



# Assessment of the Good Manufacturing Practices Inspection Program of the Bangladesh Directorate General of Drug Administration

May 2015



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# **Assessment of the Good Manufacturing Practices (GMP) Inspection Program of the Bangladesh Directorate General of Drug Administration**

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May 2015

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## **About SIAPS**

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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## **Key Words**

GMP inspection, DGDA

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## ACRONYMS

API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
BAPI	Bangladesh Association of Pharmaceutical Industries
DGDA	Directorate General of Drug Administration
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
GOB	Government of Bangladesh
M/L	manufacturer's license
MHRA	Medicines and Healthcare Products Regulatory Agency
NCL	National Control Laboratory
NMRA	national medicine regulatory authority
PIC/S	Pharmaceutical Inspection Cooperation Scheme
QC	quality control
QM	quality manual
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SOP	standard operating procedure
SRA	Stringent Regulatory Authority
WHO	World Health Organization

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## EXECUTIVE SUMMARY

As a part of its ongoing support to build the capacity of the DGDA, the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) team conducted a rapid assessment of the capacity of the Good Manufacturing Practices (GMP) inspection program at the Directorate General of Drug Administration (DGDA). GMP is part of the quality assurance system for medicines, which helps to ensure that medicinal products are consistently produced and controlled to meet the quality standards appropriate to their intended use, as required by national drug regulatory authorities. The GMP inspection is also a critical component of the medicines registration review process.

To assess the capacity of the GMP inspection program of the DGDA, the SIAPS team reviewed onsite inspection practices as well as relevant documents. To evaluate the legal framework and current tools used by the DGDA inspectorate, the SIAPS team reviewed the applicable laws, regulations, standard operating procedures (SOP), guidance documents, checklists, and inspection reports of the DGDA. To assess the current GMP inspection practices of the DGDA inspectorate, the SIAPS team accompanied DGDA inspectors to observe inspection practices at two GMP-certified manufacturing sites.

As a result of the document review and evaluation of the onsite GMP inspections by the DGDA inspectors, the following areas were found to require improvement.

### **Regulatory Framework**

Although there are laws and regulations in place authorizing the administrative power and responsibilities of the DGDA to carry out GMP inspections, the DGDA does not have a documented SOP to guide GMP inspectors. The DGDA has a checklist (dated June 11, 2007) to assist the GMP inspectors in conducting a systematic inspection, however, this question-based checklist needs to be updated and a technical session organized to enable its proper use by DGDA inspectors during GMP inspections and for documentation purposes. The DGDA does not have written directives or policies on the procedures for designating inspectors, nor training certification policies or guidance on the training required to be a qualified GMP inspector. Policies and directives related to a code of conduct (ethics) are also not available for inspectors. The DGDA has a Quality Manual based on World Health Organization (WHO) guidance, but it does not cover DGDA inspection practices or staff training practices. Therefore, a new legal provision or guidelines are needed to address these issues.

### **Inspection Resources**

The DGDA does not have dedicated GMP inspection staff since DGDA staff has dual duties as medicines registration reviewers and GMP inspectors. All DGDA staff perform a variety of duties, including office administrative functions. GMP inspections account for approximately 20% of a staff member's time. Therefore, dedicated staff needs to be designated and their knowledge

and experience developed through a structured training and certification system based on their qualifications and performance. DGDA does not have a proper training program or quality assurance mechanism to ensure the effectiveness of the training program on how to conduct GMP inspections. Therefore, it is critical to establish an in-house training program and to strengthen the minimum qualifications for a staff member to become a certified GMP inspector.

Recommendations to be implemented in the short-term:

Establish a “GMP inspector” job description, requiring minimum educational entry requirements to include training in industrial pharmacy or pharmaceutical technology, and preferably, for candidates to have pharmaceutical industry experience.

Establish a job description/SOP (learning) matrix for promotion within the DGDA geared to the attainment of learning goals.

Medium-term recommendations:

Establish in the DGDA a full-time position for a “GMP Trainer” responsible for developing GMP training programs, securing GMP training resources, and managing the administration of the training program. Ideally, this position should be filled by a person experienced in planning and managing training for adults (e.g., perhaps a teacher or administrator from a college of higher education).

## **Inspection Process**

The DGDA does not currently have a standard inspection process or GMP reporting templates for use by DGDA staff. Although a checklist is available for use during the inspection, inspectors do not actually use it during the onsite inspection. It is critical to develop and implement a SOP for the GMP inspection to improve the transparency and quality of the inspection process.

Long-term recommendation:

With the concurrence of the Bangladesh Association of Pharmaceutical Industries (BAPI), it is recommended that the DGDA apply for membership in the PIC/S.



