Rapid Assessment of the Capacity of Drug Testing Laboratory of the DGDA of Bangladesh

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Rapid Assessment on the Capacity of Drug Testing Laboratory of the DGDA of Bangladesh

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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

Drug Testing Laboratory, Pre-approval sampling test, DGDA

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ACRONYMS

DGDA	Directorate General of Drug Administration of Bangladesh
DTL	Drug Testing Laboratory
MA	Marketing Authorization
NCL	National Control Laboratory
PQM	Promoting the Quality of Medicines
SIAPS	Systems for Improved Access to Pharmaceuticals and Services Program
USAID	United States Agency for International Development
USP	United States Pharmacopeial Convention

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- Major General Md. Jahangir Hossain Mollik, Director General, DGDA
- A. A. Salim Barami, Director, DGDA
- Dr. Md. Harun-Or-Rashid, Assistant Chief, Drug Testing Laboratory, DGDA

INTRODUCTION

Background

The Directorate-General of Drug Administration (DGDA), Bangladesh's national medicines regulatory authority, has been working together with the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program to improve the medicines registration process by adopting minimum international standards for medicines registration and implementing an online medicines registration management system (Pharmadex).

SIAPS conducted a rapid assessment in August 2014 on the capacity of the Drug Testing Laboratory (DTL) of the National Control Laboratory (NCL) under the DGDA as a part of SIAPS's larger effort to strengthen the medicine registration review process of DGDA.

As a part of the medicine registration process improvement project, the DGDA has decided to change the current medicine sample testing process to ensure the test results are available in time for the DGDA assessors make their decision to grant the product marketing authorization (MA). Currently, the DTL conducts the sample testing for pre-approval; however, the product marketing authorization is often granted based on the completion of dossier reviews before the test reports become available. This allows pharmaceutical companies to release their products into the market before the quality of the applied products are assured. Therefore, the DGDA and DTL agreed to implement a parallel process of medicine registration review by submitting medicine application dossiers and samples for testing at the same time, enabling test results to be used in the decision-making process for product MA.

Objectives

The SIAPS team visited the DTL to assess the DGDA's readiness for the implementation of the medicine registration process change. The team assessed the process of requesting the reporting pre-approval sample test and discussed how to incorporate the functionality of internal communication on pre-approval sample test into the PharmaDex system.

To understand the current challenges to changing the DGDA's process, SIAPS conducted a rapid assessment of the DTL's capacity to conduct pre-approval sample testing in August 2014. The objectives of the assessment were to:

- Review the current pre-approval sample testing process and discuss how to incorporate the functionality of sampling test communication into PharmaDex
- Identify opportunities to improve the pre-approval sampling process to ensure the quality of the products before they reach the market
- Identify any weaknesses and potential disadvantages of changing the pre-approval sampling test process

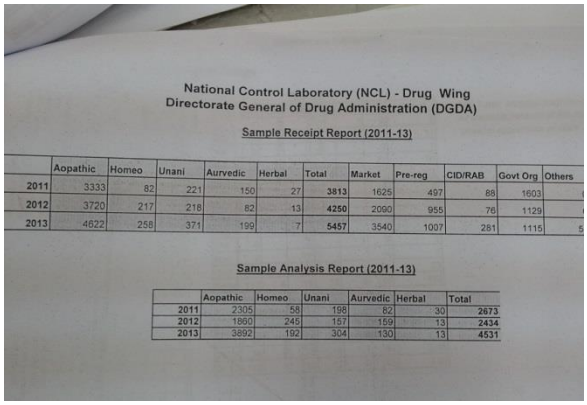
- Provide initial data to support future technical assistance to build the capacity of the DTL

Methodology

The SIAPS team visited the DTL in Dhaka, Bangladesh on August 21, 2014. They met with Mr. A. A. Salim Barami, the director of DGDA, Dr. Md. Harun-Or-Rashid, the assistant chief of the DTL Pharmacology Unit, and eight other DTL government analysts to discuss how to implement changes in the submission and reporting of pre-approval sample tests for medicine registration.

During the meeting, the officers from the DTL provided copies of relevant documents for rapid assessment on their capacity of medicine sample tests, including pre-approval tests, post-market surveillance sampling tests and other public health-related sample tests done by DTL. The reviewed documents included actual test reports, the log book of sampling tests, the organizational structure chart, a list of scientific staff with their qualifications, internal communication documents (e.g. a test request letter issued by DGDA), and the test failure record of recent years.

