# Guideline on Risk-Based Post-Marketing Surveillance of Finished Medicinal Products

## Directorate General of Drug Administration

## Health Services Division

## Ministry of Health and Family Welfare

## Government of the People's Republic of Bangladesh

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PQM Promoting the Quality of Medicines

## Message from the Director General, Directorate General of Drug Administration (DGDA)

I am happy to know that the Market Surveillance and Control Department document, "Guideline on Risk-Based Post-Marketing Surveillance of Finished Medicinal Products" has been prepared and finalized by a core support committee. This guideline will facilitate the risk-based post marketing surveillance activities of DGDA field officials and will also be helpful for stakeholders.

This guideline is prepared by the core support committee, composed of DGDA officers and experts.

I would like to thank the members of the committee, observers, and facilitators for the meticulous job they performed. I would also like to thank USP-PQM and USAID officials for their contribution during the development of this guideline.

Major General Md. Mustafizur Rahman
Director General
Directorate General of Drug Administration & Licensing Authority of Drugs

## Members of the "Guideline on Risk-Based Post Marketing Surveillance of Finished Medicinal Products" Preparation Committee

### Committee

Committee members were responsible for developing the guideline.

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### Observers

Observers were responsible offering suggestions.

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## “Guideline on Risk-Based Post-Marketing Surveillance of Finished Medicinal Products” Guideline Coordination Committee

A Coordination Committee on risk-based post-marketing surveillance activities will be formed by DGDA if required. The committee members will be selected from among relevant stakeholders, along with DGDA and NCL staff, and will support DGDA to develop its yearly plan following Annex 3.

The Coordination Committee will be responsible for suggesting amendments to the Guideline, as required, for DGDA’s approval.

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# Abbreviations

| | |
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| DGDA | Directorate General of Drug Administration |
| ISO | International Organization for Standardization |
| MSC | Market Surveillance and Control (Department) |
| NCL | National Control Laboratory |
| PMS | post-marketing surveillance |
| PQM | Promoting the Quality of Medicines (program) |
| QA/QC | quality assurance/quality control |
| RB-PMS | risk-based post-marketing surveillance |
| SOP | standard operating procedure |
| TLC | thin-layer chromatography |
| USP | U.S. Pharmacopeial Convention |
| WHO | World Health Organization |

## Definitions

**falsified:** medical products that deliberately/fraudulently misrepresent their identity, composition, or source.

**post-marketing surveillance:** surveillance activities that occur following market approval of a medicine, including maintenance of product authorization and/or registration of variations or renewals; regular inspections of manufacturers, wholesalers, distributors, and retailers; quality control testing; pharmacovigilance; promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products. Post- marketing surveillance is typically considered a key regulatory function and refers to the set of comprehensive quality surveillance activities. *(Note: For the purposes of this document, this term is used to refer to aspects of surveillance that pertain specifically to medicines quality rather than pharmacovigilance, though active coordination between quality surveillance and pharmacovigilance efforts strongly recommended.)*

**quality assurance:** an integrated system of activities involving planning, quality control, quality assessment, reporting, and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence

**quality control:** all measures taken, including the setting of specifications, sampling, testing, and analytical clearance, to ensure that raw materials, intermediates, packaging materials, and finished pharmaceutical products conform with established specifications for identity, strength, purity, and other characteristics

**substandard:** also called “out of specification,” refers to authorized medical products that fail to meet either their quality standards or specifications, or both

**unregistered:** medical products that have not undergone evaluation and/or approval by a national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation

# 1. Introduction

Quality medicines are essential for efficient disease management. Substandard and falsified medicines can cause treatment failure and adverse drug reactions, increase morbidity and mortality, and contribute to the development of drug resistance. Poor-quality medicines also increase health care costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit of public health.

Strong national post-marketing surveillance (PMS) programs capable of monitoring the overall quality and safety of medical products (e.g., medicines, vaccines, biologics and biosimilars, medical devices, diagnostic kits) and responding to public health risks can help protect people from the threats posed by substandard and falsified medicines. PMS is the important function for the effective regulation of medicines and includes all regulatory activities that monitor the quality, safety, efficacy, and use of medicines on the market. [1],[2]

To ensure the availability of quality medicines for patients in Bangladesh, the Directorate General of Drug Administration (DGDA) applies the following regulatory steps:

- Authorization/registration for marketing following the assessment of product documentation, inspection to ascertain manufacturers' compliance with the principles of good manufacturing practices and approval of product information, and inspection of outlets/pharmacies.
- Post-marketing surveillance activities.
- Implementation of regulatory actions in the event of any quality problem being found.

Effective PMS can provide information about the quality of medicines available to patients and is an important part of regulatory systems throughout the country. A risk-based approach to PMS—consisting of sampling ,visual inspection, identification and compendial testing—can be an effective medicines quality monitoring system for a resource-limited country.

This guideline outlines the processes and procedures to implement effective risk-based post-marketing surveillance (RB-PMS) activities. It provides recommendations for various methodological approaches, with a discussion of their advantages and disadvantages. It also provides suggestions for preparing the sampling protocol and reports on results obtained, which will help DGDA to implement regulatory enforcement.

## 2. Objectives of Post-Marketing Surveillance

In general, PMS activities are organized to assess the quality of medicines provided to patients and generate the data that can help to formulate strategies and plans to ensure provision of quality medicines. This activity may be organized to confirm that patients are receiving quality medicines, and give reassurance that the regulatory system is functional or alert when there is suspicion that patients are not receiving satisfactory medicines.