## INTRODUCTION

National medicine regulatory authorities (NMRA) are mandated to ensure access to medical products and to protect public health. Many NMRAs in developing countries lack transparent and accountable administrative procedures, and are often confronted by systemic challenges to fulfilling their mission. Such weaknesses have contributed to backlogs in applications for medicine registration and an inability to protect the supply chain from spurious products. The World Health Organization (WHO) estimates that about 30% of member states do not implement adequate medicine regulatory functions, including: product evaluation and registration; licensing of pharmaceutical establishments, practices and persons; inspection of manufacturers and distributors; price control; monitoring of product quality; control of promotion and advertising; and monitoring of adverse drug reactions.<sup>1</sup> The need to strengthen regulatory systems as part of health systems strengthening has only recently been recognized. As part of its overall goal of achieving desired health outcomes through the improved availability and use of pharmaceutical products, the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program provides support for regulatory capacity development by improving NMRA governance and strengthening key functions of regulatory systems in developing countries.

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<sup>1</sup> Ratanawijitrasin S and Wondemagegnehu E. *Effective Drug Regulation: A Multicountry Study*. Geneva: World Health Organization; 2002. Available at: <http://apps.who.int/medicinedocs/pdf/s2300e/s2300e.pdf>.

## BACKGROUND

In 2011, SIAPS initiated support to the Directorate General of Drug Administration (DGDA), Bangladesh's national regulatory authority responsible for regulating all medicines and other health products in the country. SIAPS conducted a comprehensive assessment and stakeholder dissemination workshop, which highlighted the institution's need to strengthen and modernize its systems and processes to improve its overall effectiveness. Since then, SIAPS has been providing technical assistance to the DGDA in priority areas, including product registration, pharmacovigilance, and online medicine data management systems. Since Good Manufacturing Practices (GMP) inspection is a critical part of medicine registration requirements to ensure the quality of medicines, current GMP inspection processes were targeted for improvement during the initial medicine regulatory assessment.<sup>2</sup> To address issues related to current GMP inspection processes, SIAPS proposed to provide the DGDA with technical assistance to improve its GMP inspection processes, including revision of associated guidelines and tools.

In May 2014, the SIAPS team visited the DGDA and accompanied inspectors on two GMP site inspections to conduct a rapid assessment, to understand current practices, and to provide capacity building training for DGDA inspectors charged with ensuring that Bangladesh's pharmaceutical manufacturers comply with the requirements of the WHO's GMPs.

The objectives of the visits were to: identify gaps/deficiencies in the DGDA's current GMP inspection process; develop a plan of action for improving the DGDA's GMP capacity in the short-, medium- and long-term; and define key parameters for the adaptation of WHO GMP guidelines. According to the Drug Acts 1940, the DGDA is required to follow the current WHO GMP guidelines for GMP implementation at pharmaceutical companies.

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<sup>2</sup> Nwokike, J., H. L. Choi. 2012. *Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh*. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health. Available from: <http://siapsprogram.org/publication/assessment-of-the-regulatory-systems-and-capacity-of-the-directorate-general-for-drug-administration-in-bangladesh/>.

## METHODOLOGY

To identify gaps/deficiencies in the DGDA's current GMP inspection process, the SIAPS team reviewed current GMP documents prior to the visit to the DGDA. Documents reviewed included:

- Current GMP inspection and post-inspection checklist
- Current Quality Manual
- List of required documents for GMP certification
- List of GMP-certified pharmaceutical manufacturers in Bangladesh
- Current GMP inspection reports
- Current GMP guidelines adopted by the DGDA

During the visit, the SIAPS team conducted key informant interviews with GMP inspectors and collected the most up-to-date and relevant DGDA documents.

To conduct the rapid situation analysis of GMP inspection practices, the SIAPS team accompanied DGDA inspectors on their visits to two pharmaceutical manufacturing sites and reviewed the GMP inspection reports on the site inspections.

Based on the review of documents and the site inspection practices, the SIAPS team developed an action plan in collaboration with the DGDA, which outlines tasks and activities to strengthen the DGDA's GMP functions in the short-, medium- and long-term, including roles and responsibilities, timelines, and required inputs.

## **FINDINGS**

### **Legislative and Regulatory Requirements and Scope**

GMP inspections of national manufacturing plants are mandatory for issuing manufacturing licenses. They are conducted by a team of inspectors from the DGDA and the Manufacturing Project Evaluation Committee. A GMP inspection is required every two years for the renewal of a manufacturing license. The Drug Act 1940, the Drug Rules 1945 and 1946, and the Drug (Control) Ordinance 1982 provide the legal basis for enforcement of compliance.

According to the Drug Rules 1946, inspectors are authorized to inspect all establishments licensed for the sale of medicines and all premises licensed for the manufacture of medicines not less than twice a year. Inspectors collect samples for testing, investigate complaints, send inspection reports to the authority, and maintain records of inspections and actions taken. There are inspection checklists for manufacturers, distribution points, and pharmacies. However, there are no comprehensive guidelines, standard operating procedures (SOP), or a quality management system to ensure that inspections are planned, conducted, documented, and followed up in a consistent way, based on risk assessment.

