PQM Promoting the Quality of Medicines

Strengthening Manufacturing Capacity to Improve Access to Quality-Assured Essential Medicines

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About PQM

The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between USAID and USP. The PQM program provides technical assistance to strengthen medicines regulatory authorities and quality assurance systems and supports manufacturing of quality-assured priority essential medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

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Abbreviations

API	active pharmaceutical ingredient
BE	bioequivalence
CAPA	corrective and preventive action
CRO	contract research organization
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
ERP	Expert Review Panel
FPP	finished pharmaceutical product
GCP	good clinical practices
GDF	Global Drug Facility
GEP	good engineering practices
GMP	good manufacturing practices
HVAC	heating, ventilation, and air conditioning
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISO	International Organization for Standardization
LMIC	low- and middle-income country
NRA	national regulatory authority
NTD	neglected tropical disease
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PQM	Promoting the Quality of Medicines
SRA	stringent regulatory authority
TB	tuberculosis
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO PQ	WHO Prequalification
WHO	World Health Organization

Program Background

Since 1992, the U.S. Pharmacopeial Convention (USP) has worked cooperatively with the U.S. Agency for International Development (USAID) to help low- and middle-income countries (LMICs) address critical issues related to pharmaceuticals. The earliest program, the Rational Pharmaceutical Management Project, implemented and evaluated country-specific drug information resource programs in selected developing countries. Subsequently, the Drug Quality and Information program focused on medicines quality control and quality assurance systems.

Building on these previous efforts, the Promoting the Quality of Medicines (PQM) program helps to ensure the quality, safety, and efficacy of medicines essential to USAID priority health areas, particularly malaria, HIV/AIDS, tuberculosis (TB), and maternal and child health. The PQM program is USAID's response to the growing development challenge that substandard and falsified medicines pose worldwide. There is increasing recognition of the threat these poor-quality medicines pose to public health, especially in LMICs, and their potential to undermine decades of investments in global health, including those made by USAID.

Using a systems-based approach, PQM offers technical assistance to LMICs tailored to fit the needs of individual countries or regions. This includes building the capacity of national regulatory authorities (NRAs) to review and approve quality-assured essential medicines and to strengthen the ability of NRAs to protect their own population from poor-quality medicines through medicines evaluation, manufacturing inspection, and surveillance. PQM also supports national quality control laboratories through hands-on training and technical assistance to improve laboratory standards. This is in part to assist those laboratories in attaining internationally recognized certifications, such as International Standardization Organization (ISO) accreditation and/or World Health Organization Prequalification (WHO PQ). PQM uses a systems-based approach that also extends to medicines manufacturers. PQM also helps manufacturing companies improve their compliance with good manufacturing practices (GMP) and develop dossiers to submit to the WHO PQ program.

Over 25 years of collaboration with USAID, USP has supported more than 40 countries in Africa, Latin America, and Asia to improve the quality assurance of medicines.

1. Introduction

Progress toward achieving global health goals — including ending preventable maternal and child deaths, creating an AIDS-free generation, and expanding universal health coverage — hinges on the availability of quality-assured essential medicines. However, ensuring a sustainable supply of these medicines can be difficult. Often few or no GMP-compliant manufacturers exist to produce a particular essential medicine, leaving shortages or gaps in the global supply. Supporting pharmaceutical manufacturers to achieve compliance with international quality standards such as WHO PQ (WHO, 2017) can help to address issues related to the supply of essential medicines.

Pharmaceutical manufacturing and management is a complex endeavor. It involves multiple companies and stakeholders, a myriad of sites, complex multilevel supply chains, and many national and international requirements and regulations that must be met to assure the quality of medicines being produced. This is further complicated by strong competition within the industry and shifting market forces, which drive frequent supply and demand fluctuations.

Fortunately, multinational pharmaceutical manufacturers continue to refine processes that increase the efficiency, reliability, and quality of production and strengthen the global supply chain. These efforts have increased the availability of and access to life-saving essential medicines across the globe. The systems, structures, processes, and practices that ensure medicines are consistently produced in compliance with quality standards appropriate to their intended use and as required by the product specification are referred to as GMP (WHO, 2016). The effective implementation of GMPs underpins and helps to guarantee the safety, efficacy, and quality of medicines.

PQM works to strengthen the capacity of pharmaceutical manufacturers to produce quality-assured medicines and collaborates with manufacturers globally to address critical shortages or gaps in the supply of essential medicines. This technical report describes the support PQM provides to manufacturers provided and the technical approach employed.

2. Support to Manufacturers

PQM works directly with manufacturers around the world to achieve compliance with the regulatory expectations of stringent regulatory authorities (such as those in the United States, Europe, and Japan), the WHO prequalification program, and the Global Fund Expert Review Panel (ERP). PQM has trained 2,016 individuals in manufacturing since 2010 *(Figure 1)*. These individuals represent 111 manufacturers from 22 countries. The sections of the pie chart in Figure 1 represent the USAID country or regional funding streams that have supported this work. Although much of PQM's support is provided to manufacturers in LMICs, our support extends to other countries, especially when a critical shortage of an essential medicine is identified. Supporting local manufacturing is increasingly important as donors look to support countries in transitioning from donor-assisted activities to those that are funded and managed locally.

