislation through parliament that enables the legal basis for conducting (unannounced) pharmaceutical inspections by the Medicine Department in the distribution chain. The objective of these inspections is to enforce licenses in the sector and to check: i) storage and distribution practices, ii) registration status of medicines in stock, iii) generic substitution (where it concerns medicine benefit packages) and use of prescriptions for antibiotics, iv) removal and disposal of expired medicines v) removal of unregistered or illegally imported medicines, and lastly vi) to conduct prospective risk-based sampling of random medicine packs for control testing.

II. Technical Capacity building

74. Engage the United States Pharmacopeia (USP) for technical support to the QCL in Bishkek (through Ministry of Industrial Development) to make a full gap analysis (short term) and develop a road map to WHO Pre-qualification based on commitment for implementation of above policy recommendations (mid-term). USP is providing the same technical assistance for a number of years already in Kazakhstan with Russian speaking staff. USP would thus be a preferred partner considering benefits of a consistent approach between the countries to achieve WHO PQ status and the possibility it would offer to conduct cross trainings between QCL in Bishkek and QCL in Almaty under the same provider.

Condition: USP has in principle expressed great interest to do this knowing that it might be yielding such an impact for the Kyrgyz Republic; the funding for their assistance could come through either the Ministry or from ADB direct; a contract terms need to be discussed and agreed in much further detail with the USP people once decisions are taken by the Ministry to go in this direction.

III. Infrastructure/equipment

75. It is recommended to provide support for ADB financing of missing analytical equipment for the laboratory in Bishkek (budget maximum estimated USD1 million); critical equipment must be financed based on purchase with annual maintenance plans in service contracts or lease options (to be explored with vendors, service fees annual total sum paid when full period was without down time). Eventually when the QCL is functioning and equipment is running well the QCL should establish its internal maintenance and engineering unit. The Medicine Department in the Ministry with the Bishkek laboratory has prepared a list (in Russian language) which needs to be reviewed against the annex of available equipment and the WHO list of recommended QC equipments for a medium sized laboratory (report annex).

Condition: Kyrgyz government commits to achieving WHO PQ standard with USP as TA (above). Robust annual maintenance plans, post warranty must be part of the specification, when equipment is being procured and budget reserved for that purpose; for smaller equipment, a separate service/engineering unit should be facilitated to perform routine maintenance on less sophisticated equipment, and utilities. A dedicated QA function in the laboratory is required to supervise that lab technicians perform their daily and weekly procedures (cleaning, and operation, routine calibration, presence and use of log books, check on outside calibration due dates and check on preventive maintenance due dates) correctly.

Condition: service contracts that include maintenance plan and spare part management for critical equipment so to minimize downtime during the normal equipment life cycle must be budgeted for and must be enabled by the central procurement regulations.
Condition: sound financial management principle should be adhered to so that critical equipment is depreciated annually and replacements are budgeted for in due time.

76. Finance a new construction for a new, better designed QC Laboratory (ISPE standard) in Bishkek (budget USD5 million, depending on size/architecture of building/land plot). Sufficiently large set up laboratory that operates with at least 3 to 5 HPLCs (for which at least 5 technicians are qualified) and at least 3 dissolution testers, a fully equipped classified microbiology section with qualified LAF/Bio safety cabinets, in compliance with safety standards and common utilities.

Condition: The Kyrgyz Government has to allow a general increase in the fees charged by the DPP for pre-market testing and post-market surveillance. QCLs charge on average a cost between a few hundred dollars up to a thousand dollar for more sophisticated tests to cover recurring laboratory costs. In budgeting, e.g. in funding requests, taking an average of USD500 per test is usually accepted and this is what a new constructed facility should be expecting as basic revenue per test. The 5 million dollars' investment can be recovered for 50% under an agreement with the Government that allows DPP to charge applicants and importers an average of USD800 per test in the first 5 years of operation followed by an average cost of USD500 thereafter. The other half (between USD2 – 2.5 million) can be proposed as a soft loan to the Government.

77. Finance the construction of a tableting plant (pharmaceutical factory, ISPE standard) for manufacture of anti-tuberculosis and other (EM) tablets in joint venture with a Kazakh GMP company to achieve product pre-qualification status with its location in the Bishkek area (USD10 million depending on size and number of production lines, portfolio of products, market survey). A GMP factory within the Kyrgyz Republic would be having an impact on the import market, attract staff and offer a great advantage to the new Pharmaceutical Inspectorate in the Ministry and to the Kyrgyz standing in the EAEC Committee. Some international operating manufacturers of tablets that have already obtained WHO pre-qualification will be interested to participate in a joint venture with the selected Kazakh company which would help to realize the project in a shorter time.

Condition: The Kazakh and Kyrgyz Governments have to be willing to enter a joint venture with private sector that enters into a loan agreement with ADB to finance a GMP plant. The cost is an estimated 10 million dollars at this stage which, once Governments express an interest, needs to be developed in more detail in a next study.