### **Regulatory Directives and Policies**

The inspectors of the central DGDA office have responsibility for reviewing dossiers for medicine registration as well as for conducting GMP inspections at sites. The inspectors at the regional offices (six divisional offices) conduct inspections of pharmaceutical companies, distributors, and pharmacies. (The organizational structure of the DGDA is shown in Annex A.)

According to the Drug Act 1940, all the technical staff of DGDA are designated as inspectors. However, the DGDA also does not have training certification policies or guidance on the training required to be a qualified GMP inspector. Policies and directives related to the code of conduct (ethics) are also not available for inspectors.

### **GMP Standards**

Bangladesh has adopted the WHO GMPs as the country's GMP code, and inspects for compliance with the WHO's GMP guidelines.

Bangladesh has 850 licensed pharmaceutical manufacturers needing GMP inspections, of which:

- Approximately 183 manufacturing locations produce western medicines.
- 583 manufacturing locations produce traditional medicines (Ayurvedic, Unani, homeopathic, and herbal).
- Approximately 84 locations have active licenses, but do not produce medicinal products.

The DGDA issues a Manufacturer's License (M/L) to each medicine manufacturing facility, which is valid for a period of two years. For new manufacturing facilities, issuance of an M/L requires passing a DGDA GMP inspection. Renewal of an M/L is required every two years to be able to continue to legally manufacture medicines in Bangladesh. A renewal by the DGDA requires it to perform a GMP inspection to assure continued compliance with WHO GMPs (the official GMP enforced in Bangladesh).

Licenses for medicines are of two types:

- Biological product M/Ls
- Non-biological product M/Ls

For a Bangladeshi company to export medicinal products, it is required to be in possession of a WHO "Certification Scheme for Goods Moving in International Commerce." This certificate is issued by the DGDA only after a special (additional) GMP inspection.

New Bangladesh legislation, which is yet to be implemented, includes regulating medical devices (non-powered) and medical equipment (powered), and the associated need to perform GMP inspections of medical device and medical equipment manufacturers. The DGDA is still in the process to understand the issues involved with inspecting for medical device/equipment GMP compliance.

The DGDA's planning for medical device/equipment registration and inspections needs to cover:

- Medical device/equipment company registration
- Medical device/equipment product registration
- Recruitment and training of DGDA staff to handle the workload for the registration of medical device/equipment.

For medical equipment registration, future staff will need to have engineering and computer hardware/software skills to cope with the product registration and GMP inspection of medical equipment manufacturers, rather than the traditional skills of a pharmacist (as is the current requirement for DGDA GMP inspectors). This educational requirement may require a change in the new legislation. The following are additional issues related to the registration of medical devices/equipment:

- Introduction of inspection risk management to prioritize inspections of medical device/equipment manufacturers.
- The DGDA has yet to determine which GMPs to follow when the legislation is implemented: ISO 13485 ("Medical devices - Quality Management Systems - Requirements for Regulatory Purposes") or ISO 14971 ("Medical Devices - Application of Risk Management to Medical Devices") or any other equivalent standard. DGDA staff

believes that WHO drug GMPs apply to medical devices/equipment, however, they do not.

Once it is determined which are the appropriate GMPs for medical device/equipment manufacturers to follow, the DGDA will need to provide: adequate office space, furniture (desks, chairs, filing cabinets, etc.) and computer support; prepare training courses for its future DGDA inspection team that will inspect medical device/equipment manufacturers; and prepare checklists to assist with GMP inspection procedures.

The current DGDA headquarters building in Dhaka is not suitable for the purpose of expanding DGDA inspection capacity because it is cramped, poorly lit, and inadequately air conditioned. There is no capacity to house additional staff for medical device/equipment registration and GMP inspection in the existing facility.

## **Inspection Resources**

### ***Staffing: Initial Qualifications and Number of Inspectors***

The DGDA currently has approximately 90 personnel on staff. Prior to January 2014, DGDA staff was approximately 25 personnel. The increase in personnel is in response to a series of recommendations on staffing and capacity building made by the WHO. The original WHO recommendation was to increase the DGDA staff by about 1,000, however, budgetary constraints of the Government of Bangladesh (GOB) Ministry of Finance reduced the approved total headcount to 300 staff, of which approximately 50 staff were to be allocated for GMP inspections. Considering the number of inspections required to be done per year, the number of inspectors is inadequate.

The DGDA has no dedicated GMP inspection staff. All DGDA staff performs a variety of duties, including office administrative functions (e.g., approving expenses, filing, and other office administration activities). GMP inspections account for about 20% of a staff member's time.

