GUIDELINES ON RISK-BASED SAMPLING & TESTING OF DRUGS

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This draft guideline is uploaded on the official website of DRAP on 29th February 2024 seeking comments and suggestions from stakeholders on the draft document. Stakeholders can submit their comments and suggestions within 15 days of uploading this document using the prescribed format, (further information on comments submission can be accessed on this link. Comments and suggestions can be forwarded via email to mehwish.tanveer@dra.gov.pk with a copy to mahvash.ansari@dra.gov.pk or can be posted at the following mailing address: Assistant Director (QC-II), Quality Assurance & Laboratory Testing, Drug Regulatory Authority of Pakistan, 3rd floor, TF Complex, 7th Mauve Area, G-9/4, Islamabad.

Drug Regulatory Authority of Pakistan

Islamabad - Pakistan

1. HISTORY

This is the first edition of these guidelines.

2. APPLICATION

This document applies to the Inspectorate and Quality Control Laboratories of Regulatory Institutions to develop a uniform protocol for the sampling and testing of drugs. The current initiative "Risk Based Drugs Sampling and Testing (RBDST)" is a systematic approach to quality control testing focusing on drugs, manufacturers, and supply chain points.

3. PURPOSE

These guidelines aim for:

i. Inspectors to perform uniform, precise, and meaningful official drug sampling for testing as part of pre-market approval and post-market surveillance.
ii. To enhance the efficiency and effectiveness of the sampling and testing activities through proper planning and implementation.
iii. To ensure the availability of quality drugs to the public by targeting the drugs with high risks by virtue of intrinsic nature or external factors.

These guidelines are drawn in conformity with the legal requirements of the Drug Act, 1976 and the DRAP Act, 2012. In the event of any contradiction between the contents of this document and any written law, the latter should take precedence. The Authority accepts no liability for any errors or omissions in this guidance document, or for any action / decision taken as a result of using this document. The Authority reserves the right to amend any part of these guidelines whenever it deems fit.

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4. GLOSSARY

Acronyms

ACE	Angiotensin-Converting Enzyme
API	Active Pharmaceutical ingredient
CoA	Certificate of Analysis
DRAP	Drug Regulatory Authority of Pakistan
DQST	Drug Quality Sampling and Testing
EDQM	European Directorate for the Quality of Medicines and HealthCare
FDA	Food and Drug Administration USA
FDP	Finished Drug Product
FTNIR	Fourier transform near-infrared
GMP	Good Manufacturing Practice
ICH	International Council for Harmonization
NRA	National Regulatory Authority
OMCL	Official Medicines Control Laboratory
QCL	Quality Control Laboratories
RBDST	Risk Based Drugs Sampling and Testing
USP-PQMS	United States Pharmacopeia- Promoting the Quality of Medicine Plus
PIC/S	Pharmaceutical Inspection Cooperation Scheme.
PSI	Product Specific Inspection
WHO	World Health Organization

5. DEFINITIONS

Batch (or Lot)	means a defined quantity of starting material, packaging material, or finished product processed in a single process or series of processes so that it could be expected to be homogeneous in the case of continuous manufacture the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity, and to complete certain stages of manufacture it may sometimes be necessary to divide a batch into a number of sub- batches, which are later brought together to form a final homogeneous batch;
Distributor / Wholesaler	means a person/ entity, buying the products for the purpose of selling again.
Drug	As defined in the DRAP Act 2012
Drug Court	means a Court established under section 31 of the Drugs Act 1976.
Expiry date	means the date stated on the label of a drug after which the drug is not expected to retain its claimed efficacy, safety, quality or potency or after which it is not permissible to sell the drug;
Export	with its grammatical variations and cognate expressions, means to take out of Pakistan by sea, land or air
Government Analyst	means a Federal Government Analyst or a Provincial Government Analyst appointed under section 16.
Import	with its grammatical variations and cognate expressions, means to bring into Pakistan by sea, land or air.
Inspector	Inspector" means a Federal Inspector or a Provincial Inspector appointed under section 17.
Label	means a display of written, printed or graphic matter upon the immediate container, or the outside container or wrapper of a drug package.
Manufacture	manufacture means all operations of production, quality control, release, storage and the related controls.
Manufacturer	means a company that carries out at least one step of manufacture.
Pharmaceutical Product	means any drug intended for human use or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form.
Pharmacy	Means a retail shop which provides pharmaceutical drugs
Prescribed	means prescribed by rules.
Quality Control	means any laboratory notified for the test/analysis of drugs and therapeutic