IV. **Short term** technical advice to strengthen regulatory effectiveness under ABEC

78. Under the ABEC corridor people are moving between Bishkek and Almaty; they may be using pharmacies on both sides to obtain the medication. Their treatment outcome may be affected if some medicine on one side is not the same (in terms of quality) as the medicine on the other side. For example, a person with high blood pressure takes daily medication and travels regularly between cities; he lives in Almaty but while in Bishkek to set up business and attending meetings ran out of his usual tablets; he writes down the medicine name and asks for the same tablet in a Bishkek pharmacy; the pharmacy in Bishkek sells him the same medicine; but after few days the man develops complications and decides to return to visit his clinic in Almaty.

79. The regulatory capacity of the Medicines Department in the Kyrgyz Republic should focus on monitoring the quality of registered medicines, especially those products/sources which appear on the EML and are registered in the Kyrgyz Republic but which have not been registered [from that source] in Kazakhstan.

a. A quick scan should be made between the two medicine registers to list medicines/sources that should be targeted for sampling (if a full down load in Excel is available from both that could be done in less than an hour).

b. The Kyrgyz Ministry should issue a decree that gives Medicine Department staff the legal power to take medicines (minimum quantity) samples from hospitals and pharmacies.

80. Because the QCL in Bishkek at the moment is not optimally equipped, for the short to mid-term (2018/2020) a MOU (or service contract) is needed between NCEM in Almaty and Medicines Department in Bishkek for samples of these medicines to be tested by NCEM laboratory for compliance with a valid pharmacopoeia using qualified reference standards. Test should include (as applicable per dosage form) at least: identification test, quantitative assay, disintegration test, dissolution tests, water content and sterility / endotoxin levels.

5. Annexes

I. Terms of Reference (Pharmaceutical Quality Assurance Expert)

Scope of Work
The Pharmaceutical Quality Assurance Expert will assess the current processes and laboratory capacity for pharmaceutical quality testing in Kazakhstan followed by a mission in the Kyrgyz Republic in August, to develop recommendations on: ***i)*** *establishing a new reference lab for quality testing of pharmaceuticals,* ***ii)*** *the processing required to share the lab capacity among Central Asian Countries,* ***iii)*** *regulatory reforms required for countries to allow quality testing in a neighboring country,* ***iv)*** *establishing an integrated regulatory information system in which the reference lab feeds into so that results from quality testing immediately inform National Regulatory Agencies.*

Expected output

1. Assessment of capacity, policies and infrastructure (including equipment) available for quality assurance of medicine in Kazakhstan, and the Kyrgyz Republic including: • an inventory of existing facilities, equipment and personnel; • a summary description of the functional status and capacity to respond to testing; demand of existing equipment and personnel skills;

• information about the existence and suitability of national post-marketing control plans; • the total number of samples tested broken down by type and purpose of testing; • information about action taken on the basis of testing results; • amount and sources of funding; • existence of development plans to expand/improve testing capacity.

2. Development partner mapping This entails providing information on activities undertaken or planned by development partners (e.g. WHO, USP) involved in supporting medicine regulatory authorities and QC labs. If available, project documents and reports should be collected.

3. Description of funding of medicine quality assurance The consultant should try to obtain detailed information on the current and envisaged funding situation of all medicine regulatory activities aimed at ensuring quality of marketed pharmaceuticals. This encompasses assessment of marketing authorization applications, inspection of manufacturing and other supply chain facilities, and laboratory testing. The information should describe amounts and sources of funding.

4. Development of recommendations to strengthen medicine quality assurance through capacity development, policies and infrastructure investments (including equipment lease and maintenance models). This should encompass high-level recommendations as well as specific technical advice to strengthen regulatory effectiveness through optimization of use of available resources and leveraging bilateral cooperation (between KGZ and KAZ).

II. Field schedule

Astana (26 June - 30 June) facilitated by Mr Almas Baitenov

- Meetings: consultant participated in eight meetings which included the Ministry of Health, the National Center Expertise Medicine (NCEM), the Republican Center Health Development (RCHD), SK Pharma (Government sole purchaser of medicines) and the World Bank office in Kazakhstan which has supported a Pharmaceutical Policy Reform process over the past years.

Almaty (02 July -11 July) facilitated by Mr Almas Baitenov

- Meetings: consultant participated in eight meetings which included the NCEM QC laboratory (general tour of premises), the Republican Centers on tuberculosis research and AIDS control, the Almaty City Health Department, the Central Clinic Hospital, USAID team and CDC/Central Asia Regional Office. Meeting with KNCV country office in Almaty on 9th July.
- Assessment of NCEM laboratory located at Baytursynov str., 40 on Tuesday 10th July. The purpose of the second visit as per our introduction was to conduct a review of more detailed QC data and to compile an inventory of existing equipment and personnel. Unfortunately, this was not possible for NCEM due to perceived confidentiality issues and needed clearance from the committee in Astana. NCEM was nonetheless helpful in our discussions that followed which resulted in an email dated addressed to Ms. Tatyana Abramova on the same day to follow up (in writing) on questions pertaining to statistics, post-marketing surveillance, strategic plans, and financial sustainability which during the visit were referred to the Pharmacy Committee, the NCEM Director in Astana and the EAEC Committee.
- Teleconference calls with Project HOPE (tuberculosis) (10th July) and with a PQM consultants team (11th July) involved in support to QC laboratories in Kazakhstan to attain WHO Pre-qualification status and improving GMP quality standards in domestic manufacture of (anti-tuberculosis) medicines.