As of March 2015, the number of pharmaceutical manufacturers of western medicines registered with the DGDA was about 277. The number of registered retail pharmacies has increased in the past two years from 107,685 in 2013 to 115,439 in 2014. There are about 30,000 unregistered pharmacy outlets.

According to the DGDA, full GMP inspections are conducted at the request of pharmaceutical companies that are interested in exporting their products and require GMP certificates. This accounts for approximately 40 to 50 companies of the 277 companies registered with the DGDA. The GMP license is valid for two years. Regular inspections, such as for a product license renewal or inclusion of an additional facility to an existing GMP-certified facility, are also valid for two years, but are not considered a full inspection. A total of 1,094 GMP inspections for manufacturing facilities producing different products were done in 2014.

The regular GMP inspection interval for manufacturers is once every two years while the regular inspection for wholesalers and distributors are twice per year. Inspections are not mandated for importers.

The DGDA has had difficulty attracting pharmacists to its ranks due to the government's non-competitive salary structure as compared to the Bangladesh pharmaceutical industry.

For a university pharmacist graduate, the total DGDA entry level salary and benefits are about 18,000 Taka per month (approximately US\$ 233 per month), while a pharmacy graduate can join the pharmaceutical industry in an entry level position and receive a salary and benefits package of about 80,000 Taka per month (approximately US\$ 1,038 per month), a four and one-half fold difference in salary and benefits.

The DGDA requires that its GMP inspectors are pharmacists; however, this is not the only profession that can perform the medicine dossier review and GMP inspection functions. The DGDA should note that other Stringent Regulatory Authorities (SRA), such as the British Medicines and Healthcare Products Regulatory Agency (MHRA), Singapore Health Sciences Authority, and the United States Food and Drug Administration (FDA), do not have such a requirement. In these countries, as long as staff are university graduates in a science-related subject (e.g., biology, chemistry, engineering, nursing, pharmacy), they may be employed as dossier reviewers or GMP inspectors, or both.

***Training Program: Training Program and Quality Assurance Program to Assure Effectiveness of the Training Program***

The WHO has offered funds to the DGDA to cover the costs of GMP training; however, it has yet to be implemented. It should be noted that the WHO's focus in its technical assistance to the DGDA is primarily in the areas of vaccines and biologicals, rather than in medicines, in general.

The DGDA does not have an established in-house training program for GMP inspectors and there is no quality assurance mechanism to assure the effectiveness of any training program. All GMP staff training is done by arranging for new/junior officers (assigned the DGDA rank of "Superintendent") to accompany an experienced GMP inspector and learn on the job.

This training methodology for GMP inspectors is inadequate because:

- There is no standard training syllabus that is followed. Each senior inspector uses his/her own inspection knowledge, preferences, and style.
- During the tours of manufacturing facilities, it is difficult for DGDA junior staff to hear the questions asked by the senior inspector and to understand the purpose behind each question. It is also difficult for DGDA junior staff to hear the responses given.

It was observed during plant tours at both manufacturing facilities (Eskayef Bangladesh Ltd. and Renata Ltd.) that the junior DGDA staff lost interest in the proceedings, and often drifted away from the main inspection group.

- Since there are no DGDA SOPs for inspection practices nor is the checklist followed during GMP inspections, there is no consistency in the GMP inspections performed, nor is consistent GMP training provided by different senior DGDA inspectors.

There is no competency assessment of junior DGDA staff to determine whether training received has been adequate to allow him or her to perform inspections independently, as a prerequisite for promotion.

## **Inspection Procedures**

Although there is a routine procedure at the DGDA on how to conduct a GMP inspection, there are no written documents available to guide inspectors on how to prepare for inspections, what documents should be collected in advance, and the SOPs for conducting inspections and post-inspection activities.

The DGDA has a Quality Manual (QM) based on WHO guidance (the latest edition is dated 2012), but this QM does not cover DGDA GMP inspection practices or staff training practices.

The day-to-day relevance of the QM is questioned; the QM appears to have been written solely to satisfy a WHO recommendation that the DGDA have a QM. This is especially noticeable in the fact that the DGDA headquarters building has cramped offices, no air conditioning, and inadequate lighting, and as such, does not conform to the QM requirement stated in chapter 4.4, “Work Environment.” Even the ongoing renovations of the DGDA Dhaka headquarters building will not bring the facility in line with the DGDA QM requirements.

On the DGDA website,<sup>3</sup> none of the links provided relate to GMPs or make the latest copies of WHO GMPs available nor the WHO’s “Supplemental GMP Guidance” documents.

A level below the DGDA QM is the departmental SOPs (written in Bengali). However, they do not include SOPs on GMP training, SOPs on how new DGDA staff become qualified as GMP inspectors, or how a DGDA inspection is to be performed.