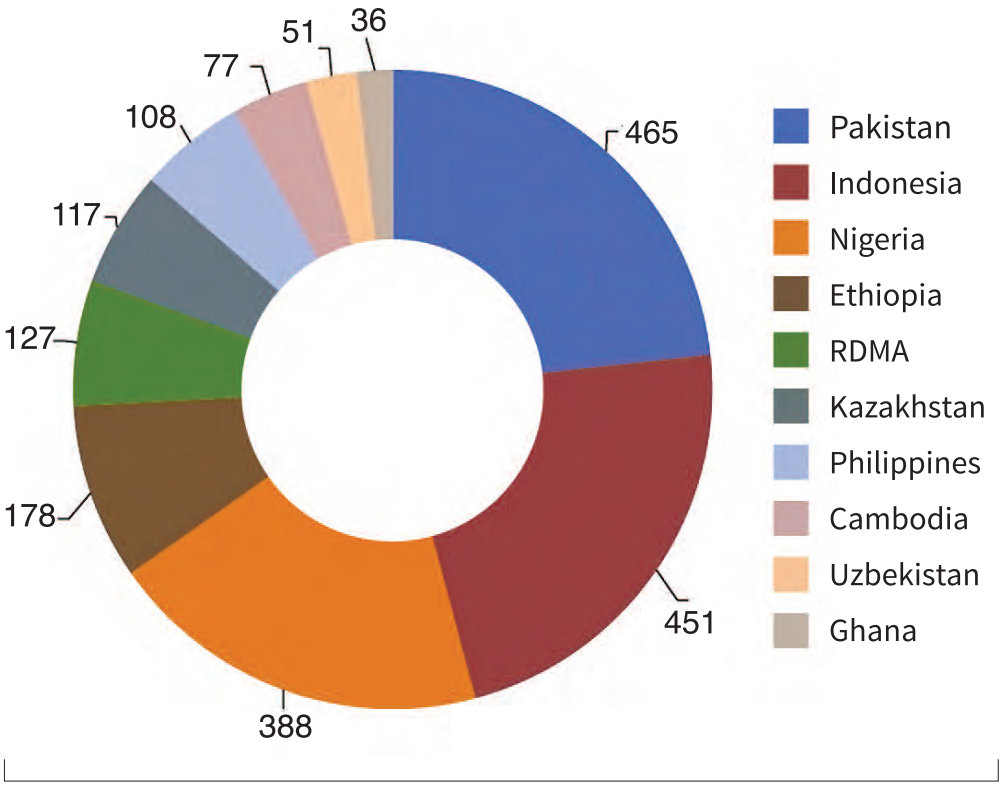

Figure 1: *Total individuals trained on GMP by country (2010 — 2017) N = 2,016*[1]

PQM staff members have deep expertise in regulatory systems and manufacturing. Several of PQM's technical experts have prior experience working in the pharmaceutical industry or with regulatory agencies or the WHO prequalification program. This understanding of the intricacies of the industry and the challenges facing manufacturers in LMICs enables PQM to provide appropriate, practical, and hands on support.

[1] Individuals attending more than one training may be counted more than once.

The technical assistance provided focuses on many disciplines within regulatory compliance, and recognizes that manufacturers face challenges unique to their settings. The PQM program works closely with each manufacturer in several areas, including the following:

- Support product research and development, scale-up, and technology transfer.
- Conduct onsite GMP assessment and mock audits.
- Develop and support the implementation of a corrective and preventive action (CAPA) plan.
- Provide technical training to support the preparation of quality dossiers.
- Support GMP compliance.
- Assess the compliance of clinical research organizations in the conduct of bioequivalence (BE) studies for priority essential medicines.
- Review and provide guidance on the design of BE study protocols prior to study launch.
- Provide continued technical assistance following submission of the dossier until the product has been approved.

However, supply is only one aspect of ensuring the availability of quality-assured medicines. PQM recognizes that strengthening the systems that underpin pharmaceutical manufacturing includes regulation. Therefore, PQM also provides technical assistance to national regulatory authorities and regional bodies to implement and institutionalize good dossier review and good inspection practices that facilitate the scale-up of local manufacturing, refine and strengthen local standards, and ultimately ensure that quality-assured medicines are available globally.

3. Technical Approach

PQM takes a pragmatic approach to identifying manufacturers that have the basic infrastructure and systems in place to support quality as well as the commitment to reach international levels of compliance. In addition to the use of Requests for Expression of Interests, PQM also hosts technical workshops on medicines quality. These workshops raise awareness about pharmaceutical quality and provide information to medicine regulatory authorities, pharmaceutical manufacturers, and other stakeholders on how PQM can help strengthen their medicines quality assurance systems. Among other topics, these workshops cover:

- WHO prequalification process
- WHO collaborative registration procedure
- Stringent regulatory authority (SRA) product approval
- Global procurement processes (e.g., those of the Global Drug Facility (GDF), UNICEF)
- Current GMPs
- Pharmaceutical management systems
- Cleaning validation
- Requirements of the Common Technical Document (CTD) format for dossiers
- Data integrity

An example agenda from these workshops is provided in Annex 1. Example of a Workshop Agenda. Participants typically represent pharmaceutical manufacturers, regulatory authorities, and other relevant organizations. PQM often partners with technical experts in the field, including those from WHO; the Global Fund for HIV/AIDS, Tuberculosis and Malaria; and GDF.

Over the course of the workshop, participants learn what underpins an effective quality assurance system; how to improve their internal system; and subsequently how to better position themselves for global, regional, and domestic supply of quality-assured medicines. Content is delivered through several mechanisms:

- *Presentations* from PQM staff, as well as external experts, on processes, standards, and guidelines relevant to pharmaceutical and regulatory systems
- *Case studies* and structured discussions on specific real world problems (see Annex 5. Case Study Example for an example)
- *Panel discussions* on trending topics in global manufacturing and regulation that allow participants to learn from and interact with global experts
- *One-on-one meetings* with PQM staff to discuss relevant topics in greater detail and explore opportunities for technical assistance

These workshops also emphasize and promote opportunities for participants to network and exchange ideas to improve an understanding of the challenges in different contexts and maximize learning from the experiences of others while developing a stronger grasp of the global pharmaceutical manufacturing landscape.