Figure.1. Reviewing documents at DTL



National Control Laboratory (NCL) - Drug Wing
Directorate General of Drug Administration (DGDA)

Sample Receipt Report (2011-13)

	Aopathic	Homeo	Unani	Aurvedic	Herbal	Total	Market	Pre-reg	CID/RAB	Govt Org	Others
2011	3333	82	221	150	27	3813	1625	497	88	1603	
2012	3720	217	218	82	13	4250	2090	955	76	1129	
2013	4622	258	371	199	7	5457	3540	1007	281	1115	

Sample Analysis Report (2011-13)

	Aopathic	Homeo	Unani	Aurvedic	Herbal	Total
2011	2305	58	198	82	30	2673
2012	1860	245	157	159	13	2434
2013	3892	192	304	130	13	4531

Figure. 2. Documents provided by DTL

The SIAPS team also conducted brief key informant interviews to understand their current process and their readiness to adopt the proposed pre-approval sample testing process.
The questionnaires for these interviews were selected from Module 14 ("Quality Control Laboratory") of the WHO's *Practical Guidance for Conducting a Review*[1]. In order to focus the assessment on the lab's capacity to conduct pre-approval sample testing for marketing authorization, the questionnaire was restricted to:

[1] World Health Organization, Practical Guidance for Conducting a Review (based on the WHO Data Collection Tool for the Review of Drug Regulatory Systems), 2007.

- Organization and Structure (Module 14.3): To assess the readiness in switching the current internal communication and approval system to online communication system using PharmaDex. Questions were asked regarding the linkages among organization and how the exchange of information is implemented.

- Human Resources and Inputs (Module 14.6): To assess the human resources in both quantitative and qualitative aspects. Questions were asked on:
    - The number of scientific staff involved in the testing activities
    - The number of pharmaceutical products tested and certificates issued per product category
    - The number of pharmaceutical products tested and failed to be compliant
    - The number of MA suspended or withdrawn based on the results issued by DGDA

- Infrastructure and Equipment (Module 14.7): To assess the availability and capacity of required testing equipment and scientific staff. Questions were asked on:
    - The number of scientific staff involved in the testing activities
    - The surface of the QCL
    - The number of scientific staff compared to the surface
    - The number of analysis not performed because of lack of adequate equipment

- Records and Outputs (Module 14.11): To assess how the output (test reports) from the sampling test process can be used as an input for the marketing authorization review process. Questions were asked and documents were collected on:
    - Procedures for documentation control
    - Internal procedures for the receiving sample test request
    - Internal procedures for testing, reviewing and approving the final report
    - Internal procedures for the management of samples
    - Staff members and their qualifications
    - Internal trainings for scientific staff
    - Log books of sampling tests, including requests and final reports

The SIAPS team also followed up with the DTL in cases where the data or answers were not available during the site visit.

RESULTS AND FINDINGS

Organizational Structure

There are approximately 50 scientific staff members in the National Control Laboratory (NCL), including DTL. DTL is a separate department responsible for testing medicine samples, while the vaccine wing is responsible for testing vaccines and biologics.

DTL is composed of seven units: Bacteriology Units 1 and 2; Pharmacology Unit; and Chemical Units 1-4. Each unit is composed of one head person and 5-6 technical staff.

Medicine sample testing requests are distributed to each unit depending on the types of medicines and the volume of requested tests.

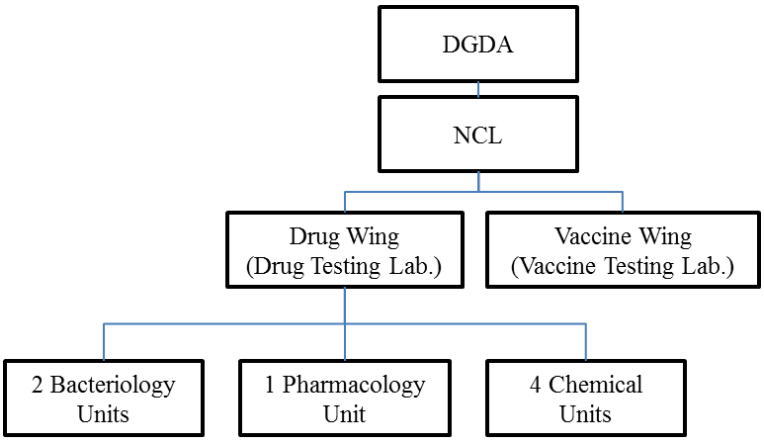


Figure. 3 Organizational structure of DTL

Staffing and Technical Capacity

The DTL analysts responsible for conducting tests and producing test reports explained that additional technical trainings for technical staff are necessary, particularly with regard to conducting certain laboratory tests and using testing equipment. The average lead time to complete the pre-approval sampling test is one month, and there is no serious backlog issues caused by the delay of pre-approval sampling tests. Once test reports are prepared by analysts, the head of the unit reviews and approves the test reports.