DGDA's main objectives in implementing effective PMS are as follows:

- To evaluate the quality of medicines in the market, in different areas and regions and at various levels of the distribution/supply chain, as well as of imported medicines, in order to assess patients' exposure to poor-quality medicines and propose appropriate actions.
- To evaluate the quality of specific medicines used in the national health program.
- To identify possible causes of inferior quality of specific medicines.
- To implement plans to address the problems identified by the PMS activities.
- To test the quality of medicines and support DGDA in identifying manufacturers that are not in compliance with quality standards and regulatory measures.
- To identify whether, within a selected category of medicines, any substandard and falsified products have penetrated the market in selected areas or regions and to propose possible strategies and implementation plans to prevent this kind of incidence.

## 3. Post-Marketing Surveillance Management and Timeframe

The primary aim of PMS is to reduce harm to patients and enforce medicines quality standards. To protect patient from substandard and falsified medicine, it is crucial to monitor post-marketing of medicines throughout the country, with efficient management of surveillance activities within a logical timeframe.

The timing of sample collection is important, as seasonal changes in environmental conditions may impact the quality of medicines collected (e.g., falsified antimalarials may be more common during malaria season, and access to outlets in rural areas may be impeded in the rainy season).

Surveillance activities may include (but are not limited to) the following:

- Approved yearly plan (according to Annex 3) of surveillance activities.
- Timeframe for different activities.
- Personnel responsible for completing different steps within the estimated timeframes.
- Selection of area.
- Training and monitoring activities, testing of samples.
- Results compilation.
- Data analysis.
- Final report.
- Decision-making.
- Dissemination of results to relevant stakeholders.
- Reinforcement action (if required).

It is important to plan for the financial resources expected for surveillance before it commences.

# 4. General Considerations for Effective Post-Marketing Surveillance

## 4.1. Legal Mandate

The following section of Drug Act 1940 provides the legal basis for post-marketing surveillance:

22. (1) Subject to the provisions of section 23 and of any rules made by the Government in this behalf, an inspector may, within the local limits for which he is appointed, and in any other area with the permission of the licensing authority,

(c) take samples of any drug which is being manufactured, or being sold or is stocked or exhibited for sale or is being distributed;

23. (2) Where the Inspector seizes any drug or any other article under section 22, he shall tender a receipt therefore in the prescribed form.

23 (3) Where an Inspector takes a sample of a drug for the purpose of test or analysis, he shall intimate such purpose in writing in the prescribed form to the person from whom he takes it and, in the presence of such person unless he willfully absents himself, shall divide the sample into four portions and effectively seal and suitably mark the same and permit such person to add his own seal and mark to all or any of the portions so sealed and marked: Provided that where the sample is taken from premises whereon the drug is being manufactured, it shall be necessary to divide the sample into three portions only:

Provided further that where the drug is made up in containers of small volume, instead of dividing a sample as aforesaid, the Inspector may, and if the drug be such that it is likely to deteriorate or be otherwise damaged by exposure shall, take three or four, as the case may be, of the said containers after suitably marking the same and, where necessary, sealing them.

23 (4) The Inspector shall restore one portion of a sample so divided or one container, as the case may be, to the person from whom he takes it, and shall retain the remainder and dispose of the same as follows: -

(i) one portion or container he shall forthwith send to the Government Analyst for test or analysis;

(ii) the second he shall produce to the Court before which proceedings, if any, are instituted in respect of the drug; and

(iii) the third, where taken, he shall send to the warrant or, if any, named under the provision to sub section (3) of section 19.

As per 22 (c) and 23(3) provisions, DGDA inspectors can take any amount of sample and/or following the full quantity sampling as required for completing full phase of testing and regulatory actions. If any medicine found unregistered or non-compliance to Marketing Authorization, prosecution submitted by respective inspector to magistrate court, mobile court and drug court for taking legal action.

## 4.2. Governance

Effective PMS requires good governance mechanisms that are accountable; demonstrate transparency in testing and disseminating results; maintain confidentiality where required; avoid conflicts of interest; are equitable, inclusive, and consensus oriented; and follow the rules of law

(Ref–Drug Act 1940 §22–23 and Drug Control Ordinance 1982 §16–17) for proper regulatory actions. Regulators should be accountable to the public while remaining independent from the influence of government or industry in making decisions. DGDA has the full authority to amend this guideline when necessary.

### 4.3. Resources and Financing

DGDA should provide adequate resources to ensure the sustainability of PMS activities, including regulations, processes, budgetary provisions, and human and technical resources to implement an effective PMS strategy. DGDA should mobilize the required funds before beginning sampling and testing activities. DGDA should use a comprehensive risk assessment to optimize the use of limited resources, including financial and human resources, in the areas that need them the most. Risk-based approaches may be used to determine the types of medicines that will be sampled, sampling locations, and the appropriate analytical test to perform (as per the sampling plan and protocol in Annexes 2 and 3).

### 4.4. Human Resources and Capacity

Qualified and proficient staff with relevant education, training, skills, and experience should be assigned to perform regulatory activities. Duties, functions, responsibilities, necessary competencies (education, training, skill, and experience), and specific policies should be clearly defined and updated as needed. Capacity development is critical in making PMS sustainable; as such, a training plan for staff should be developed, implemented, and updated periodically. The National Control Laboratory (NCL), which performs medicines quality testing, should comply with international standards and guidelines, such as ISO 17025 or World Health Organization (WHO) prequalification, to ensure the reliability and accuracy of test results. Field-level staff should also be trained appropriately by the DGDA and NCL subject matter expert/trainer to perform field-level visual inspection or testing of medicines. Finally, medicines quality and PMS topics should be incorporated in relevant health-related training programs, including those for the pharmacy, laboratory, and regulatory functional units involving PMS activities.