Importantly, workshops are not the only mechanism through which PQM identifies potential manufacturers. In certain situations, technical partners such as WHO and GDF suggest manufacturers that may have the necessary capacity to achieve international compliance but require targeted technical assistance.

Manufacturers interested in receiving PQM technical assistance must submit an expression of interest with supporting documentation. These expressions of interest are evaluated against strict criteria to determine if the manufacturer is an appropriate candidate for technical assistance. Figure 2 shows PQM's work flow for identifying manufacturers and providing technical assistance.

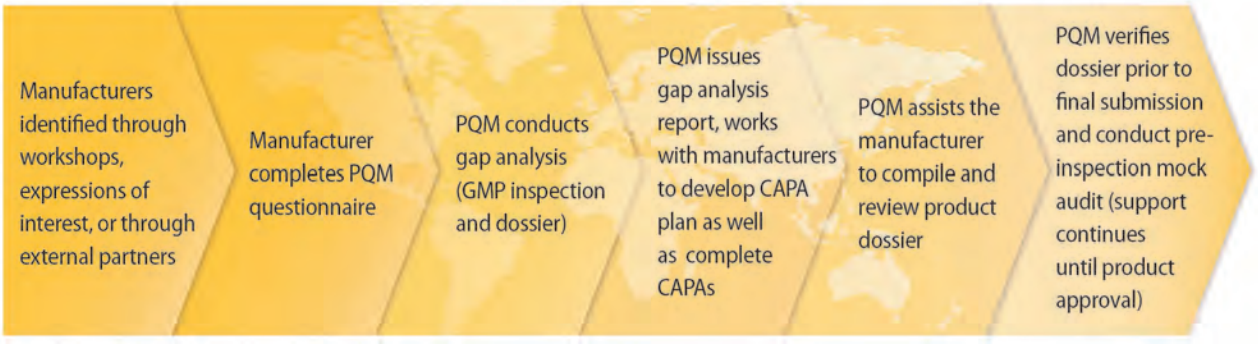

Figure 2: *Manufacturing services work flow*

After submitting an Expression of Interest, manufacturers are requested to complete a questionnaire, which provides baseline information to help determine whether the manufacturer has the potential to reach international levels of compliance. To obtain additional information on a manufacturer's capacity, PQM often conducts a desk review and an onsite GMP inspection for manufacturers that pass initial levels of screening. These activities provide the information required to make a preliminary decision on whether PQM can support the manufacturer. Three additional considerations guide the decision to work with a particular manufacturer:

- *Medicine.* PQM's mandate requires that technical assistance targets medicines that treat certain priority public health diseases. Our focus is on medicines that treat tuberculosis, maternal and child health diseases, neglected tropical diseases, and malaria. PQM provides support to manufacturers of both active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), focusing our technical assistance where it is most needed. For example, PQM provided support to a manufacturer to prequalify isoniazid API to address a global shortage of the FPP which is a critical medicine used in the treatment of tuberculosis.
- *Willingness to invest.* PQM's support is almost exclusively technical in nature. It is therefore imperative that a manufacturer has a commitment to investing in strengthening the infrastructure and systems that support quality assurance. For example, a well-designed and validated heating, ventilation, and air conditioning (HVAC) system is central to any GMP facility. If PQM's inspection identifies necessary improvements to the HVAC system, it is incumbent upon the manufacturer to address the required upgrades and maintenance costs.

- *Management commitment.* The commitment of senior management to develop and maintain products that meet international quality standards is critical for PQM technical assistance to the manufacturer to be effective. Investment in the production of medicines to treat infectious diseases is not ordinarily perceived to be as commercially lucrative as investing in lifestyle medicines or more prevalent non-communicable diseases. PQM researches the market forces shaping the supply and cost of priority public health medicines extensively. This enables PQM to articulate the business case and public need to produce these products which often helps secure management buy-in.

Assuming the operational and technical drivers exist, an initial gap analysis is conducted based on the onsite inspection and review of the product dossier. The gap analysis report is then used to develop a CAPA plan, which establishes timelines, outlines capacity-building activities, identifies and mitigates project risks, and highlights internal investment that might be needed by a manufacturer. Based on the current state of the manufacturer and technical needs of the project, specific PQM personnel are identified to own the overall implementation of the project. Project activities may include support for facility redesign, trainings, and documentation. These activities generally lead to the completion of three deliverables:

- *Product dossier.* PQM works with the manufacturer to address deficiencies in the dossier and compile the dossier in line with the CTD format. Prior to submission of the dossier, PQM performs a final technical review to ensure completeness and quality. After submission, PQM assists manufacturers to address queries.
- *Pre-inspection mock audit.* Before inspection by WHO or an SRA, PQM performs a mock audit as a final check and preparatory step for the manufacturer. PQM structures the mock audit in line with international good inspection practices according to ICH, WHO, and Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidelines. Often the manufacturers have no experience hosting inspectors from these organizations or from SRAs. PQM's support prepares the manufacturer for what to expect during the inspection and also optimizes the inspectors' time and resources during the inspection process.
- *Product prequalification and/or approval.* Inspections can identify critical, major, and minor findings. As a result, our support continues throughout the dossier assessment process. The program works either remotely or in person with the manufacturer to address findings in a timely manner. Support includes preparation of responses to inspection inquiries and post-approval assistance.