The DTL does not have any in-house training system, program or materials to train junior or new staff, or to evaluate their technical capacity for additional training. Limited human resources capacity and the lack of skilled technical staff prevent the lab from fully utilizing its current testing facilities.

Process of Pre-Approval Sample Testing

Currently, when applications for product marketing authorization are received, DGDA reviews the application dossiers for approval before DGDA sends out the sampling test request letters to DTL. The sampling test request is only made when the dossier review is complete and approved for marketing authorization. The request letter issued by DGDA contains all of the necessary information to conduct sample tests, including the test methods, analytical data and certified test report of the samples submitted by the applicant. DTL is not involved in reviewing dossiers on the specification and test methods of the products under review. Once the request letters and samples are received by DTL, DTL only conducts tests and sends out the test reports to DGDA.

Under the current process, applicants often release their products onto the market after the DGDA has completed the dossier review, but before the sample testing report is completed and the applicant is notified of the results. DGDA therefore does not have a mechanism to check or control the quality of products before they reach consumers, posing a serious safety risk.

Although the flowchart of medicine registration shows that the sample test results should be available before product registration is completed and marketing authorization is granted, DGDA does not currently have or enforce a tracking system to stop companies from releasing a product onto the market once its dossier review is complete and it has been recommended for registration.

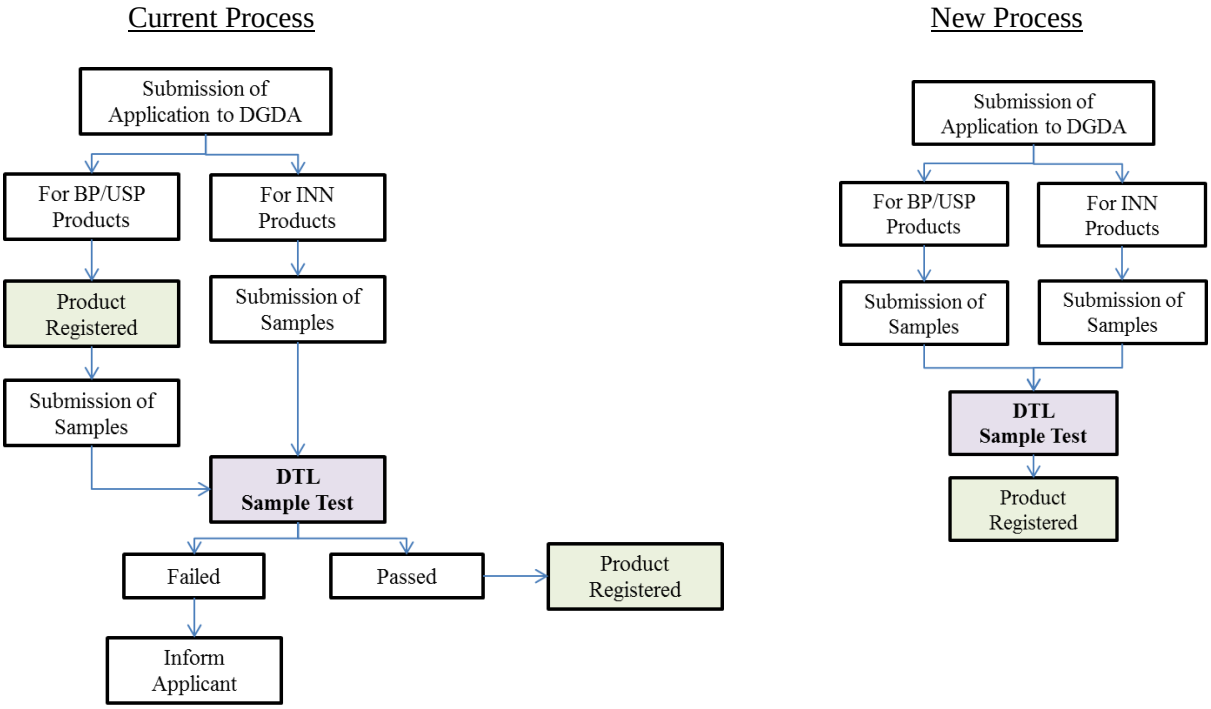


Figure. 4 Proposed process change: before vs. after

Current Burden of Pre-Approval Sample Testing

The number of pharmaceutical products tested annually in the framework of an application for marketing authorization has increased rapidly in recent years. There were 1,007 samples tested in 2013, more than double the 497 tested in 2011.

Table 1. Pre-Approval Sampling Test 2011-2013

Year	2011	2012	2013
Number of samples tested for marketing authorization	497	955	1,007

Currently, the DTL does not conduct pre-approval sample testing on active ingredients; DTL conducts sample tests only on finished pharmaceutical products. Approximately 70% of the tests carried out by DTL in the past three years are post-market surveillance. In 2013, DTL conducted 3,540 post-market surveillance tests. DTL is also responsible for other sampling tests, including those requested by the Armed Forces and other government organizations, such as the Institute of Public Health.

Table 2. Number of Tests Requested (2011-2013)