### 4.5. Management and Planning

DGDA's PMS activities should be planned periodically (as per Annex 3) and executed throughout the year using a risk-based approach to determine sampling and testing priorities across different medicinal products in the public and private medicines supply chains. The Coordination and Planning Committee might support DGDA's PMS authority to develop its periodic plan based on national priorities and also assess potential risk factors. The Committee can provide guidance and suggestions to DGDA on how to manage or execute the plan. DGDA should develop a robust, evidence-based document management system, as strong evidence-based reporting will help toward taking regulatory actions against substandard and falsified medicines, including removal and disposal of defective and noncompliant medical products from the market.

### 4.6. Sampling and Testing

Based on PMS objectives prioritized according to a country's specific needs, sampling and testing should be conducted using an approved, effective, and rational methodology that is

developed by a national regulatory authority (as per previous experience regarding the medicines market and protocol). Similarly, resources should be optimized by using tiered approaches to testing (e.g., 3-Level Approach). Risk-based sampling methods should be used to target activities to areas and medicines that are most vulnerable and represent the greatest risk to public health.

## 4.7. Coordination and Communication

To implement effective PMS programs and activities, DGDA must coordinate closely with all officials involved in sampling and testing. DGDA should coordinate with relevant staff to establish a plan with well-defined roles and responsibilities for all employees involved. In accordance with standard operating procedure (SOP) (NRA-NRS-001), DGDA should communicate with stakeholders and the various DGDA departments/units to ensure involvement and participation. DGDA should also hold public consultations during the development or revision of regulations and guidelines relevant to the national PMS program. Regulations and guidelines should be made available to all relevant stakeholders after publication. DGDA should also inform relevant stakeholders about their roles and responsibilities.

The role of retail pharmacies, wholesale pharmacies, government hospitals, private hospitals, and national program/procurement agencies shall be as follows:

- Inform DGDA officers about any suspect of falsified medical products.
- During sampling, provide support related to sampling to the DGDA Inspector.
- After sampling, inform the Marketing Authorization Holder about the sampling of products/medicines by DGDA officials.
- Preserve all relevant documents of the sample product (e.g., challan, invoice, cash memo) in his/her custody until the disposal of the product.
- Until further instruction, preserve the quantity of sampled product provided in a sealed and suitable condition.

The role of Marketing Authorization Holders (manufacturers/importers) shall be as follows:

- Until further instruction, preserve the quantity of sample provided in a sealed and suitable condition.
- Send the test criteria of the samples to DGDA's laboratories; in addition, in the case of INN products, provide reference standards, method, and/or dossier.
- For future reference, provide the customer (e.g., retail pharmacy, wholesale pharmacy, hospital) with all relevant documents (e.g., challan, invoice, cash memo) of each product.
- In the case of substandard products, take immediate initiative for disposal, recall, raise a rapid alert, and disseminate to the public via mass media in consultation with DGDA.

The role of the Bangladesh Chemist and Druggist Somiti (BCDS) shall be as follows:

- During sampling, provide support related to sampling to the DGDA Inspector (e.g., give witness).
- Assist in recalling the product.

## 4.8. Sustainability

It is important to ensure that a PMS program is supported by appropriate legal frameworks, staffed with a qualified and proficient regulatory workforce, and financed through regular and adequate government or donor support to continue its operations. The program should be targeted to achieve sustainable PMS functions within budget. Regular strategic planning efforts with key stakeholders are also critical in ensuring that approaches, assumptions, and priorities for the PMS program remain relevant over time.

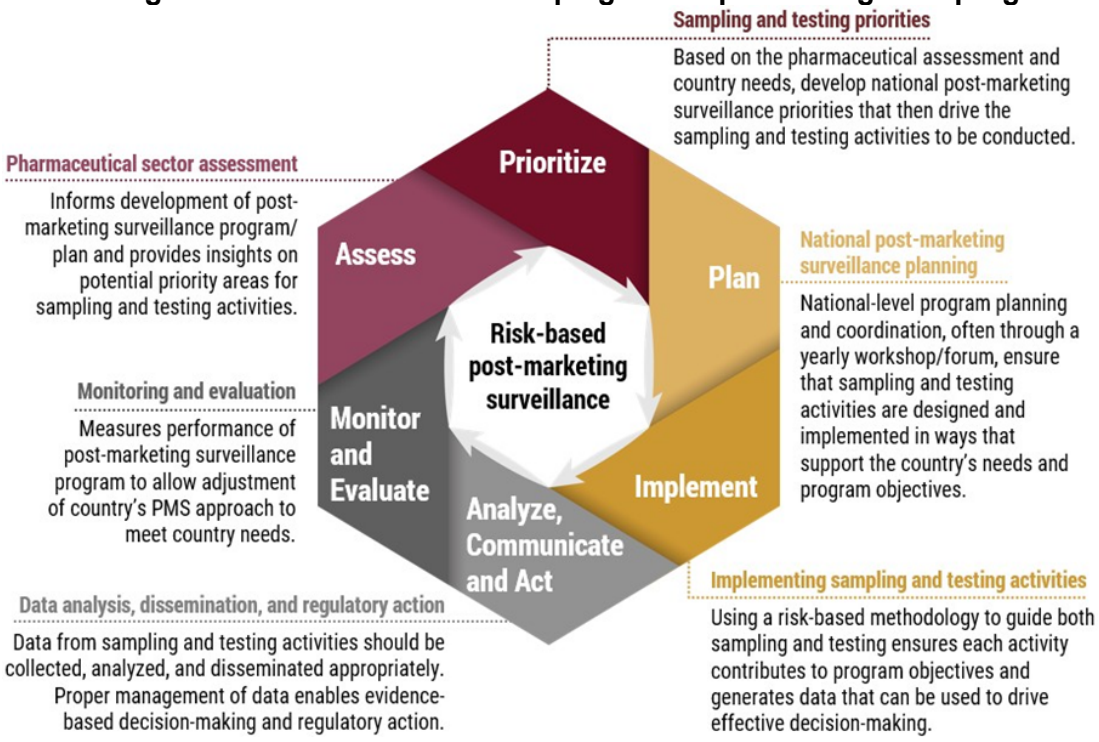
## 5. Risk-Based Approach to Post-Marketing Surveillance

Since 2010, DGDA has been conducting PMS on a regular basis. This guidance document is intended to help design and implement technically sound, strategic, and RB-PMS programs.