Although a fair number of the priority products have low profit margins, the structures and quality systems established and strengthened by PQM's technical assistance may be applied to other product lines with potentially higher margins. The experience gained through the interaction with the WHO PQ program and SRAs further strengthens the ability of manufacturers to manage product approval processes in the future. After a manufacturer receives SRA approval or WHO PQ for a product, the manufacturer is able to participate in global procurement programs, including those managed by UNICEF and the Global Fund. Such opportunities help ensure the sustainable production of quality-assured priority medicines. This is demonstrated in that approximately half of the manufacturers PQM supported to achieve WHO PQ (API or FPP) have at least two prequalified products.

In addition to the topics covered in PQM's workshops and trainings *(see page 5)*, PQM also provides trainings to contract research organizations (CROs), national health programs, manufacturers, and NRAs on several topics to help ensure that the clinical requirements for product approval can be met. These trainings build on the initial work and content of the medicines quality workshops. The three major categories of trainings are:

1. *Advanced Dossier Assessment.* This training focuses on enhancing the skills of participants in the areas of safety, efficacy, and quality assessment of pharmaceutical products. See Annex 2. Example of an Advanced Dossier Assessment Training Agenda for an example agenda.
2. *Advanced GMP Inspection and PIC/S Training.* This training covers the activities and processes associated with performing GMP inspections of both sterile and non-sterile manufacturing facilities. It also examines the role of the various stakeholders involved, skills that an effective inspector should possess, common deficiencies, and the role of PIC/S in inspections. See Annex 3. Example of a GMP Inspection and PIC/S Training Agenda for an example agenda.
3. *Bioequivalence, Good Clinical Practices (GCPs) & CRO Inspection training.* This training provides an overview of methods and guidelines for designing in vivo BE studies. It examines WHO, U.S. FDA, European Medicines Agency (EMA), ICH, and other GCPs, as well as the various aspects of a BE study, from GCP guidelines and types of study protocol designs to bioanalysis, statistical analysis, and reporting. The training also focuses on CRO conformance with study design. See Annex 4. Example of a Bioequivalence and Contract Research Organization Inspection Training for an example agenda.

4. Program Results

As a result of PQM's technical assistance, 19 APIs and 9 FPPs have been approved by an SRA or prequalified by WHO as of November 2017. Table 1 lists the products that have received approval.

Several of the APIs listed below (capreomycin, kanamycin, levofloxacin, rifampicin, and streptomycin) were the first quality-assured sources for those medicines available for the public health market. Additionally, the approval of three FPPs (capreomycin, cycloserine, and kanamycin) has resulted in price reductions of 30 percent or more.

Table 1: *List of products that have received approval with PQM support*

No.	Product	Manufacturer	Status	Year
1	Zinc Sulfate FPP	Lab Pharm Rodael	WHO PQ	2012
2	Cycloserine FPP	Dong-A Pharma	WHO PQ	2012
3	Streptomycin API	Shengxue Pharma	Spanish NMRA	2013
4	Isoniazid API	Second Pharma	WHO PQ	2013
5	Capreomycin API	NCPC Pharma	WHO PQ	2014
6	Capreomycin API	Hisun Pharma	WHO PQ	2014
7	Levofloxacin API	Langhua Pharma	WHO PQ	2014
8	Mebendazole API	Yabang Pharma	EDQM CEP[1]	2014
9	Azithromycin FPP	HEC Pharma	WHO PQ	2014
10	Capreomycin FPP	Hisun Pharma	WHO PQ	2015
11	Moxifloxacin API	Hisun Pharma	WHO PQ	2015
12	Kanamycin API (non-sterile)	Fuzhou Fuxin	US FDA	2015
13	Kanamycin API (non-sterile)	Fuzhou Fuxin	WHO PQ	2015
14	Moxifloxacin API	HEC Pharma	EDQM CEP	2015
15	Kanamycin FPP	Interpharma/SHP	Global Fund ERP[2]	2015
16	Kanamycin API (sterile)	Fuzhou Fuxin	WHO PQ	2016
17	Mebendazole API	Changzhou Yabang Pharma	WHO PQ	2016
18	Cycloserine API	Dong-A Pharma	WHO PQ	2016
19	Streptomycin API	NCPC	WHO PQ	2016
20	Rifampicin API	Shenyang Antibiotic Manufacturer	WHO PQ	2016
21	Levofloxacin API	Shangyu Jingxin Pharma	WHO PQ	2016
22	Praziquantel API	Shanghai Jiayi Pharma	EDQM CEP	2016
23	Cycloserine API	Hisun Pharma	WHO PQ	2016
24	Streptomycin FPP	NCPC	WHO PQ	2017
25	Oxytocin FPP	PT Sanbe Farma	WHO PQ	2017
26	Amoxicillin FPP	PT Sanbe Farma	UNICEF ERP	2017
27	Praziquantel API	Hisun Pharma	WHO PQ	2017
28	Capreomycin FPP	NCPC	WHO PQ	2017

[1] The CEP is a certificate of suitability that the European Directorate for the Quality of Medicines and Healthcare (EDQM) provides after the assessment and approval of a product.
[2] Global Fund's ERP can provide time-limited approval of products for procurement based on pressing public health needs.