Detracting from an efficient work environment at the DGDA headquarters building is the fact that visitors and other people seem to crowd the corridors and offices. This was particularly noticeable when the SIAPS team conducted interviews with DGDA staff: individuals in the room from prior meetings (often non-DGDA staff) did not leave the office, and meetings were frequently interrupted by other visitors entering and remaining in the office. Under such working conditions, it is questionable how DGDA staff can concentrate on tasks that need to be performed and how they can effectively perform their functions.

## **Inspection Strategy and Inspection Methodology**

Bangladeshi companies are designated by the DGDA as being “large,” “medium,” and “small.” This categorization does not impact on the frequency of the DGDA’s GMP inspections, the

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<sup>3</sup> <http://www.dgda.gov.bd/>.

length of time spent by DGDA staff performing a GMP inspection (in terms of the number of days to perform the inspection), or the number of DGDA staff allocated to perform the GMP inspection.

The categorization is also not supported by a written definition of how a company is allocated a “size” designation. The DGDA should use a risk management process to rationalize its GMP inspection schedules and inspection frequencies.

There does not appear to be a standard GMP inspection template or checklist guiding the DGDA inspectors on how GMP inspections should be performed and, as a result, there is no uniformity in how GMP inspections are performed by DGDA staff for the various pharmaceutical manufacturing facilities.

In theory, the DGDA’s GMP inspections are:

- Required to be performed by law once every two years.
- Each inspection is typically scheduled for a duration of one day, however, the DGDA inspectors are rarely onsite for more than three or four hours, probably due to traffic concerns and the need to not work more than an eight-hour day..

Thus, in practice, the inspections performed by the DGDA last for about one-half a day, at a maximum, every two years. This GMP inspection duration needs to be compared to the time spent by SRAs (e.g., Pharmaceutical Inspection Cooperation Scheme [PIC/S] countries, such as Australia, Canada, European Union, Malaysia, Singapore, United States) whose biennial inspections are performed by at least two experienced inspectors for a minimum of three full days for a non-sterile oral dosage form (capsules or tablets).

- Each DGDA inspection is typically performed by a team of three DGDA staff, including a trainee inspector (Superintendent). During the inspection, the team members always stays together; the team members do not split up to cover more company operations during the limited time spent at the manufacturer.

Many Bangladeshi companies (e.g., both Eskayef Bangladesh Ltd. and Renata Ltd.) make many different types of products at a single campus. For example, at Renata’s Gazipur campus, in accordance with GMP requirements, Renata has separate manufacturing and quality testing operations in separate buildings for the manufacture of:

- Active pharmaceutical ingredients (api) for oncology products
- Cephalosporin products
- General pharmaceutical products
- Oncology (anti-cancer) products
- Penicillin products
- Potent sensitizing products

Each of these manufacturing operations requires its own independent biennial (once every two years) GMP inspection, however, the entire Renata Gazipur site is currently inspected biennially for only about one-half a day, making it impossible to perform a proper inspection of six different manufacturing operations at a single campus.

Both Eskayef and Renata work on a 24 hour/7 days per week basis. The DGDA has performed GMP inspections during only the day shift of weekdays and, according to both companies, the DGDA has never inspected the facilities during the evening or night shifts, or on weekends. This is a major inspection deficiency.

### *Observations of the DGDA GMP Inspection Process and Suggestions for Areas of Improvement*

**Note:** The observations given below were made during GMP inspections performed by DGDA GMP inspectors at the Eskayef Bangladesh Ltd. and Renata Ltd. facilities. It was intended that the inspections mimic typical DGDA inspections.

Both pharmaceutical companies inspected are not single factories on a company campus; rather, they have multiple factories on a single campus, each needing one day for inspection every two years under current DGDA policies.

The Eskayef facility includes four separate factories for the manufacture of:

- Liquid sterile pharmaceutical products
- Sterile pharmaceutical products
- Cephalosporin pharmaceutical products
- General pharmaceutical products (tablets)

The Renata facility includes six separate factories for the manufacture of:

- API for oncology products
- Cephalosporin products
- General pharmaceutical products
- Oncology (anti-cancer) products
- Penicillin products
- Potent sensitizing products

It is impossible to inspect a single factory in what the DGDA calls its one-day inspection, but which, in reality, is one-half a day on site, let alone to inspect four or six factories at a single campus.

### ***Pre-Inspection Preparation***

Both inspections started with the senior DGDA inspectors announcing a list of documents that they would like to review. There was no apparent pre-determined inspection plan, and the list of documents requested seemed scattershot.

### ***SOP for Conducting Inspections***

As stated above, the DGDA does not have a SOP to guide inspectors in the conduct of inspections. As a result, during the site inspections, the questions asked seemed to lack focus and were often vaguely worded, leading the companies' staff to seek clarification on what exactly was being asked.