Year	Allo-pathic	Homeo-pathic	Unani	Ayurvedic	Herbal	Total	PMS	Pre-approval	CID/ RAB	Govt. Org.	Others
2011	3,333	82	221	150	27	3,813	1,625	497	88	1,603	0
2012	3,720	217	218	82	13	4,250	2,090	955	76	1,129	0
2013	4,622	258	371	199	7	5,457	3,162	1,031	121	1,093	50

Table 3. Number of Test Reports Issued (2011-2013)

Year	Allopathic	Homeo	Unani	Ayurvedic	Herbal	Total
2011	2,305	58	198	82	30	2,673
2012	1,860	245	157	159	13	2,434
2013	3,892	192	304	130	13	4,531

In 2013, the DTL received 5,457 test requests and completed and issued the test reports for 4,531 of them (83%). Compared to the completion rates in 2011 (80%) and in 2012 (65.4%) this is a significant improvement, particularly considering the volume increase in 2013. This has been made possible through infrastructure—including equipment—updates, which have been carried out with aid from the WHO in recent years.

However, due to the limited technical capacity, DTL was not able to conduct all the tests requested for pre-approval sampling tests. This is largely due to insufficient skilled human and other resources. In addition, some specific tests are still beyond the ability of the lab to perform. However, DTL is gradually increasing its capacity to cope with these growing needs.

Corrective Actions to Address the Failed Pre-Approval Sample Testing Cases

The number of pharmaceutical products that fail quality testing is still consistently high. The failure rate is suspected to be even higher than reported as the current sample size is too small to have a meaningful understanding or data to judge if the failure rate really shows the current situation of quality of medicines in the country.

The average sampling test failure rate on samples for pre-approval from the 2011-2013 period was reportedly 13.13%. The high failure rate also demonstrates the importance of conducting these tests before the products reach the market.

When a product fails pre-approval quality tests, DGDA informs the applicant of the results. However, currently neither DGDA nor DTL takes administrative follow-up actions when pharmaceutical companies release their products before pre-approval sampling test reports are issued, except informing them of the test results. When poor-quality products are released to the market, the administrative efforts to recall products, including police enforcement, are very limited.

Overall, sample testing—including pre-approval and post-market surveillance tests—failure rates have remained constant over the past seven years. However, these data are not reliable, as the number of samples collected has greatly each yaer. Of the 2,687 samples tested in 2011, 4% percent failed, up from failure rate was 2.63% in 2012 and 3.2% in 2013. The number of non-compliant samples from the 2011-2013 period shows that it fluctuates depending on the sample size of each category of the products.