Laboratory (QCL)	goods.
Qualified Person	means a person responsible for assuring the quality of drugs.
Recall	means the removal of specific batch/batches of a therapeutic good/product from the market for reasons relating to the quality, safety or efficacy and/or if they are not in line with the particulars provided in registration / enlistment application of the product.
Registered drug	means any drug registered under section 7.
Specifications	when applied to a drug mean- (i) such specifications as may be prescribed; or (ii) when the specifications are not prescribed, the specifications as contained in the most recent edition of any of the following publications, namely: - (1) the Pakistan Pharmacopoeia; (2) the International Pharmacopoeia; (3) the European Pharmacopoeia; (4) the United States Pharmacopoeia; (5) the British Pharmacopoeia; (6) the British Pharmaceutical Codex; (7) the United States National Formulary; and (8) such other publication as may be prescribed: Provided that, if the specifications do not appear in the most recent edition of any such publication, the specifications appearing in the next preceding edition of such publication in which the specifications appear shall apply; or (iii) if no specifications are either prescribed or contained in any of the publications referred to in sub-clause (ii), the specification approved for the purpose of registration under this Act.
Storage	means storage for sale and "to store" or "stored" shall be construed accordingly.
Substandard and Falsified (SF) Products	Substandard drug means a drug as defined in Section 3 (zz) of the Drugs Act, 1976. Whereas Falsified products include Spurious, Adulterated, Misbranded and Counterfeit drugs (as defined in Section 3 (zb), 3 (a), 3 (s) and 3 (f) of the Drugs Act 1976 respectively).
Supply chain	means transfer of ownership of API i.e. the upstream supply chain (sources and path of ingredients that go to the manufacturer) and the product i.e. downstream supply chain (path of the finished product after it leaves the manufacturer) for each requirement regarding pedigrees/transaction records, authentication / verification.

6. INTRODUCTION:

The core mandate of the Drug Regulatory Authority of Pakistan (DRAP) is to ensure the availability of quality, safe, and efficacious drugs to the masses at reasonable prices through effective coordination and enforcement of the Drugs Act, 1976.

The tools used to achieve this mandate are:

- Authorization/registration for marketing with the assessment of products documentation, inspection of manufacturers' compliance with the principles of good manufacturing practices (GMP) and approval of products' information.
- Post-marketing surveillance activities including maintenance of products' authorization/registration through variations or renewals, regular inspections of manufacturers, wholesalers/distributors/retailers, quality control testing, and pharmacovigilance; and
- Implementation of regulatory actions if any quality problem is found.

The implementation of these tools needs substantial resources including infrastructural, monitory, human and knowledge resources. To optimize these resources of the national regulatory system (DRAP, Provincials and States Drug Control Administration). The DRAP has initiated the use of risk-based approaches in its functions and practices. The current initiative "Risk Based Drugs Sampling and Testing (RBDST)" is a systematic approach to quality control testing focusing on drugs, manufacturers and supply chain points with maximum/high risk hence it involves prioritization considering maximum output at optimum resources.

The guidance document for this initiative (RBDST/DRAP/001.19) has been prepared in assistance with documents such as ICH Q9 (Quality Risk Management), WHO working document QAS/15.630, and USP-PQM guidance document for implementing risk-based post-marketing quality surveillance in low and middle-income countries.

7. RISK-BASED SAMPLING CRITERIA:

In addition to samples taken by the inspectors in a relation to reports, complaints and intelligence on the compromised quality (substandard or falsified) of drugs being

manufactured by a legitimate manufacturer(s) or the unauthorized manufacturer(s) available at any manufacturing site or any sale outlet or sampling for pre-qualification for procurement by any government agency, the following risk-based criteria will be used in sampling and testing of active pharmaceutical ingredients, excipients, packaging material, and finished products.