The DGDA inspectors, as stated earlier requires more training, and as result often accepted the company's verbal responses at face value, without asking for documentation (reports, SOPs, etc.) to provide confirmation that the answers provided were, in fact, correct.

Both inspected facilities operate on a three-shift basis, seven days a week (24/7), but the DGDA never inspects companies operating on a 24/7 schedule outside the dayshift or at all on weekends. This may also due to the lack of policies in place in order to conduct such inspection.

The inspectors seemed unfamiliar with key manufacturing and analytical test methods employed by the companies. They also seemed to be unable to ask the most pertinent/appropriate questions to determine GMP compliance. These are key issues when inspection time is severely limited.

At several times during the inspection, the DGDA inspectors seemed to be lecturing the company's staff (or perhaps, the accompanying DGDA junior staff) on GMP-related issues. On one occasion, this behavior went on for 15 to 20 minutes, detracting from the total time available for the GMP inspection.

The DGDA inspectors asked for job descriptions of senior managers, but did not review the job descriptions of first-line supervisors, the staff who have the most day-to-day impact on product quality and GMP compliance. There was no inquiry on the link between job descriptions and the associated SOP matrix, nor were any checks performed that timely training had been provided, and that the training had been shown to be effective.

There was very little depth to the inspections. Most questions were superficial (e.g., "Do you have an SOP on .....", but never checking the SOP for its contents), potentially due to the inspectors' lack of training, or lack of time onsite, or both.

The DGDA inspectors maximized their time at the facilities, by using an inspection technique called "follow the flow," where the inspection starts at the raw materials warehouse, works its way through production, and ends at the finished products warehouse and the quality control (QC) laboratory.

While this is a very common GMP inspection technique, an inordinate and excessive amount of time was spent dealing with relatively minor issues in the raw materials warehouse (at the start of the inspection), leaving insufficient time to ask more than a couple of superficial questions in the QC laboratory, where critical GMP deficiencies issues frequently occur.

The DGDA inspectors were unknot quite familiar with electronic systems and the validation process of the systems. Key issues missed during the inspections were:

- Not querying the lack of user names and passwords on sterilizer controls, allowing anyone (including visitors) to unofficially change the sterilization cycle settings (Eskayef).
- Not querying that usernames/passwords were shared by staff (Renata), hindering the ability to know who specifically performed any work.
- Not querying that Excel spreadsheets used in chemical quality control laboratories had not been validated (Eskayef and Renata), bringing into question the validity of results published in Certificates of Analysis.

### ***Format and Content of Inspection Reports***

DGDA inspectors are not following an inspection template or checklist, which results in inconsistent inspections among companies.

### ***Post-Inspection Activities***

During the site visits, the DGDA team was unaware of previous inspection findings and did not use the opportunity to assess whether prior observations had been effectively addressed.

During the years 2013 to 2015, DGDA issued warning letters, product facilities closures, and counterfeit medicine bans for specific products as a result of GMP inspections at about eight companies. These are probably the extreme cases. In most cases, corrective actions were issued with regard to specific products due to counterfeit issues.

Manufacturers can appeal the cases through the Bangladesh “mobile or drug court.”

### ***Storage of Inspection Data***

The DGDA does not have a computerized system to store inspection data. Filing of inspection data is done manually. Inspection data are only available in paper copies, often in handwritten reports.

## RECOMMENDATIONS

Based on the review of relevant documents and the site inspections, the following recommendations are made for the DGDA to improve its GMP inspection practices.

### **Short-Term (Implementation in Less than 6 Months):**

#### ***Inspection Resources: Staffing (Initial Qualification), Training Program, and Training Certificate Policies/Guidelines***

Establish a “GMP inspector” job description, requiring minimum educational entry requirements to include training in industrial pharmacy or pharmaceutical technology, and preferably, for candidates to have pharmaceutical industry experience.

Establish a job description/SOP (learning) matrix for promotion within the DGDA geared to the attainment of learning goals.

Provide in-depth training for GMP inspectors in such areas as:

- GMP basics
- Facility design and maintenance
- Pharmaceutical unit operations
- Pharmaceutical water systems (design, maintenance and operation)
- QC chemistry laboratory systems
- QC microbiology laboratory systems
- Validation technology
- Warehousing and supply chain management systems

Establish a policy for GMP inspectors to accompany all SRA inspections (e.g., from Canada, Singapore, United Kingdom, United States) whenever they inspect any pharmaceutical company in Bangladesh, as a learning tool for mid-level DGDA staff.

Establish a cadre of GMP inspectors whose only job in the DGDA is to perform GMP inspections of biotechnology and pharmaceutical manufacturers; they should not perform other tasks in the DGDA, such as drug registrations and administrative tasks.