5. Future Directions

As GMP compliance of manufacturers is strengthened and companies look to expand their product lines, the PQM program will continue to support these efforts by promoting approaches that ensure sustainable manufacturing, including:

- Strengthening NRA ability to provide training to the local pharmaceutical industry and ensuring access to quality-assured public health commodities.
- Supporting countries to develop and incorporate GMP—along with good laboratory practices, good distribution practices, and good clinical practices—into tertiary and training school curricula.
- Enabling online access to specialized PQM training materials.

Increasingly, countries are expressing an interest in and need for additional training opportunities in vaccines, biologics, biosimilars, and other emerging areas that are beyond the current mandate of PQM. Future programs will need to address these gaps to support effective regulation and manufacture of products of public health importance.

This report has outlined the manufacturing support provided by PQM and the importance of this work in increasing the supply of quality-assured medicines. PQM's approach to this work has been described with the intention of encouraging increased collaboration among stakeholders to strengthen pharmaceutical systems and combat substandard and falsified medicines globally.

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[Accessed 15 September 2017].

Annex 1. Example of a Workshop Agenda

DAY 1

Time	Topic	Presenter/Speaker
08:30- 09:00	Workshop registration	All
09:00-09:30	Welcome/Opening Workshop objectives	PQM
09:30-10:00	PQM technical assistance for manufacturers and regulatory authorities • Overview of PQM program • Overview of technical assistance available to manufacturers and regulatory agencies	PQM
10:00-10:30	WHO Prequalification process • Introduction of the PQ program • Overview of the PQ process • Benefits to the manufacturers Prequalification Team	World Health Organization
10:30-10:45	Q&A/Discussion	All
10:45-11:00	**Coffee Break**	
11:00-11:45	Updates on the global TB control • Global TB burden • Treatment approaches	WHO
11:45-12:30	Introduction to Global Drug Facility (GDF) • Introduction of GDF • Tender process • Quality assurance procedures	GDF
12:30-13:00	The Global Fund overview • Introduction of the Global Fund • Benefits to the manufacturers • ERP process • Country transition to procurement of medicines with domestic funding	Global Fund for AIDS, Tuberculosis, and Malaria
13:00-13:15	Q&A/Discussion	All
13:15-14:00	**Lunch**	
14:00-14:45	Updates on global NTD control • Global NTD burden • Treatment approachesWorld Health Organization	
14:45-15:15	USAID's contribution to combat NTDs • Leadership in implementation of large-scale treatment programs for NTDs	USAID/Core NTD – Penelope Smith
15:15-15:30	Q&A/Discussion	All
15:30-16:00	**Coffee Break**	

DAY 1

Time	Topic	Presenter/Speaker
16:00-16:30	**Case Study 1** – Experience of WHO prequalified supplier • Experience of going through the WHO PQ process • Benefits and challenges • Experience with PQM	Pharmaceutical Manufacturer
16:30-17:00	**Case Study 2** – Experience of WHO prequalified supplier • Experience of going through the WHO PQ process • Benefits and challenges • Experience with PQM	Pharmaceutical Manufacturer
17:00-17:15	Q&A/Discussion	All
17:15-17:30	Wrap-up	PQM
All Day	One-on-one sign-up sheets available all day	PQM and Manufacturers

DAY 2

Time	Topic	Presenter/Speaker
09:00-09:15	Recap of day one activities	PQM
09:15-10:15	CTD Dossier and PQM experiences • WHO's CTD requirements • Common deficiencies observed by PQM	PQM
10:15-10:30	Q&A/Discussion	All
10:30-10:45	**Coffee Break**	
10:45-11:45	Introduction to data integrity • What is data integrity? • Risk management in DI	PQM
11:45-12:00	Q&A/Discussion	All
12:00-13:00	**Lunch**	
13:00-14:00	GMP requirements and PQM experiences • WHO's GMP requirements • Common deficiencies observed by PQM	PQM
14:00-14:15	Q&A/Discussion	All
14:15-15:15	Risk assessment – cleaning validation • Introduction of risk assessment • Introduction of EMA guidelines (including PDE calculation) • How to implement EMA guidelines	PQM
15:15-15:30	Q&A/Discussion	All
15:30-15:45	**Coffee Break**	
15:45-16:15	Collaborative registration procedure • Introduction • Benefits to manufacturers and regulators	WHO

DAY 2

Time	Topic	Presenter/Speaker
16:15-16:45	Country experience • Experience • Benefits and challenges	NRA
16:45-17:00	Q&A/Discussion	All
17:00-17:15	Wrap-up of workshop	PQM
All Day	One-on-one sign-up sheets available all day	PQM and Manufacturers

DAY 3

Time	Topic	Presenter/Speaker
09:30-11:00	Meeting with NRAs and NTP members to discuss DLM and BDQ training workshop with Q&A	PQM/NRA/NTP
11:00-11:15	**Coffee Break**	
11:15-12:15	One-on-one with manufacturers	PQM/Manufacturer
12:15-13:15	**Lunch**	
13:15-15:15	One-on-one with manufacturers	PQM/Manufacturer
15:15-15:30	**Coffee Break**	
15:30-18:30	One-on-one with manufacturers	PQM/Manufacturer

Annex 2. Example of an Advanced Dossier Assessment Training Agenda

DAY 1

Time	Topic	Presenter/Speaker
08:00- 8:30	Workshop registration	All
08:30-12:30	• Opening remarks • Introduction to training course, workshop modalities and objectives Presentations: • API: General information • API: Specification and control	PQM
12:30-13:30	**Lunch**	
13:30-17:00	Presentations: • API: Stability data and evaluation • Pharmaceutical product development	PQM