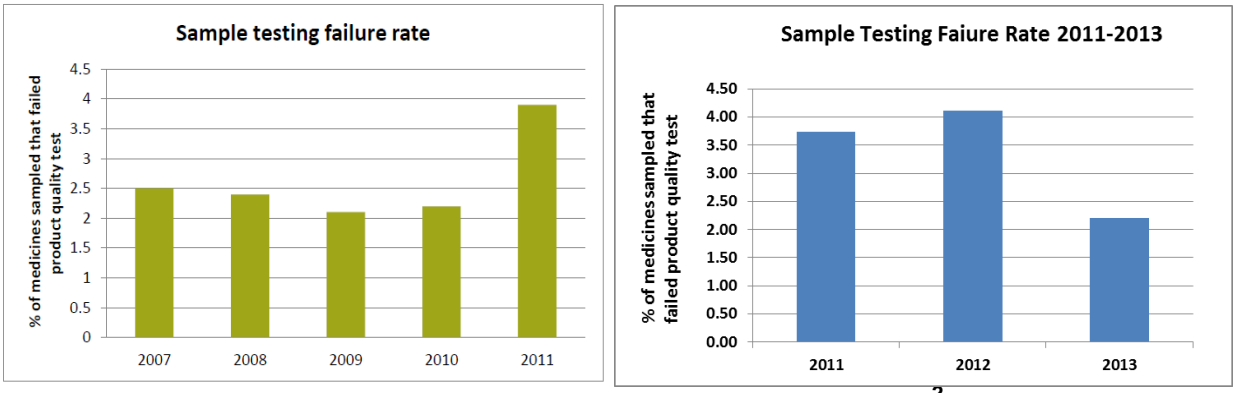


Figure. 5 Sample testing failure rate by NCL in 2007-2011[2] vs. 2011-2013

[2] SIAPS USAID, Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh, 2012. Available from: http://siapsprogram.org/publication/assessment-of-the-regulatory-systems-and-capacity-of-the-directorate-general-for-drug-administration-in-bangladesh/

Table 4. Number and Failure of Non-Compliant Samples (Substandard) 2011-2013

Year	Allopathic	Homeo	Unani	Ayurvedic	Herbal	Total
2011	82/2,305 = 3.56	3/58 = 5.17	12/198 = 6.06	14/82 = 17.07	0/30 = 0.00	111/2,673 = 4.15
2012	35/1,860 = 1.88	7/245 = 2.86	3/157 = 1.91	18/159 = 11.32	1/13 = 7.69	64/2,434 =2.63
2013	112/3,892 = 2.88	6/192 = 3.13	10/304 = 3.29	12/130 = 9.23	5/13 = 38.46	145/4,531 = 3.20

For example, the failure rate of Ayurvedic medicines (Hindu traditional medicine) seems very high (38.46%) in 2013. However, the high rate may have been inflated by the small sample size (5 failures out of 13 tested samples). DTL needs to establish clear guidance on planning the size of sample testing in order to obtain meaningful data that can truly represent the overall quality of medicines in the country.

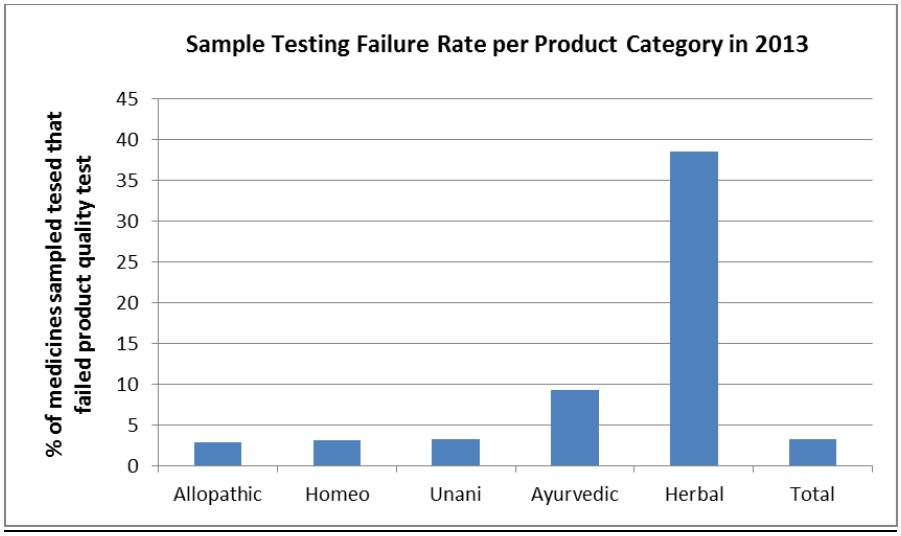


Figure. 6 Number of pharmaceutical products tested by DTL that failed in 2013

RECOMMENDATIONS

In order to ensure that all medicine samples are tested and meet quality standards before the products reach the market, it is necessary to change the current pre-approval sample test process. However, immediate technical assistance is needed to build the staff's capacity to conduct sample tests for quality of products, as the technical staff needs additional training to fully utilize renovated facilities, including new test equipment.

