Policy Position

Best Practices for In-Country Testing and Sample Management

Introduction

Independent quality control of pharmaceutical products[1] is performed in many National control laboratories (NCLs) of National Regulatory Agencies (NRAs). In-country quality control is performed for three testing categories: (1) registration testing, including lifecycle management[2], (2) import testing[3] and (3) market surveillance testing[4]. In-country quality controls are performed in order to:

- Monitor and confirm the quality of finished products for product registration and upon importation and/or in the local supply chain;
- Ensure that control tests and the methods used can be reproduced; and/or
- Investigate suspected substandard or falsified medicines

Quality control of products may by performed by visual identity testing (in the case of changes made to the product label) or by laboratory testing. Samples can be required for both types of assessment and country regulatory requirements with varying procedures, timelines and sample volumes apply to for different quality control categories.

In-country quality control testing by independent laboratories is necessary to prevent the distribution of unsafe or non-conforming products. Regulatory convergence and harmonization in this area can provide more opportunities for strengthening regulatory oversight while applying limited resources more effectively. Today's common international standards for manufacturing, distribution, evaluation and inspection lead to increasing convergence and harmonization. This will not only facilitate regulatory communication, but also other foster international cooperation through information-sharing, work-sharing, reliance and recognition[5]. Implementing these strategies can help NRAs to increase regulatory efficiency while decreasing the need for in-country testing of samples.

In this paper, IFPMA will describe challenges faced by Industry for in-country testing and provide recommendations for more efficient management of samples.

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[1] The term "pharmaceutical product", or simply "product", will be use in this paper to refer to small molecules, biologicals and/or vaccines.

[2] The term "registration testing" will be used in this paper to refer to testing in conjunction with registration procedures (new registrations, license renewals, line extensions, post-approval changes).

[3] IFPMA (2016) Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products. Position Paper.

[4] Garbe, Joerg H.O.; Karl Ennis; Guido M. Furer; Maria G. Jacobs and Stephan K. Roenninger (2015) Import Testing of Pharmaceutical Products Has Limited Safety Benefits and Can Add Risk to Patients. Pharmaceutical Technology Europe. 27(8):s6 - s20.

[5] WHO (2016) Good regulatory practices: guidelines for NRAs for medical products. Working document QAS/16.686.

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Key Messages

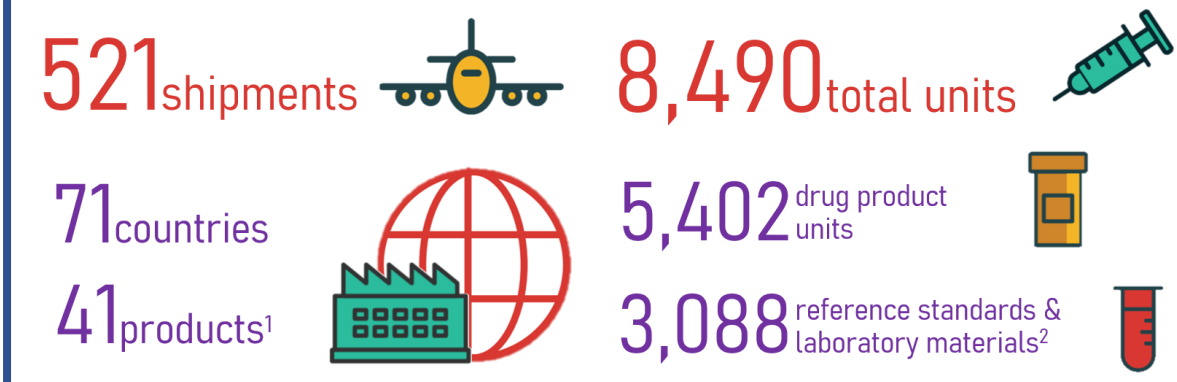
1) IFPMA recommends increasing regulatory focus on in-country quality control on risk-based market surveillance testing, which confirms the quality of imported and local products at patient level. In addition, it can help identifying substandard and falsified products within local supply chains. A focus on identity testing as part of the release specification can be applied. Physical samples of product are taken from the market and are usually replaced by the MAH.
2) Use of physical product samples for quality control testing should be minimised as much as possible, specifically for highly innovative and complex products, to maximise supply availability for use in patients.
3) IFPMA recommends more collaboration between regulators and implementation of reliance on testing from networks of regional control testing laboratories to eliminate redundant import testing and speed up supply to patients.
4) Waivers based on clearly defined risk-based conditions, increased transparency, international standards and simplified procedures should be implemented. This is specifically important in the context of pandemics or natural disasters to ensure uninterrupted supply of medicines.
5) For registration testing, mock-ups or pictures as well as certificates of analysis should be used instead of real product samples. This is already established practice in many major markets.