Effective RB-PMS programs can optimize the use of resources and support sustainable PMS programs that are integrated and implemented as a core regulatory function.

Figure 1 depicts the key aspects of developing and implementing an RB-PMS program.

**Figure 1. Framework for developing and implementing PMS programs [6]**




### 5.1. Assess: Conducting a Pharmaceutical (Medicine) Sector Assessment

Prior to initiating an RB-PMS program, and periodically as needed during regular planning processes, an assessment of the local medicine market/pharmaceutical sector should be conducted. This could be done via a retrospective data analysis, formal or informal visits, or a review of previous surveillance results (a potential public health medicines requirement from the national health program in country). When developing its PMS goals, objectives, and activities, DGDA should taking into account the previous experiences of DGDA field officials, NCL's capacity, possible risk factors affecting medicine quality, and current law and legislation.

## 5.2. Prioritize: Determining Medicines Quality Sampling and Testing Priorities

Based on the reassessment results, DGDA shall identify its unique sampling and testing needs. Below are examples of sampling and testing priorities that may be kept in mind during PMS activities:

- ***New product:*** medicines that are new to the market, especially brand name products.
- ***Expensive medicines:*** medicines that are very expensive.
- ***Fast-selling products:*** medicines that are top selling in the local market.
- ***Medicines having manufacturing and therapeutic complexity:*** medicines that may have risks associated with manufacturing complexity or dosage form, safety/efficacy (e.g., narrow therapeutic window), demand (e.g., high-burden diseases), therapeutic indication (e.g., infectious diseases), or other factors.
- ***Medicines having stability issue:*** medicines that are temperature/heat/light sensitive and/or have a tendency toward degradation (e.g., oxytocin).
- ***Medicine in port of entry/bulk procurement:*** medicines at key ports of entry (airport, seaport, land port). This type of monitoring serves as a first-line intervention, has been shown to affect the trading of poor-quality medicines, and requires close collaboration among regulatory, customs, and law enforcement authorities.
- ***Medicines from donor organization:*** medicines donated by a development partner/donor (e.g., the Global Fund), which must meet specific quality requirements to be used all over the country.
- ***National priority medicines:*** medicines required for national health programs (e.g., malaria; tuberculosis; family planning; and maternal, newborn, and child health).

## 5.3. Plan: Preparing to Implement Post-Marketing Surveillance Programs

The sampling and testing plan must ensure that sampling is unbiased and that data are meaningful and accurate enough for use in decision-making.

As per ICH's requirement (Technical Requirements for Pharmaceuticals for Human Use guidelines; e.g., the United States and countries in Europe), DGDA may consider/include the following factors in its RB-PMS plan.

DGDA inspectors carry out sampling according to an established and approved yearly plan (based on the attached Annex 3). Medicines sampling must be carried out by trained inspectors according to government rules and approved SOPs. The sampling plans should avoid any type of bias or conflict of interest. Field-level inspectors send the suspicious/doubtful sample to NCL for testing following a risk-based testing procedure (SOP No. NC-QA-GNL-066) once field-based screening has been completed. The roles of NCL and DGDA are follows:

- NCL shall carry out confirmatory testing according to regulations and guidelines (official verified/validated test methods in product dossiers, or compendial methods).
- Data are analyzed by NCL and reported to DGDA, which is responsible for sharing with relevant stakeholders or in the public domain and taking enforcement action (where applicable).
- DGDA shall conduct follow-up actions.

The PMS plan should be prepared and managed by the PMS team or a nominated planning and coordination committee that consists of representatives from DGDA, NCL, and relevant stakeholders. The committee should also be responsible for addressing issues around budget allocation and for advocating for the PMS program.

## 5.4. Implementing Risk-Based Post-Marketing Surveillance Programs

DGDA must constantly balance the risks and benefits of the medicines available in the market.

Assuring medicines quality is challenging and costly and requires close collaboration and coordination with relevant stakeholders. The application of risk-based approaches offers an opportunity to establish effective, affordable, and sustainable medicines PMS systems.

### 5.4.1. Key Sampling Considerations

Sampling and testing programs should establish inclusion and exclusion criteria, as well as substitution criteria. The following issues should be considered during sampling:

- If the selected sampling outlet is closed, DGDA officials have the authority to open the shop.
- If the medicine being sampled is not found in the selected sampling outlet, then the nearest health institution in the same area serve as a substitute.
- If the minimum quantity of medicine is not available in any outlet for sampling, there is no need to take sample. Instead, another outlet should be used. Guidance should be taken from the Market Surveillance and Control (MSC) Department in such case.
- If the seller is not willing to provide a sample, the inspector should procure via DGDA's budget.
- If the medicine in the outlet has less than a 6-months shelf-life, the sample may be sent to NCL on an urgent basis. NCL should complete full-phase testing, as DGDA can make a decision for regulatory actions.