Bishkek (06 August – 18 August) facilitated by Mr Djakypov Kylychbek

- Meetings: consultant participated in series of meetings which included the Ministry of Health, Republican Diagnostic Center, Republican tuberculosis center, Republican HIV center, the Epidemiological Surveillance unit and the infectious Disease Control center, the Department for Drug Provision and Medical Equipment, the Medical Academy, the National Center for Accreditation (KCA), a range of private sector laboratories (clinical diagnostics) and partners (WHO, UNICEF, and KfW). The latter (German KfW bank) co-financed a new BSL-3 tuberculosis reference laboratory in Bishkek that has been functioning well (as designed) for the 5 past years and is aiming to become a WHO tuberculosis supranational laboratory. The World Bank office in Bishkek was not available to meet us due to illness of staff member.
- Assessment of the MOH Quality Control laboratory located in Bishkek at 25 Akhunbaev Str., 186. The laboratory is ISO-17025 certified by the KCA (the Kyrgyz Center for Accreditation). The purpose of our visit was (as in Almaty) to review the existing equipment, and capacity of the quality control function in the medicine regulatory process. All equipment present was reviewed for its (calibration) status.

III. Equipment scan Bishkek QC lab

Equipment status (calibration calendar available 37 items)

Working status/calibrated	**need some repair**	**out of use/obsolete**
AREA 1		
Water bath (1)	Disintegration tester	TLC UV254 view chamber
Friability tester (1)		Muffle furnace
Shaker (2)		Hot plate
Visual inspection unit (1)		Moisture balance
Weighing balance (up to 3 kg) (1)		Standalone A/C unit
Microbalance (1)		
pH meter (1)		
Cutter (herbs) (1)		
AREA 2		
UV Spectrophotometer (1)		Polarimeter (1)
Microscope (1)		Refractometer (2)
Magnet mixer		Melting point apparatus (1),
sieves (multiple)		
Glass pipettes (not class A)		
AREA 3		
HPLC Agilent, installed 2014 (1) (HPLC)		Solution preparation unit
AREA 4		
Glassware dryer (1)		Distiller unit
		Milli Q water filtration (no filters)
AREA 5		
Dryers Memmert (2)		Sample Fridge (household
spec),		
Ultrasonic bath		
Centrifuge (repaired couple of times already)		
AREA 6		
	Dissolution tester (Erweka) (4 of 8 media vessels broken)	
AREA 7 (upstairs)		
Some type A glassware		HPLC (Waters) (2)
Microbalance		Refrigerator
Ultrasonic bath		
Centrifuge		
pH meter		
Millipore water filter		
AREA 8 (upstairs)		
		Spectrophotometer (Varian)
		Spectrophotometer
(ThermoSci)		
		Osmometer
AREA 9 (upstairs)		Coulter (particulate matter, sub visible)
		Shimadzu
		Melting point apparatus

AREA 10 (upstairs)
Microbiology suite, Media prep, LAF/BSC 20 years old, maintained by 1 person, incubators (lab furniture needs upgrade)

IV. Equipment list as recommended by WHO for a medium sized QC laboratory

Microscope 1 or 2
Equipment for thin-layer chromatography 1
Thin-layer chromatography multispotter 1
Developing chambers 6
Atomizers 6
Ultraviolet viewing lamp 1
Potentiometric titrimeter 1
Micro-Kjeldahl equipment (including fume flasks) 1
Soxhlet extraction apparatus (60 ml) 3
Pycnometers 2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml) 6 of each
Micrometer calipers 1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml) 6
Sieves (assorted sizes) 1 set
Centrifuge (floor model) 1
Shaker (wrist-action) 1
Vortex mixers 2
Water-bath (electrical, 20 liters) 2 or 3
Hot plates with magnetic stirrers 3 or 4
Vacuum pump (rotary, oil) 2
Vacuum rotary evaporator 1
Drying oven (60 liters) 2 or 3
Muffle furnace (23 liters) 1
Vacuum oven (17 liters) 1
Desiccators 2 Refrigerator (explosion-proof) 2
Freezer 1
Ultrasonic cleaners (5 liters) 2
Laboratory glassware washing machine 1
Water distilling apparatus (8 liters/hour) 1
Water deionizing equipment (10 liters/hour) 1
Fume hoods 2
Melting-point apparatus 1
Polarimeter 1
pH meters (with assorted electrodes) 2
High-performance liquid chromatograph with variable wavelength Ultraviolet/visible detector 3 or 4

Tablet hardness tester 1 and Friability tester 1

Ultraviolet/visible spectrophotometer, double-beam 2
Infrared spectrophotometer with pellet press 1
Agate mortar with pestle 1
Gas chromatograph (flame ionization, direct and static head space injection) 1 Refractometer 1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro determination of water) 2 Oxygen flask combustion apparatus 1
Disintegration test equipment (1 basket for 6 tablets) 1
Dissolution test equipment (for 6 tablets/capsules) 2