Challenges

Requirements for in-country quality control and inspection of samples can vary across NRAs and may result in unnecessary, lengthy, and costly processes (manufacturing, distribution, and testing) that delay the availability of safe, efficacious, and high-quality medicines. Especially when NRAs decide to hold the review process unless samples are concurrently submitted and tested.

Measuring the burden of testing & sampling

data collected over the period of 1 year



[1] *Products in scope of data collection: 16 biological products, 25 chemical products*
[2] *Laboratory materials: e.g., chromatographic columns, test reagents, cell lines*

Data were collected from a multinational pharmaceutical company to quantify the implications caused by registration testing/sample management. The annual figures summarize material shipments to support regulatory activities (new registrations, license renewals, line extensions, post-approval changes).

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Evidence shows that a high number of countries (> 70), require samples/testing to support regulatory activities highlighting the high degree of logistics, the increased complexity of the process for the manufacturers and the NCLs, in addition to the significant number of product units (in this example a total of 5402 in 2018) that could not be delivered to the patients. Moreover, the time required for registration testing can take up to 12 months.

Additional figures and specific information on samples management practices in Africa are provided in the Annex.

- Challenges with manufacturing, distributing and storing samples

Producing commercial samples can be challenging, especially for products that have not yet been deployed in the market. A manufacturer may require around 60 to 180 days from the time of request to obtain a sample (if it is not locally produced); this lead time may depend on the product's characteristics and specifications (e.g., small molecules, biologicals, vaccines). Furthermore, samples – especially biologicals – are complex to produce and transport throughout the cold chain.

Notably, for requests made prior to the first production, manufacturers would need to align sample production with supply schedule and meet applicable testing and storage conditions. Furthermore, it is not always possible to have a sample pack available if a country has a special pack requirement. An additional issue is that many biologicals are manufactured in smaller volumes than vaccines or small molecules. Providing large quantities of samples to multiple countries has a more significant impact. In these instances, less product is available on the market which may cause a shortage in supply.

Additional risk of supply interruption is caused by the inspection/testing of the medicines and loss of remaining shelf-life[6].

With regards to the distribution, a medicinal product sent to any destination, should comply with Good Distribution Practices[7] until its reception, even if it is not intended to be used or commercialized.

In addition, for product samples that require a specific storage condition (e.g., 2-8°C) there is a need to ensure appropriate:

- Transport and storage from first shipment from the factory to its final destination (e.g., NCLs /NRAs premises, or distributor warehouse) where challenges can be encountered at customs;
- Route and reliable transporters for samples with special requirements (sensitive to temperature change, light, etc.) and for the receiving NRAs to have trained customs agents, adequate release and storage procedures, and the needed infrastructure to store the samples; and
- Locally adapted devices to ensure cold chain maintenance.

[6] J. Garbe, M. Jacobs, S. Rönninger (2017), Import Testing: An Outdated Practice? Opportunities for Improved Access to Safe and Efficient Medicines, Therapeutic Innovation & Regulatory Science, 51(5): 620-624.
[7]WHO (2020), 54th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations Annex 7 - Good Storage and Distribution Practices for medical products

In the context of post-approval changes (PACs), requests for samples manufactured with a particular change for which approval has been requested, may be challenging in terms of planning, shipment and feasibility. It may simply not be possible to manufacture specific versions of a product prior to its final market authorization.