### 5.4.2. Elements of Risk-Based Sampling

***Selection of Medicines***

Controlling the quality of all the thousands of medicines registered is extremely difficult and often unfeasible. Applying risk-based approaches to select medicines for sampling and testing as part of a PMS program is imperative. For example, sampling and testing activities could target newly introduced medicines on the market, brand-name medicines with limited safety and efficacy data, medicines with complex formulations, medicines known to have stability issues, medicines to which antimicrobial resistance is increasing, medicines in high demand, or manufacturers or suppliers with previous quality issues.

***Selection of Geographical Area***

Based on the sampling and testing plan, risk-based selection should first be applied to the geographical areas where the sampling of medicines will be conducted. Such criteria could include poor storage conditions, poor access, high disease burden, population size, porous border zone, level of drug resistance, presence of an illicit market, complexity of supply chain, and specific issues reported by prior inspections. Areas with a high risk of compromised medicines quality and/or patient safety should be prioritized. Selection criteria should be identified and applied during the initial planning.

***Collection Sites and Sampling Methods***
Risk-based assessments inform the selection of the geographical area and type of medicines to be sampled, and they must be similarly applied to select the sampling sites (e.g., depot/wholesale, retail outlet, hospital). Drug distribution occurs through public, private, or informal supply chains, each of which carries different risks. When developing site selection criteria, necessary considerations include the local knowledge of the supply chain for target medicines, the availability and accessibility of target medicines, and information on where patients obtain medicines.

DGDA should map/identify all medicines outlets in the sampling area by name and location, and the sampling method should be in accord with drug rules (Ref Drug Act 1940 section 22 & 23). Because poor-quality medicines are regularly found in hard-to-reach and unregistered outlets, it is important to establish sentinel sites in carefully selected locations that pose the greatest risk to the population. It is suggested that samples collected have at least 6 months until expiry, as this allows sufficient time for testing before the product expires.

***Sample Collection***
Under RB-PMS sampling, a statistical formula should be used to determine the number of samples to be collected. This should be well developed using the sampling format in Annex 2.

However, the number of units to collect per sample depends on the objectives of the sampling and testing activity, the type of medicine, planned tests, and the approved medicine specification following Annex 2. For example, in the case of identification of sildenafil in traditional medicine, the DGDA inspector may initially collect the required quantity of sample (as per protocol/SOP/specific test requirement) only for field-based visual inspection (as Level 1) and identification test (as Level 2). If a doubtful result is found, the inspector may collect an additional quantity (complying with the DGDA requirement) of the sample from the same source (as per the established DGDA rules mentioned in section 4.1) of this guideline and send to the NCL for compendial testing (as Level 3) for final decision-making and necessary enforcement action (where applicable).

***Handling, Storage, and Transportation of Samples***
As part of sample selection criteria, DGDA should consider the chain of custody required to preserve the integrity of each medicine from the collection sites to the location where quality testing will occur. Inappropriate handling, storage, and transportation of samples affect the overall integrity of medicines and can compromise results.

- Avoid excessive mechanical vibration during transportation.
- Store in the original container (primary packaging material), where available, and label accordingly.
- Store away from direct sunlight and excessive humidity during storage and transportation.
- Label each sample with the location of collection, number of samples collected, name of the sampler, and any observation at the time of collection.
- Samples that are light or heat sensitive may require special handling, transportation, and storage conditions. If cold storage is indicated, store in an appropriate container and monitor the temperature during transportation.

The public sector supply chain, for example, typically comprises the central medical store, district hospitals, health centers/pharmacies, informal outlets, and virtual outlets. If quality failure is observed at the central medical store after conducting risk-based sample collection and testing, it may not be necessary to sample at other levels. On the other hand, when quality failure is observed at the district hospital, it may be necessary to sample at the central medical store to determine the effect of transportation on the medicines distribution network in the country.

***Lot Sampling and Testing***

Lot sampling and testing is suitable for use at ports of entry and government procurement. Sampling and testing of medicines lots before distribution (when possible) establishes a baseline of quality for the product and could lead to a significant reduction of substandard and falsified medicines to be used for a national health program.

### 5.4.3. Risk-Based Approach to Testing or Multi-Level Testing

Medicines quality testing is an important component of PMS in DGDA. As the testing of medicine is costly and time consuming, NCL may follow a risk-based approach for medicines testing or prioritize the testing parameters as per the approved SOP (No. NC-QA-GNL-066).

Because legal action and public health decisions depend on analytical testing results, testing of medicines should be done by qualified laboratory personnel according to authorized specifications. Depending on the objectives of each sampling and testing activity, implementing a tiered approach to testing may drastically reduce the number of samples to be collected and the types of tests to be performed without affecting the overall quality of PMS. For example, if the initial screening of the sample from the divisional level showed a fail result in any parameter of visual inspection (e.g., discoloration in solid dosage form or foreign particle in injectable products), it may not be necessary to conduct additional compendial testing of the sample. However, to take legal action, an approved report containing respective nonconformance from NCL shall be mandatory.

Use of the 3-Level Approach allows countries to screen a large number of samples across many geographic areas at limited cost. The 3-Level approach includes the levels described below.

***Level 1 (Visual Inspection)***

Simple visual inspection may identify important characteristics related to product quality (e.g., registration status, expiry, product packaging) or issues with the physical characteristics of the dosage form (e.g., presentation, color, texture, and viscosity, presence of foreign particle).

Testing at this level can be primarily performed in the field at the point of sampling and can be used to identify falsified, substandard, unregistered, or incorrectly labeled medicines. For example, if a box of aspirin is discolored and moldy, the immediate action is to notify the manufacturer for further investigation and justification rather than additional field screening or compendial testing.

This visual inspection should be mandatory and performed on all collected samples. Before assessing other aspects of quality, field officials may follow a checklist as per (but not limited to) Annex 1/(NRA-MSC- 007).