DAY 2

Time	Topic	Presenter/Speaker
08:30-12:30	Presentations: • FPP: Manufacturing • FPP: Specification and control • FPP: Manufacturing process and process validation, non-sterile	PQM
12:30-13:30	**Lunch**	
13:30-17:00	Presentations: • FPP: Analytical method and method validation • FPP: Stability data and evaluation	PQM

DAY 3

Time	Topic	Presenter/Speaker
08:30-12:30	Presentations: • Bioequivalence and interchangeability: Introduction and principles • BCS based bio waiver and dissolution profile	PQM
12:30-13:30	**Lunch**	
13:30-17:00	Presentations: • Sterile product: Introduction Case studies	PQM/participants

DAY 4

Time	Topic	Presenter/Speaker
08:30-12:30	Presentations: • API data assessment in CTD Discussion Case studies	PQM/participants
12:30-13:30	**Lunch**	
13:30-17:00	Presentations: • FPP data assessment in CTD Discussion Case studies	PQM/participants

DAY 5

Time	Topic	Presenter/Speaker
08:30-12:30	Presentations: • PD dossier assessment in CTD Tips and model questions/answers Discussion Case studies Training wrap-up/closing	PQM/participants
12:30-13:30	**Lunch**	

Annex 3. Example of a GMP Inspection and PIC/S Training Agenda

DAY 1

Time	Topic	Presenter/Speaker
08:00- 08:30	Workshop registration	All
08:30-09:00	Welcome/Opening Workshop objectives	PQM
09:00-10:00	**Module 1.1** – what is GMP?	PQM/external experts
10:00-10:15	**Coffee Break**	
10:15-11:30	**Module 1.2** – The role of inspector and lead inspector, Preparation for the inspection, types of inspection, The 4 phases of the inspection	PQM/external experts
11:30-12:00	**Group session 1.2** – Develop strategies for situations that may arise during an inspection	Participants
12:00-13:00	**Lunch**	
13:00-13:30	Feedback from group session 1.2	All
13:30-14:30	**Module 1.3** – GMP inspection case studies: common deficiencies, prevention of contamination, prevention of mix-up, validation, lab raw data records and retention	PQM/external experts
14:30-15:15	**Group session 1.3** – Using Ishikawa 6M analysis to frame questions Feedback from group session 1.3	Participants
15:15-15:30	**Coffee Break**	
15:30-16:00	Feedback from group session 1.3	All
16:00-17:00	Module 1.4 – GMP inspection of APIs	PQM/external experts

DAY 2

Time	Topic	Presenter/Speaker
08:00- 08:30	Recap for day 1	All
08:30-09:30	**Module 2.1** – Building design for a non-sterile facility, basic concepts – prevention of cross contamination, building plan, personnel flow, material flow and waste flow	PQM/external experts
09:30-10:00	**Group session 2.1** – non-sterile building plan review	Participants
10:00-10:15	**Coffee Break**	
10:15-10:45	Feedback from group session 2.1	All
10:45-12:00	**Module 2.2** – Focus on inspection of non-sterile pharmaceuticals water systems, compressed gases, power supply, lighting, and other utilities. Good Engineering Practices (GEP), and utilities validation and GMPs for critical services – water and gases. What inspectors should look for, how to prepare for asking questions	PQM/external experts
12:00-13:00	**Lunch**	
13:00-15:15	**Module 2.3** – GMP Inspection of Oral Solid Dosage Forms (OSD), and non-sterile liquids Finished Pharmaceutical Products (FPP) Module 2.4 – Good Engineering Practices (GEP) and HVAC, and equipment used for non-sterile FPP.	PQM/external experts
15:15-15:30	**Coffee Break**	
15:30-17:00	**Module 2.5** – Engineering Inspection for Non-engineers – pumps, washers, compressed gases, vacuum, utilities, standby 'gensets', tanks, metallurgy, periodic and preventative maintenance master plan, calibration master plan.	PQM/external experts
17:00-17:30	Q&A	All

DAY 3

Time	Topic	Presenter/Speaker
8:00-8:30	Recap for day 2	All
8:30 – 10:00	**Module 3.1** – Sterile Product Inspection: Water for injection systems, steam and clean or pure steam, compressed gases for sterile production, power supply, lighting, and other utilities for sterile. Good Engineering Practice (GEP), and utilities Validation and GMPs for Critical Services-Water, and Gases.	PQM/external experts
10:00-10:15	**Coffee Break**	
10:15-11:30	**Module 3.2** – Sterilisation processes: dry and moist heat under pressure (autoclaves), gas (Ethylene Oxide, Hydrogen peroxide), and gamma irradiation. Principle of Fo and Fh.	PQM/external experts
11:30-12:00	**Group session 3.2** – Calculation of Fo for a moist heat under pressure cycle	Participants
12:00-13:00	**Lunch Break**	
13:00-13:30	Feedback from group session 3.2	All
13:30-15:15	**Module 3.3** – Clean rooms, clean room classification, and clean room certification using ISO14644 – design concepts and inspection strategies. 21 CFR classified clean rooms and WHO-PIC/S Grade A, B, C and D cleanrooms. HEPA and ULPA filters.	PQM/external experts
15:15-15:30	**Coffee Break**	
15:30-16:00	**Module 3.4** – Inspection of Personnel • Organization Chart • Job descriptions for key personnel • Training procedures and records	PQM/external experts
16:30-17:00	**Module 3.4** – Inspection skills: technique of asking questions, taking good records and notes, investigation techniques, body language, cultural awareness	PQM/external experts
17:00-17:30	Q&A	All