7.1. Active Pharmaceutical Ingredients

Sr. No.	RISK TYPE	EXAMPLES
1.	Animal origin (special concerns for contamination by pathogenic microorganisms).	Heparin, Warfarin, Glucosamine, Chondroitin Sulfate, etc.
2.	Pharmacological Class/indication	Azithromycin, Chloramphenicol, Sofosbuvir, Famotidine, Indomethacin, Barbital etc.
3.	Harmful impurities as part of manufacturing (Genotoxic / carcinogenic)	Sertraline (I-Naphthol and 1, 2-Diclorobenzene) Valsartan, Amlodipine besylate, Nelfinavir mesylate, losartan, carbamazepine, phenytoin, cefotaxime.
4.	Toxic residual solvents.	Benzene, Carbon Tetrachloride, 1,2-Dicloroethane, 1, I-Dicloroethene, 1,1, I-Trichlorethane.
5.	Viral risk in case of RDNA-based drugs.	Polio vaccine, Rabies vaccine, and Hepatitis B vaccine.
6.	High technology of quality control.	Delayed/sustained release pellets/granules, APIs with multiple impurities.
7.	Multiple API manufacturers for a single medicinal product.	Different synthetic routes or purity grades thereby may contain different impurities or different concentrations of the same impurity e.g. Cefixime, Cephradine, Sofosbuvir, Ladipasvir, etc.
8.	APIs have both human and Animal use.	Prednisolone, Piroxicam, Levothyroxine, Amoxicillin, Metronidazole, Chloramphenicol, Gentamycin etc.

7.2. Excipients

Some excipients used in the production of different dosage forms pose risks of different types such as compendial or non-compendial grade, Carcinogenic potential contamination by microorganisms or risk of known toxic impurities.

i. Compendial or Non-compendial e.g. Starch, Celluloses, Gums, etc.
ii. Transmissible / Bovine spongiform encephalopathy (TSE/BSE) e.g. lactose, Gelatine, Starch.
iii. Known toxic impurities e.g. Glycerine, talc.
iv. Micro-organisms e.g. Mag. Stearate, Starch.
v. Carcinogenicity e.g. Artificial flavours, colours, talc etc.

7.3. Packaging Material

Packaging materials such as glass, plastics, metals, rubber and aluminium foil are subjected to various quality control tests such as hydrolytic resistance test, leakage test, test for leachable and extractable and thin-holes etc. These tests are normally not performed properly or even not performed by the pharmaceutical manufacturers hence pose risks to the dosage forms.

7.4. Finished Products

S. No.	RISK TYPE	EXAMPLES
1.	Drugs that are new to the market.	Sofosbuvir, Ladipasvir, Velpatasvir, Dexlansoprozole, Epigliflozin, Cinnacalcet, Sacubitril etc.
2.	Manufacturing complexity.	Sustained release / delayed release tablets, patches, sterile products etc.
3.	Problematic Bioavailability	B-blockers, Calcium Channel blockers, ACE inhibitors.
4.	Stability (Temp / Humidity / Light sensitivity)	Amoxycillin / Clavulmic Acid tablets, Aspirin tablets, Mecobalamine tablets, B-lactam antibiotics etc.
5.	Safety / efficacy (Narrow therapeutic window)	Digoxin tablets, Aminophyllin tablets, Levothyroxin tablets, Narfarin tablets, Phenytoin tablets etc.
6.	Demand (High burden disease)	Anti-diabetics, Anti-hypertensives, Anti-tubercular drugs, Anti-viral (Hepatitis) etc.
7.	Therapeutic indication (e.g. infections disease)	Anti-biotics, Antifungal drugs.
8.	Specific dosage form: i. Solubility ii. Dissolution	

	iii. Potency iv. Sterility v. Dose variability	i. Low solubility e.g. gliclazide, glimepride, pioglitazone, Velpatasvir, tacrolimus, cinnacalcet etc. ii. Problematic dissolution e.g. Diclofenac potassium tablets, Pantoprazole tablets, Ciprofloxacin tablets. iii. Potency e.g. a-calcidol, Betamethasone dipropionate, triamicinolone acetonide, alprazolam, respiridone etc. iv. Sterility e.g. all injectable drugs. v. Dose variability e.g. MDIs.
9.	Donation drugs	Mebendazole tablets, Birth control pills etc.
10.	Program drugs	Tuberculosis control program, Mothers & Child Health Program, Malarial Program etc.
11.	Imported drugs especially those manufactured / packed / analyzed at different sites / countries.	Different class drugs fall in this category.
12.	Drugs for special / target population (children, aged people).	Rivastignine tablets, Donepezil tablets, Cefixime syrup, Clarithromycin drops, Paracetamol etc.
13.	Therapy drugs – Long term.	Anti-diabetics, Anti-lipidemic, Anti-hypertensive drugs.
14.	Critical life-saving products.	Adrenaline, Hydrocortisone Injection, Methyl prednisolone Injection etc.
15.	Products likely to be falsified.	Anti-biotics, Anti-malarials, Anticancer, Sex stimulants.
16.	Rare disease drugs.	Ampholericin B (Leshmaniasis), Cyclosporine (Acquired Aplastic Anemia), Viroconazole (Aspergillosis) etc.