There is a need to augment DGDA GMP inspection staff with specialists, depending on the company inspected and their products.

There is a particular need for chemists to be seconded from the National Control Laboratory (NCL) to accompany all DGDA inspections. These chemists may properly inspect the operations of the chemical quality control laboratories at pharmaceutical manufacturing companies for compliance to GMP requirements.

There is a need for microbiologists to be seconded from the NCL to accompany DGDA inspections of sterile product manufacturing facilities. These microbiologists may inspect the operations of the microbiological chemical quality control laboratories at pharmaceutical manufacturing companies for compliance with GMP requirements.

For inspections of sterile product manufacturing facilities, there is a need for engineers familiar with the design and operation of pharmaceutical water systems and Heating, Ventilation, and Air Conditioning (HVAC) systems to be seconded from other Ministry of Health and Family Welfare departments.

It is recommended that the DGDA start using available internet information sources as a basis for training (e.g., FDA Warning Letters, European Medicines Agency EurdraLex database, WHO Notices of Conformance), as well as using web-based GMP training available online. Internet training resources include:

### ***Intergovernmental Sources***

- International Conference on Harmonization
- Pharmaceutical Inspection Cooperation Scheme
- World Health Organization

### ***Governmental Sources:***

- Canada: Health Products and Food Branch Inspectorate
- United Kingdom: MHRA
- United States: FDA

### ***Professional Organization Sources***

- Drug Information Association
- International Pharmaceutical Federation
- International Society of Pharmaceutical Engineers
- Parenteral Drug Association
- Regulatory Affairs Professional Society

### ***Commercial Training Sources***

- Inglasia
- Micron Video

During the GMP training provided to DGDA staff on the last two days of the SIAPS visit to the DGDA, it was learned that out of the approximately 50 junior DGDA staff hired in January 2014, only a few had seen or read the WHO GMPs. It would seem appropriate that staff hired to perform GMP inspections should have an early exposure to the WHO GMPs, rather than waiting five months for this issue to arise and this gap to be identified. It is recommended that the DGDA immediately implement a program to make junior inspectors aware of the requirements of GMP.

### ***Inspection Performance Standard***

Inspections are currently, typically performed by two senior and one DGDA junior staff member. It is recommended that factory inspections be performed by at least two teams, consisting of two senior staff and two junior staff on each team. When on site, these teams need to split into separate groups, each covering different areas of company operations. In this way, the teams will be able to review more of a company's operations in the limited time available for the inspection.

Instead of categorizing pharmaceutical manufacturing companies as being "large," "medium," or "small," and without this categorization having any practical meaning, it is better to establish a risk management system to guide the prioritization of pharmaceutical company inspections, inspection frequency, inspection duration on site, inspection team size, and inspection team competencies. The inspection "risk management" criteria should be in writing and should be based on:

- Product type: sterile/non-sterile (patient risk)
- Company capabilities and resources, including the amount of support that the Bangladeshi company receives from any multinational partners (e.g., Eskayef receives routine and regular support for its operations from Denmark's NovoNordisk).
- Prior compliance history: companies with product recalls and frequent adverse drug event histories require more frequent inspection than companies without such histories.
- Prior inspection history: companies that had critical or major deficiency findings during a prior inspection require more frequent inspections, and more frequent inspections than the routine biennial inspection currently performed.

### ***Inspection Procedures***

Time is lost during inspections when the DGDA inspection team arrives at the facility and announces the documents that it would like to review. Inspection efficiency would be enhanced by e-mailing or faxing the list of documents to be reviewed to the company several days prior to the inspection. In this way, the company can have the documents available for review immediately upon the arrival of the DGDA inspection team. An even better inspection efficiency could be achieved if the company to be inspected were to e-mail the documents to the DGDA inspectorate two weeks prior to the inspection for DGDA to review at their offices. This would also allow the inspection team time to prepare in-depth questions in advance and related to the materials provided.

### **Medium-Term (Implementation within 6 to 18 Months):**

#### ***Inspection Resources: Staffing (Initial Qualification), Training Program, Training Certificate Policies/Guidelines***

Establish in the DGDA a full-time position for a "GMP Trainer" responsible for developing GMP training programs, securing GMP training resources, and managing the administration of

the training program. Ideally, this position should be filled by a person experienced in planning and managing training for adults (e.g., perhaps a teacher or administrator from a college of higher education).

### ***Quality Management System***

Augment the current DGDA QM with sections regarding training, and develop and implement associated SOPs with respect to GMP inspector training.

### ***Inspection Performance Standard***

DGDA inspectors should incorporate PIC/S Aide Memoires<sup>4</sup> or a more comprehensive checklist system into their GMP inspections to assure that:

- Key GMP quality concerns are covered during a GMP inspection.
- Questions asked during the various company inspections are consistent.