Inspectors should confirm that the product is registered and not expired. When unregistered or expired products are detected, inspectors should discuss the findings with the regulatory authority to determine appropriate next steps.

Figure 2 provides a flow diagram for conducting visual screening.

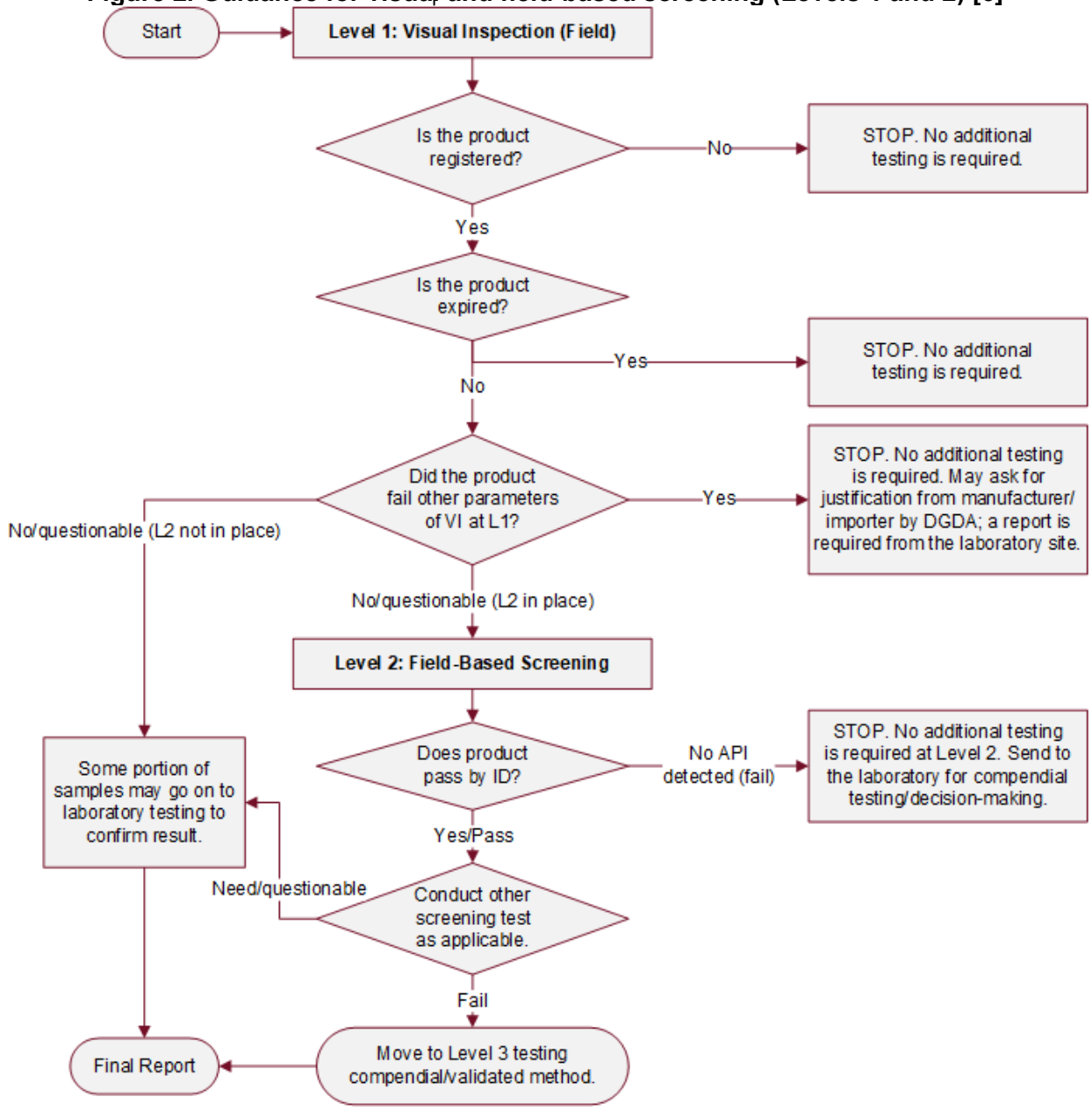
If the product passes visual inspection or if a determination cannot be made (e.g., deviations are not clearly discernable against expected product presentation), then the product should proceed to testing at Level 2 or be sent to NCL for further compendial testing as Level 3.

***Level 2 (Field-based Screening)***

Level 2 involves analytical testing of product quality using field-based screening technologies. Field-based screening technologies (e.g., Minilab™, Raman, thin-layer chromatography (TLC)) may be used to identify potential product quality issues that may not be detected at Level 1 and can further reduce the number of samples that require compendial testing (Level 3). Suspicious samples identified by visual inspection may undergo further screening (Figure 2) using one or more advanced screening tests, such as TLC and Raman and/or near infrared spectroscopy (using portable or handheld spectrometers).

This level of testing is qualitative to semiquantitative and, depending on the capability of the screening technology utilized, provides information on the identity of the active ingredient, possible degradation, and/or impurities. Alternatively, based on which screening tools are used and the tests performed, the regulatory authority may choose to send a portion of the passed samples to the laboratory for compendial testing (Level 3) to confirm the results. Samples that fail field-based screening tests may be retested at the compendial level to confirm results.

**Figure 2. Guidance for visual and field-based screening (Levels 1 and 2) [6]**




***Level 3 (Compendial Testing or Testing following Validated Method)***
Compendial testing provides the most extensive information on product quality, but it is also the most complex, expensive, and time-consuming type of testing.