DAY 4

Time	Topic	Presenter/Speaker
8:00- 8:30	Recap for day 3	All
8:30-10:00	**Module 4.1** – Inspection of the Risk Management Plan Risk Analysis (RA), Root Cause Analysis, Cause and Effect Analysis, Fault Tree Analysis, ICH Q7, 8, 9 and 10, RA tools (FMEA, FMECA, etc.)	PQM/external experts
10:00-10:15	**Coffee Break**	
10:15-10:45	**Module 4.2** – Hazard Analysis of Critical Control Points (HACCP) Cause and Effect Diagrams; Introduction to Ishikawa analysis	PQM/external experts
11:30-12:00	**Group session 4.2** – Risk analysis: setting the inspection agenda, scheduling inspection activities	Participants
12:00-13:00	**Lunch Break**	
13:00-13:30	Feedback from group session 4.2	All
13:30-15:15	**Module 4.3** – Investigation of fraud: laboratory fraud, documentation fraud, change of premises without notification aka 'Neutral Licences', 'transfer licences'	PQM/external experts
15:15-15:30	**Coffee Break**	
15:30-17:00	**Module 4.4** – Inspecting the Quality Control Laboratory Chemical, Physical, and Microbiology Laboratory • SOPs, registers and records • Quality management system • Premises, environment • Sampling and sample handling • Work allocation • Personnel • Premises, environment • Equipment • Reagents and culture media, preparation and control • Reference materials and reference cultures • Sample handling • Testing Methods – Verification, Validation and Technology transfer. • Materials management - Laboratory Reagents and culture media, Reference standards, Waste materials, Miscellaneous materials such as auxiliary materials, lubricants, detergents, disinfectants. • On the alert for the big issue – Laboratory Fraud	PQM/external experts
17:00-17:30	Q&A	

DAY 5

Time	Topic	Presenter/Speaker
8:00-8:30	Recap for day 4	All
8:30-10:00	**Module 5.1** – Inspection of the Quality Management System • Responsibilities of the quality units and production • Complaints and Recalls • Deviation control and change control • OOS and investigation • Contract agreements • Material release • Document control • Self-inspection **Module 5.2** – Validation, the Validation Master Plan, Process Validation and the new FDA and PIC/S - EMEA continuous process validation; Process Analytical Technology. • Validation and qualification status (matrix) and schedule, Equipment qualification • Process validation • Cleaning validation • Computer validation	PQM/external experts
10:00-10:15	**Coffee Break**	
10:15-12:00	**Module 5-3** – Prevention of cross-contamination, Introduction to cleaning validation, emphasis on toxic and narcotic substances – practical examples of validation formats and protocols. Sanitation program, Establishment of limits and frequencies **Module 5.4** – Materials management: Starting materials, active pharmaceutical ingredients. Intermediate and bulk products, Finished products, Rejected and recovered materials, Recalled products, Returned goods: • Storage – quarantine, release, reject • Materials • Receipt, handling and storage • Identification • Sampling • Status control • Weighing/dispensing • Temperature (and humidity) monitoring • Primary, and secondary packaging materials, printed labels and packaging	PQM/external experts
12:00-13:00	**Lunch Break**	

DAY 5

Time	Topic	Presenter/Speaker
13:00-15:15	**Module 5-5** – Quality Assurance functions, including Good documentation practices, establishing and maintaining records and raw data, and laboratory raw data	
	Module 5-6 – Hygiene Master Plan: Personal hygiene, personnel training, Environmental monitoring, Sanitation program, Establishment of limits and frequencies	PQM/external experts
15:15-15:30	**Coffee Break**	
15:30-17:00	**Module 5.7** – The Annual Product Review or Product Quality review: cGMP requirements and introduction to trending and trend analysis, Statistical Process Control - basic control data theory - attributes and variables control charts.	PQM/external experts
	Module 5.8 – Contract Manufacture and Technology Transfer: Contract giver responsibilities, contract accepter responsibilities	
17:00-17:30	Q&A	

DAY 6

Time	Topic	Presenter/Speaker
8:00-8:30	Recap for day 5	All
8:30-10:00	**Module 6.1** – Pharmaceutical Inspection Co-operation Scheme (PIC/S) see http://picscheme.org and http://picscheme.org/en/publications • Harmonization of GMP guidelines • Mutual Recognition of Inspections/Audit • Harmonization of GMP Requirements and Uniform Inspection System • PPIC/S Site Master File • PIC/S GMP Guidelines part 1, and part 2 (API) • PIC/S Inspectors' Guidance documents (Aide memoirs) • PIC/S Inspection report format • PIC/S use of 'Should'!	PQM/external experts
10:00-10:15	**Coffee Break**	
10:15-11:30	**Module 6.2** – PIC/S Annexes of relevance to WHO PQ • Annex 1 - Sterile pharmaceutical production • Annex 2 – Biological • Annex 8 – Sampling of starting and packaging materials • Annex 9 – Manufacture of liquids, creams and ointments • PIC/S Design, validation and control of water systems with, IQ, OQ & PQ validation guidelines and EP/USP standards & microbiological controls	PQM/external experts
11:30-12:00	**Group Session 6.2** – Review of Water System schematic according to PIC/S guidelines	Participants
12:00-13:00	**Lunch Break**	
13:00-13:30	Feedback from group session 6.2	All
13:30-15:15	**Module 6.3** PIC/S Annex 15 – Validation, including sterile process validation and validation of aseptic processes.	PQM/external experts
15:15-15:30	**Coffee Break**	
15:30-16:00	**Module 6.4** – PIC/S Annexes • Annex 19 – Reference and Retention Samples • PIC/S Annex 11 compared to 21 CFR11 • Annex 20 – Quality Risk Management	PQM/external experts
16:00-16:30	Q&A	All
16:30-17:15	Training wrap-up/closing	All