PIC/S Aide Memoires cover the following areas of GMP inspections:

- Assessment of quality risk management practices
- Inspection of APIs
- Inspection of biotech manufacturers
- Inspection of medicinal gases
- Inspection of packaging
- Inspection of quality control laboratories
- Inspection of utilities

In addition to the current biennial GMP inspection as part of an M/L renewal, the DGDA should perform an additional GMP inspection when a company requests certification under the WHO “Certification Scheme for Goods Moving in International Commerce,” to enable the company to export pharmaceutical products. It is recommended that the biennial inspection, performed using the Bangladesh GMPs (which are the WHO GMPs), and the additional WHO certification inspection (also performed to assess compliance with WHO GMP standards) be merged into a single inspection, and thus save on duplication of DGDA inspection efforts.

### ***Inspection Procedures***

Many Bangladeshi companies (e.g., Eskayef Bangladesh Ltd. and Renata Ltd.) make many different types of products at a single campus. At a minimum, each of the six Renata factories at its Gazipur campus needs a full day onsite inspection every two years. As recommended below, this barest minimum inspection should be significantly increased in duration to be consistent with the norms practiced by the Association of Southeast Asian Nations (ASEAN) and other PIC/S countries.

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<sup>4</sup> <http://www.picscheme.org/publication.php?id=14>.

It is strongly recommended that the DGDA increase the time spent on GMP inspections at each Bangladeshi pharmaceutical manufacturing facility. The current practice of spending about one-half a day at each manufacturer allows time to only barely skim the surface of determining GMP compliance and identify GMP deficiencies that can adversely impact the health of the population of Bangladesh.

The DGDA needs to significantly boost its GMP inspection manpower in order to perform meaningful GMP inspections at pharmaceutical factories. Based on SRA GMP national inspectorate data, the typical average time needed to inspect a pharmaceutical factory is:

- API facilities: 3 days
- Non-sterile finished dosage forms facilities: 5 days
- Sterile dosage forms facilities: 8 days

In other words, to mimic PIC/S inspections, the DGDA would need to be on site at Renata's Gazipur facility for a total of about 40 days every two years, compared to the current one-half day every two years.

Traffic in Bangladesh is a serious problem for DGDA inspectors. While a GMP inspection may be planned to last a full day, due to the high volume of traffic, the GMP inspection usually lasts three to four hours, at most. In such instances, it is recommended that DGDA staff stay at a local hotel overnight prior to the planned inspection day so that they can be on site to perform the inspection by 8:00am (or whatever the normal DGDA staff starting time is).

### **Long-Term (Implementation Longer than 18 Months):**

#### ***PIC/S Membership***

With the concurrence of the Bangladesh Association of Pharmaceutical Industries (BAPI), it is recommended that the DGDA apply for membership in the PIC/S.

PIC/S is an association of worldwide national medicines GMP inspection agencies, comprising about 45 countries (including many ASEAN countries). Membership in the PIC/S will strengthen the GMP standards in Bangladesh and enable the Bangladeshi pharmaceutical industry to enhance its efforts to export pharmaceutical products to Europe, the United States, and other SRA countries.

Membership in the PIC/S will have specific beneficial effects for the DGDA and the Bangladeshi pharmaceutical industry, including:

- Raising Bangladesh GMP standards to SRA GMP standards, thereby helping the local pharmaceutical industry boost its exports worldwide.
- Even with an observer status during the three- to five-year PIC/S accession process, membership in the PIC/S will provide GMP training for inspectors at PIC/S annual international meetings.

- Membership will allow the DGDA to benefit from joint inspections with other SRA agencies (members of the PIC/S) and the sharing of inspection reports from other PIC/S member states, minimizing the need for international travel by the DGDA to inspect overseas manufacturing facilities that export pharmaceuticals to Bangladesh.

It should be borne in mind that accession to the PIC/S is typically a five-year process, and that a fee needs to be paid to start the accession process. Accession to the PIC/S currently costs US\$ 9,100.<sup>5</sup>

It is assumed that BAPI will regard this recommendation positively and find it in its own best interests as membership would enhance the ability of the country's pharmaceutical manufacturers to significantly boost exports. As such, it might be willing pay the fee, and the subsequent fee for the DGDA's annual membership in the PIC/S.

### ***Inspection Resources: Staffing***

It is recommended that the DGDA petition the GOB to increase the DGDA inspector's salary to make it competitive with the Bangladeshi pharmaceutical industry salaries. There is currently a four and one-half fold disparity in salary and benefits between entry-level pharmacists working for the DGDA and those for entry-level pharmacists working in the pharmaceutical industry.

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<sup>5</sup> Details on the PIC/S accession process may be found at <http://www.picscheme.org/accession.php>.

## ANNEX A. ORGANIZATIONAL STRUCTURE OF THE DGDA