7.5. Supply Chain Points Risks

S. No.	SUPPLY CHAIN	RISK TYPE
1.	Manufacturer	➢ History of non-compliance / Drugs failure. ➢ Multiple dosage forms. ➢ Large number of Registered Drugs. ➢ Major market share holder. ➢ Elapsed time since last inspection. ➢ Newly licensed manufacturer.
2.	Importer	➢ In-appropriate storage conditions. ➢ Business run without the involvement of qualified / authorize person.

3.	Wholesale / Distributor	➢ In-appropriate storage conditions. ➢ Premises run by non-qualified / authorize person.
4.	Pharmacy/Medical Store	➢ In-appropriate storage conditions. ➢ Un-licensed premises. ➢ Premises run by non-qualified / authorize person.

8. RISK-BASED SAMPLING PROCEDURE:

8.1. Sampling

8.1.1. Sampling Process at Manufacturing Site

a. Samples should be taken in a suitable container/ original packing using an adequate sampling method to preserve the integrity of the sample and also to avoid exposure risks.
b. Samples should be taken in sufficient quantity (Refer to CDL, DRAP, guidance document) to help possible required QC tests performed by the laboratory on the sample.
c. Sample should be taken, sealed, divided into portions, and sent to the laboratory for test/ analysis as per provisions of section 19(2) & (3) of the Drugs Act, 1976.
d. Samples collected should have preferably be at least 06 months of remaining expiry in order to allow sufficient time for analysis by the laboratory, extension in time period and retesting by the appellate as case may be.
e. The medicine labels and package leaflet should not be removed or damaged.
f. Cleaning/Hygiene and Storage conditions at the site (temperature, humidity, access of light, and any other observation) should also be recorded in the prescribed form.
g. If possible photographs of the storage area, the stocks stored and samples may be taken which will be sent to the laboratory along with the samples.
h. In case of sampling being done from the manufacturing facility, the manufacturer's batch certificates of analysis along with the method of testing (especially when the manufacturer's method is not in any pharmacopeia) and reference standards of the API and impurity(s), if required, should also be obtained with the samples, recorded on the sample form and send to the laboratory along with the samples.

8.1.2. Sampling Process at Sales Outlets

Special considerations while sampling from sales outlets may include:

a. Samples should be taken in original containers/packing without removing/damaging labels, package leaflets and other objects being part of the finished products packs.

b. In circumstances where available samples are less in quantity than as required under rules.

c. Legal documents such as warranty, inventory records, qualified person's supervision, and good storage and dispensing practices at the outlet should also be checked and their copies be obtained.

d. The sampling process may be strengthened by using screening techniques such as FTNIR Spectrophotometry, Roman Spectrophotometry, etc., especially searching for falsified drugs.

e. Letter of authorized distributor, if relevant, should also be checked.

8.1.3. Sampling Process at Port (Import/ Export Consignment)

Special considerations while sampling at port (import/export consignment) may include:

a. Sampling should be done in such a way that representative samples of the consignment to be taken for test/analysis.

b. Adequacy of the storage conditions at the port and system for monitoring storage conditions during shipment be checked and recorded.

c. Necessary documents such as drug registration letter, import or export authorization letters from DRAP and other import or export documents should also be checked and their copies should be obtained.

Note: The Inspector may ask guidance during sampling at any site from notified person in Directorate of Quality Assurance and Lab Testing and the Lab Director/Government Analyst.

8.2. Storage and Transportation

Storage and transportation of the samples to the testing laboratory should be done according to the requirements set out in paragraph 2.3 of *WHO Guidelines for sampling of pharmaceutical products and related materials*. It should be done as quickly and straight as possible so as not to jeopardize the quality of collected samples.

- The samples should be kept in their original packaging and under storage conditions as specified on the label; freezing should be avoided and, where required, the cold chain should be retained.
- For transport all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport. Any residual space in the container should be filled with a suitable material.
- In case of temperature-sensitive drugs, temperature data loggers may be included within shipments to document adequate temperature in prolonged transit.
- A covering letter, copies of sample collection forms and, if available, copies of manufacturers' batch certificate of analysis should accompany the samples.
- In the case that collectors are not transporting samples directly to the testing laboratory, samples with the accompanying documents should be sent by a courier service. Laboratory concerned should also be informed through email. For each shipment it should be clearly indicated that samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market.
- Copies of sample collection forms and, if available, copies of manufacturer's batch certificates of analysis should also be sent to the survey coordinator or person preparing the survey report.