Computerization of recording the entire process from the requesting sample test to reporting final test report can be incorporated into PharmaDex. However, the internal approval process needs to be updated accordingly to remove redundant paperwork for internal approval.

To improve the transparency of test reports, the reviews of initial reports also needed to be recorded. Additional technical assistance may be needed if training on how to review test reports is needed to build the capacity of reviewers. The following recommendations have been made to provide guide to develop strategies and short and mid-term plan action plans:

1) Build local technical capacity to conduct required sampling tests: Promoting the Quality of Medicines (PQM) program at USP can assist DTL in building the capacity of its staff by expanding the scope of tests they can conduct and fully utilizing existing lab equipment.

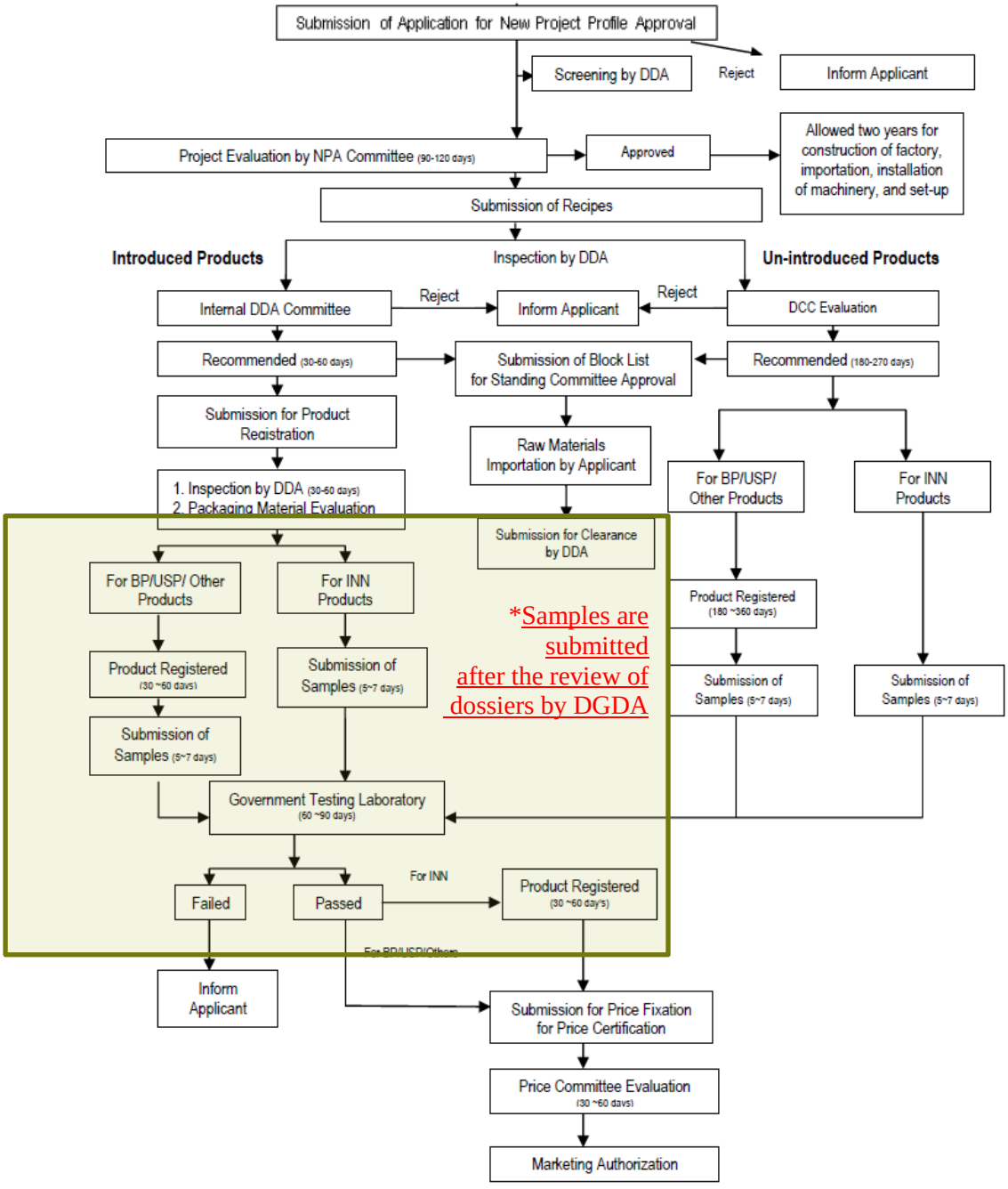
2) Address the current human resources challenges in order to handle appropriate quantity of sampling tests for post-market surveillance: In 2013, DTL was able to conduct and issue test reports on 83% of requested sample tests. To conduct all requested sample tests, DTL needs to recruit adequate number of technical staff. The number of sample test requests, including pre-approval sample test requests, has increased dramatically. Therefore, DTL needs to increase human resources in line with the increase in test requests.