Compendial testing should be carried out on suspected samples that failed field-based screening tests and, depending on the requirement, on a portion of samples to confirm the results from Level 2. The use of pharmacopeial methods or other validated methods approved by NCL/ DGDA is recommended. Note that if a product fails a test at Level 2 (e.g., the sample does not pass disintegration), the same test should be performed at Level 3 using compendial methods before initiating tests for other quality attributes. If the result from Level 2 is confirmed at Level 3, then no further testing is needed. If, on the other hand, conducting the same test using

compendial methods does not confirm the result from Level 2 testing, it is recommended that the analyst proceed with the suggested prioritization of compendial testing. However, for Level 3 testing, NCL may follow its approved risk-based testing procedure.

*Note: DGDA field officers are allowed to send the suspected medicines directly (after Level 1 testing: visual inspection) to NCL in case of the unavailability of a Level 2 testing facility or of any kind of confusion or requirement of clarification of doubtful test result; field officials may send the samples to NCL from any level of testing.*

## 5.5. Analyze, Communicate, and Act

Field inspectors and laboratory analysts should report results to DGDA as soon as confirmed data or results are available.

Depending on the data presented to DGDA and the potential public health importance of the findings, the authority may take a variety of actions, including—but not limited to—testing samples further, requesting additional information or clarification from market authorization holders, or another appropriate regulatory action such as a recall.

It is also necessary to share results with relevant stakeholders, both those involved in the sampling and in the testing exercise. Sharing this information publicly can have a direct impact on the health and wellbeing of patients and populations.

DGDA should take the following actions based on evidence of substandard and falsified medicines:

- Issue notice of warning to the company with specific corrective and preventive action recommendations.
- Take legal action against the substandard and falsified medicine manufacturer/importer, seller, and/or distributor (where applicable).
- Develop/revise and implement a voluntary recall process, relevant guidelines, and SOPs for DGDA.
- Medicine manufacturer/importer/seller/distributor should provide all necessary information of recalled products as directed by DGDA.

## 5.6. Monitoring & Evaluation: Measuring Post-Marketing Surveillance Capacity

The effectiveness of RB-PMS for DGDA to monitor medicines quality depends on many interconnected factors. In building DGDA's PMS capacity, it is important to consider the existing available legal provisions, infrastructure, systems, governance, roles, and responsibilities of each stakeholder (if applicable) and human resource skills, expertise, and ability to utilize available tools such as SOPs/guidelines/protocols, testing technologies, manuals, and training materials. Each of these components should be measured using an appropriate methodology and set of indicators. The approach to building DGDA's PMS capacity should, as much as possible, be systematic as well as pragmatic in its design, implementation, and monitoring, all of which would help optimize the use of limited resources.

DGDA should have in place a monitoring and evaluation (M&E) plan that includes indicators, targets, and a timeline. DGDA should have staff dedicated to M&E.

### 5.6.1. Data collection methods and techniques

Data should be collected using predefined indicators. For effective RB-PMS, every step of each activity must be documented and preserved. DGDA should use a combination of techniques to collect data, including the following:

1. ***Desk review:*** Review technical documents and records, which could include drug laws, executive orders, PMS inspection records, and DGDA and NCL annual or mid-term reports.
2. ***Semiformal or formal discussions and consultations:*** Discussion may be held with responsible officials within DGDA.
3. ***Field inspection:*** Field inspection is performed to collect data, including pharmaceutical products for quality testing as appropriate, to gain information on supply and distribution chains.
4. ***Existing PMS data review:*** DGDA may consider/review its existing medicines quality monitoring program data, quantitative data on samples, and test results generated during field operations.

### 5.6.2. Methods for data analysis, reporting, and presentation

Both qualitative and quantitative data collected for each predefined indicator (e.g., number of PMS samples collected, number of samples tested, number of satisfactory or substandard and falsified products) should be examined, analyzed, and (where appropriate) computed into percentages by the responsible personnel under the supervision of the MSC Department. Where necessary and appropriate, these data should be presented in tables or other graphic depictions for better visualization. In the analysis, both the number and proportion (numerator/denominator) expressed as a percentage (%) should be used for selected indicators. Most indicators are expressed in numbers to explicitly reflect the actual data, which may not provide a true picture if expressed as a percentage. If a percentage is expressed, it may enhance the reader's understanding if numerical numbers are also provided.

# Annexes

## Annex 1: Visual/Physical Examination Checklist

### Test Results and Observations

| No. | Parameters | Specification(s) | Result | | Results/Other Observation |
|---|---|---|---|---|---|
| | | | Pass | Fail | |
| 01. | Labelling (e.g., brand name, generic name, pharmacopeial reference, manufacturer name with address, label claim, number/quantity of samples, DAR no., manufacturing date, expiry date, storage condition, indication, special instruction) | Should be matched with the DGDA Directory. | | | |
| 02. | Size, shape, color, and design of primary and secondary packaging materials | Should be matched with the DGDA Directory. | | | |
| 03. | Odor (immediately upon opening the outer and immediate containers) | No odor, except for flavored tablets and those with active ingredients normally having characteristic odor. | | | |
| 04. | Uniformity of size (visual inspection) | Uniform in size | | | |
| 05. | Uniformity of shape | Uniform in shape | | | |
| 06. | Uniformity of color | Uniform in color | | | |
| 07. | Color of tablets/capsules in bottle (in case of glass container) | Uniform in color | | | |
| 08. | Uniformity of coating (may be film coated, sugar coated, or enteric coated) | Uniform in coating | | | |
| 09. | Tablet core fully covered | Uniform coating with core fully covered | | | |
| 10. | Polishing | Uniformly polished and free of adhering fine powders. | | | |
| 11. | Markings (e.g., scoring, letters) | Uniform and identical | | | |
| 12. | Breaks | Free of breaks | | | |
| 13. | Cracks | Free of cracks | | | |
| 14. | Splitting | Free of splitting | | | |
| 15. | Capping and cavitation | Free of capping or cavitation | | | |
| 16. | Embedded surface spots or contamination | Free of embedded surface spots or contamination | | | |
| 17. | Foreign particulate contamination | Free from foreign particulate | | | |
| 18. | Evidence of embedded or adherent foreign matter | Free of evidence of embedded or adherent foreign matter | | | |
| 19. | Pinhole | Free of pinholes in capsules | | | |
| 20. | Presence of empty capsules | Free of any empty capsule | | | |
| 21. | Presence of open or broken capsule | Free of open or broken capsule | | | |
| 22. | Capsule not intact; cap separate from body | Capsule intact | | | |
| 23. | Stickiness | Non-stick | | | |
| 24. | Container/bottle free of extraneous material | Container/bottle free of extraneous material | | | |
| 25. | Color and odor of the solution/ suspension | Uniformly colored and contains flavor which is mentioned on the bottle/container | | | |