9. RISK-BASED TESTING:

The risk based testing will primarily consider the USP-PQMS three level approach that proposes that testing be conducted at three levels i.e. field based visual inspections (First level), field-based screening tests (second level) and laboratory tests using compendial or other approved methods (third level). Other risk based considerations will include the following:

- Testing be done by the laboratory while considering all the information provided by the inspector with the samples.
- Sample of injectable preparations will be tested immediately after receipt for any adulteration by any foreign particles, fibers, glass particles or colour change and provisional report will be submitted to the inspector for immediate corrective action followed by final report containing results of all relevant tests performed on the sample.
- Sample taken in response of current international concerns on quality, safety and efficacy be given top priority in testing.
- Samples suspected to be spurious, falsified, falsely-labelled or counterfeit will be tested on priority. The identification test will be the main test in such cases.

- Samples with apparent physical defect will also be tested on priority.
- Samples with short shelf life will also be tested on priority.
- Sampling place/location and sample age will especially be considered so that efforts for any degradation product and choice of proper analytical method can be made.
- Testing will be done using validated/verified pharmacopeial methods or other approved methods in strict accordance with according to Drugs (Specifications) Rules, 1978.

10.PRE-APPROVAL SAMPLE COLLECTION AND TESTING:

The pre-approval inspection, for products to be manufactured locally or imported, will include the collection of samples for validation of the analytical methods and quality assessment by the DRAP. Normally the sample size should be sufficient for three full analyses. Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

- Tablets and capsules: 300 units of production;
- Injections (single component): 100 units of production;
- Injections (combination): 100 units of production plus 10 samples of each component;
- Oral powders for reconstitution: 10 units of production; oral liquids: 1 litre.

It is important to collect, with the samples, the relevant manufacturer's analytical documentation, namely a copy of the analytical methods used by the inspected laboratory and the report of the analyses performed by the applicant on the batch sampled. A method validation report may be of some use in better understanding and reproducing the analytical methods. Problems encountered in the performance of the analyses may be resolved by an exchange of information between the applicant and the government laboratory.

Samples are tested in accordance with methods described in the application. If there are problems with the methods that require additional information from the applicant, the laboratory director must review the situation and decide whether the applicant should be contacted. The written request should be included in the documentation submitted to the review analyst.

Each method validation/verification report should contain the following:

- The identification of the test samples received, a description of the product tested, and confirmation of conformity with the product described in the application.
- The original analytical worksheets with calculations, the results of all tests performed, comments by the analyst(s), associated spectra, chromatograms, etc., and a comparison of the results obtained with the applicant's data and with the applicable specifications.
- An evaluation of each test performed by the applicant and the laboratory.
- A recommendation as to whether the methods are acceptable, acceptable only after specified changes have been made, or unacceptable.

If samples have not been collected in the course of a pre-approval inspection, the results of the analytical examination of the samples submitted by the applicant may nevertheless be used as supporting information.

The reserve samples, associated documentation, and copies of laboratory reports should be stored in an orderly and retrievable way for a specified time period. It is usually recommended that all material should be kept for a minimum of 3 years or for 1 year after the expiry date of the finished product. The quality assessment will be more relevant in the case of imported samples as commercial batches may already be produced by the manufacturer.

11.REPORTING AND REGULATORY ACTIONS:

The government analyst to whom a sample of any drug has been submitted will report as per provisions of Section 22(1), (2) & (3) of the Drugs Act, 1976.

The regulatory actions, if any, will be made as per relevant provisions of the Drug Act, 1976, which may include:

i. Recall of the stock from the market.
ii. Seizure of the stock.
iii. Order for "not to dispose of" the stock.
iv. Prosecution in Drug Court.
v. Suspension and / or cancellation of registration.
vi. Product specific inspection.
vii. Warning.
viii. Non approval for registration.
ix. Any other.

REFERENCES

1. WHO Working document QAS/15.630, Guidelines on the Conduct of Surveys of the Quality of Drugs, June, 2015.
2. WHO Technical Report Series, No. 902, Guidelines on Pre-approval Inspections, Annexure 7, 2002.
3. USP-PQM – Guidance for implementing, Risk-Based Post-Marketing quality surveillance in low- and middle-income countries, February, 2018.
4. EDQM – OMCL Network of the council of Europe General Document, PA/PH/OMCL (06)3 9R, February, 2016.
5. Food and Drug Administration, Compliance Program Guidance Manual – Drug Quality Sampling and Testing (DQST) – Human Drugs, November, 2015.

Note: For detail study the researcher is advised to consult the reference guidelines.

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