3) Automate the internal communication process and management of sampling tests data: SIAPS can provide additional technical assistance to incorporate the internal approval process changes into PharmaDex. Instead of sending sample request letters via email, DTL will be able to track down the records of pre-approval sample test requests and test results online.

4) Improve the data management system to analyze test results and take appropriate corrective actions to address non-compliant test results, especially with post market surveillance cases: Together with DGDA, DTL can strengthen enforcement activities by issuing warning letters, confiscating products, or recommending that DGDA recall products when samples are confirmed to be non-compliant.

5) Further assessments: An equipment assessment is necessary to identify what DTL still needs to complete all requested tests. Further assessment is also needed to assess whether DTL conducts all the necessary tests with the proper amounts of samples.

ANNEX A. FLOWCHART OF CURRENT PRE-APPROVAL SAMPLE TEST3



[3] SIAPS USAID, Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh, 2012. Available from: http://siapsprogram.org/publication/assessment-of-the-regulatory-systems-and-capacity-of-the-directorate-general-for-drug-administration-in-bangladesh/

ANNEX B. SAMPLE TEST REQUEST LETTER ISSUED BY THE DGDA (COPY)

GOVERNMENT OF THE PEOPLE'S REPUBLIC OF BANGLADESH
DIRECTORATE GENERAL OF DRUG ADMINISTRATION
105-106, MOTIJHEEL COMMERCIAL AREA
DHAKA-1000.

No.DA/Harbal-45/11/ 10474

Date: 18-08-2014.

To
The Government Analyst
Drug Testing Laboratory
Institute of Public Health
Mohakhali
Dhaka.

Sub:- **Samples of test and analysis**

A samples of drug name "Bitter Mallon (Momordica Charantia L. CurcurbitCurcurbitaceae) 400mg Capsule" bearing code number **DA/(R)H-53/14** manufactured by **M/S. Total Herbal & Neutraceuticals, Dhaka Industrial Area, Plot No. B-31, Ruhitpur, Karanigang, Dhaka** is sent to you in original packing with proper seal of this office for test and analysis.

Each ampoule/vial/tablet/capsule/100gm powder/100ml oral liquid/100ml external liquid/ suppository/ointment/is claimed to contain:-

ACTIVE INGREDIENTS

Serial No.	Name of the substance	Quantity
01.	Bitter Mallon 400mg Capsule (Momordica Charantia L. CurcurbitCurcurbitaceae)	100 (One hundred) Capsule.

You are requested to carry out the following test and analysis and report whether the samples conforms with claims as regard to quality and quantity at your earliest.

1. Appearance/odour/colour
2. Clarity
3. pH
4. Loss
5. Weight per ml.
6. Total Solid
7. Ethanol content
8. Limit of particle size
9. Weight variation/volume variation
10. Average weight/volume per unit
11. Moisture content
12. Chemical identification (Qualitative)
13. Acid neutralising capacity &Oxide Ointment
14. Quantitative analysis
15. Disintegration test
16. Friability test
17. Hardness test
18. Biological potency test
19. Sterility test
20. Pyrogenicity test
21. Toxicity test
22. Limit text for.....
23. Test for Histamine
24. Phenonol co-efficient
25. Stability test (accelerated Stability test)
26. Impurities, if any
27. Gross adulteration, if any
28. Suitability for use as amedicine.
29. Any other test (to be specified)

The test method, analytical data and certified test report of the samples as supplied by the firm is attached.

For Director General
Directorate General of Drug Administration
Dhaka.