Annex 4. Example of a Bioequivalence and Contract Research Organization Inspection Training Agenda

DAY 1

Time	Topic	Presenter/Speaker
08:00- 8:30	Workshop registration	All
08:30-12:30	• Opening remarks • Introduction to training course, workshop modalities and objectives Basics of regulation: • Background of the regulations • Declaration of Helsinki • GCP (WHO, ICH, etc.)	PQM/participants
	Breakout session	
12:30-13:30	**Lunch**	
13:30-17:00	Basics of regulation (continued): • BE guidelines; study design and statistical assessment • Good Clinical Laboratory Practice (GCLP) Responsibilities according to GCP • IRB/IEC • Investigator/CRO – SOPs and instructions • Sponsor	PQM/external experts

DAY 2

Time	Topic	Presenter/Speaker
08:00-11:00	Audit and/or inspections – prior to onsite visit • Differences/similarities between audits and inspections • Different site types of inspection	PQM/external experts
11:00-11:15	**Coffee/Tea Break**	
11:15-12:15	Audit and/or inspections – prior to onsite visit • Triggers for inspection • Preparation for BE inspections • Characteristics of an inspector	PQM/external experts
12:15-13:15	**Lunch**	
13:15-15:15	Audit and/or inspections – at the site • Performance of the clinical part • Enrollment of subjects • Informed consent • Organization, personnel and facility • Application to RA and IRB/IEC • Conduct of the study • Safety reporting • Handling of Investigational Medicinal Product • Handling of BE samples • Laboratory safety samples • Source data • Trial Master File: essential documents and archiving • Quality control – monitoring	PQM/external experts
15:15-15:30	**Coffee/Tea Break**	
15:30-17:00	Break out session	PQM/participants

DAY 3

Time	Topic	Presenter/Speaker
08:00-11:00	Audit and/or inspections – at the site • Performance of the analytical part • Clinical laboratories	PQM/external experts
11:00-11:15	**Coffee/Tea Break**	
11:15-12:15	Audit and/or inspections – at the site • Performance of the analytical part • BE assessment • Pharmacokinetic analysis	PQM/external experts
12:15-13:15	**Lunch**	
13:15-15:15	Audit and/or inspections – after the site visit • Fraud and misconduct • Reporting and follow up • Common findings • Clinical trial • IEC/IRB • BE trial • BE studies – summary and conclusions	PQM/external experts
15:15-15:30	**Coffee/Tea Break**	
15:30-17:00	Break-out session Closing remarks	PQM/participants

Annex 5. Case Study Example

Consider the following applicants information in the dossiers for Ganciclovir sodium to be used in Ganciclovir sodium for injection manufacturing and discuss the questions described below. Ganciclovir sodium drug substance is synthesized by a 4 reaction process.

Reaction 1 -Deacetylation Reaction (Ganciclovir base formation)
To a suitable reactor triacetyl-ganciclovir, methylamine and ethanol is charged; by deacetylation reaction, ganciclovir is obtained.

Reaction 2 Salt formation
Ganciclovir base from Step 1 is mixed with HCl solution in purified water.

Reaction 3 Desalting Reaction
Ganciclovir hydrochloride from Step 2 is mixed with NaOH solution in purified water; Ganciclovir is obtained by desalting reaction.

Reaction 4 Salification & Dehydration Reaction
Ganciclovir from Step 3 is mixed with NaOH solution in purified water. Crystallization is carried out with 95% ethanol. The solids are isolated, reflowed and heated with dehydrate ethanol to obtain ganciclovir sodium.

The final API specification from the applicant is

Standard (e.g. Ph. Int., Ph. Eur., BP, USP, House)		**USP**
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (Type/Source/Version)
Appearance	White or off-white crystalline or crystalline powder.	Visual
IR	Conforms to the spectrum of the reference standard.	USP
HPLC in Assay	The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in Assay.	USP
Water	Not more than 2.0%	USP
pH	Between 10.8 and 11.4.	USP
Heavy Metals	Not more than 0.001%	USP
Ganciclovir related compound A Total impurities	Not more than 0.3%. Not more than 1.0%.	USP
Assay	It contains not less than 99.0% and not more than 101.0% of ganciclovir sodium ($C_9H_{12}N_5NaO_4$), calculated on the dry basis)	USP
Bacterial Endotoxins	Not more than 0.84 EU/mg	USP
Microbial Limits Bacterial Yeast and Molds Escherichia Coli	Not more than 1000 CFU/g Not more than 100 CFU/g Absent	USP

Questions

By considering the above information and applicable monograph, please discuss the following cases and write the questions to be submitted to accept this section of the dossier.

1. Describe any other additional information you may need to complete this section of the dossier?
2. What is the starting materials in the route of synthesis and why? What will be its contribution and control mechanism towards the specification of the final API?
3. At which step does the final drug substance has been formed?
4. List all the potential impurities including its source and discuss each with regard to the final drug substance specification.
5. The applicant has claimed the USP as reference standard. The USP monograph for Ganciclovir states only for ganciclovir compound A impurities. In your desk research, the EP monograph for Ganciclovir states there are six specified impurities (A to F) and if detected two other impurities as impurity I & J. What is your assessment outcome and your question to the applicant with regard to the specification of the API and what should be included in the updated specification of Gancilovir drug substance with regard to API related impurities?