| No. | Parameters | Specification(s) | Result | | Results/Other Observation |
|---|---|---|---|---|---|
| | | | Pass | Fail | |
| 26. | Presence of foreign particles (liquid) | Free of foreign particle | | | |
| 27. | Taste of the liquid/organoleptic taste | Taste mentioned on the label/container | | | |
| 28. | Others (specify) | | | | |
| 29. | PIL | | | | |

## Annex 2: Format for Risk-Based Sampling

### 1. Selection of area for sampling: Put (√) marks

| Name of area | Type of area | Sampling point | Associated risk factor |
|---|---|---|---|
| Division:<br>District:<br>Upazilla/Thana:<br>Others: | □ Urban<br>□ Rural<br>□ Hill tracts<br>□ Broader area<br>□ Remote area<br>□ Over populated area<br>□ Riverine area<br>□ Others: | □ Retail pharmacy<br>□ Wholesale pharmacy<br>□ National program<br>□ Depot<br>□ CMSD<br>□ Manufacturing facility<br>□ Government hospital<br>□ Private hospital/clinic<br>□ Community clinic<br>□ Others: | □ Incidence/prevalence of the disease<br>□ Sudden breakout of disease<br>□ Potential to abuse<br>□ Areas with complex distribution systems<br>□ Others (please specify): |

### 2. Selection of medicines to be collected as sample

| Selected medicine | Physical form | Therapeutic category | Associated risk factor |
|---|---|---|---|
| | □ Solid (e.g., tablet/ capsules/powder)<br>□ Semisolid (e.g., cream/ paste/gel/suppositories)<br>□ Liquid (e.g., syrup/ solution/emulsion/ suspension)<br>□ Gaseous (e.g., inhaler/ aerosols)<br>□ Injectable product<br>□ Vaccine<br>□ Medical device<br>□ Biological product<br>□ Others: | □ Cardiovascular<br>□ Respiratory<br>□ Tuberculosis<br>□ Gastrointestinal<br>□ Renal<br>□ Neurologic<br>□ Psychiatric<br>□ Hormone preparation<br>□ Urologic<br>□ Rheumatologic<br>□ Ophthalmic and otolaryngologic<br>□ Dermatologic<br>□ Antibiotic<br>□ Others: | □ Fast moving<br>□ Costly product<br>□ Imported product<br>□ Medicines with stability issue<br>□ Manufacturing complexity<br>□ National priority<br>□ New product<br>□ Medicines of manufacturers with previous quality compliance issue/history of manufacturing substandard and falsified products<br>□ Laboratory testing capacity<br>□ Others (please, specify): |

### 3. Number of units per sample

The distribution of collected samples (total quantity) against each test requirement:

| Level of test | Test parameter | No. of units per sample | Remarks |
|---|---|---|---|
| Level 1 | Visual inspection | | |
| Level 2 (field-based screening) | Identification by TLC | | |
| | Disintegration | | |
| | Others (specify) | | |
| Level 3 (laboratory testing) | Identification | | |
| | Assay | | |
| | Dissolution | | |
| | pH | | |
| | Weight/ml | | |
| | Others (please mention) | | |
| | | | |
| | | | |
| | | | |
| **Total** | | | |

***Sampling quantity determination 10 (statistical formula):***

Minimum sample size = $[Z^2(p)(1-p)]/d^2$, where:

$Z$ = critical value (e.g., 1.96 at 95 % confidence level)

$p$ = prevalence (e.g., failure rate)

$d$ = confidence interval

Note: The minimum quantity of sample is as follows:

- for tablet/capsule: 1 strip containing at least 4 dosage units
- for liquid or injectable or semisolid dosage form: at least 1 container

*Level 1: Visual inspection, will be done by field officer at the point of collection.*

*Level 2: Screening test using Minilab™ or other available screening devices; will be done by field officer at sentinel site.*

*Level 3: Confirmatory test in laboratory, will be done at DGDA's laboratories. Sampling will be as per legal mandate 4.1.*

Comments:

## 4. Sample collection records

Recorded as per:

□ DGDA approved form

□ Visual inspection checklist

□ Others (specify):

## 5. Sample storage and shipping

As per:

□ Manufacturer's recommendation

□ DGDA standard procedure

□ Others (specify):

## 6. Sample analysis

| Prepared by (Name) | Designation | Sign and date |
|---|---|---|
| | | |

## Annex 3: Yearly Plan for Risk-based Sampling, DGDA, Bangladesh

**Year: _____**

| No. | Product/ Generic Name | Type of Medicine | Risk Factors | Proposed Manufacturers | Preferable Area/ Region for Sampling | Preferable Sampling Spot | No. of Sampling/ Year | Responsible Person | Sampling Status | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **Note:** | | | | | **No. of Sample** | | | | | |

## 6. References

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