Finally, the lack of harmonized global guidelines defining the type of medicinal product, type of tests or the number of repeat tests needed when requesting samples proves to be a significant hurdle.

All the challenges mentioned above are related to finished products. However, requirements of Active Pharmaceutical Ingredients (API) samples may also be a considerable regulatory hurdle. These requests add an extra layer of complexity that can delay product registration and patient access.

- Challenges with testing

Redundant testing puts further strain on NRAs and industry, both when it's done for the approval of new products or to approve variations to registered products packaging or manufacturing processes. If the conduct of analytical methods is required for registration, this may lead to a significant delay in the regulatory approval as a result of the following:

- Typically, the full set of analytical methods is established, including very complex product-specific methods, e.g., potency assays.
- NCLs face an increasing complexity of test methods and faster development of new technologies/devices as a result of strong technical progress/innovation.

In case samples are tested at the final destination, it is important to have sufficiently equipped and trained laboratory personnel to perform the tests and maintain their capability on a long-term basis. Methods need to be implemented at NCLs which adds to the delay and complexity of regulatory processes. Specific materials or equipment and appropriate storage conditions (e.g., ultra-low freezers) may not be readily available. In some cases, manufacturers have to provide materials and reagents (e.g., reference standards, control solutions and cell lines) as well as specific equipment (e.g., in-house apparatus) to allow in-country testing. Due to import requirements and shipping routes (e.g., cell lines shipped on dry ice or in liquid nitrogen), the material transfer may take significant time and requires additional scrutiny in order to ensure compliance with international standards and local legislation. Especially for therapeutic proteins, monoclonal antibodies and vaccines, reproducing analytical methods may be cumbersome, particularly for in-house (non-compendial) methods.

Depending on the test, there may be risks of detecting a false-positive out of specification (OOS) result, due to methodological difficulties or to the inherent variability of some tests. Resolving any OOS result can be time-consuming and further delays the review. This delay is critical when dealing with biological products, given their residual shelf-life[8].

[8] WHO (2020), 54th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Annex 8 - Points to consider for setting the remaining shelf-life of medical products upon delivery

Recommendations to waive testing & sample requirements when not needed

Reliance and recognition based on decisions conducted by other NRA's experts review, is useful in creating synergies, strengthening collaboration, avoiding duplication of regulatory efforts in general and facilitating capacity building. A series of considerations on regulatory reliance highlighting its benefits have been published by IFPMA[9].

In particular, in the case of in-country testing and sample inspection, reliance can help by:

- Simplifying the regulatory procedures for the management and testing of samples;
- Waiving in-country quality testing based on clearly defined conditions;
- Reducing the volume of sample requirements; and ultimately
- Phasing out the need of samples when testing is not conducted (e.g., visual inspections)

IFPMA is proposing to rely on Certificates of Analysis (CoA) that are issued by

- health authorities of countries with mature NRAs[10], or
- manufacturers of products that are inspected and approved by a mature NRA

The recognition by mature NRAs ensures, that the manufacturer

- provides evidence that the product manufacturing, testing and storage/distribution systems are well controlled and validated, including GMP certificates and/or mature NRA approval;
- has implemented a proper Quality Management System (QMS) to assure compliance; and
- is under regular control of independent auditing and globally recognized inspectorates (e.g., PIC/S members) or the inspectorates of other mature NRAs, e.g., as described in the WHO Certificate of Pharmaceutical Product (CPP) procedure

This will also ensure that the medicinal product reaches the patient in a timely manner[11] and risk of supply interruptions are minimized[12].

In conjunction with reliance, post-marketing surveillance (PMS) can address some of the concerns with waiving in-country testing or sample requirements. It is generally the case that the samples provided, e.g. at the point of renewal of a license, may not be of much value compared to the sample randomly taken during PMS activities, which happens much closer to the patient at the end of the supply chain. Countries are better off relying on robust PMS systems both at country level and at regional levels if the goal of the samples is to assess the quality of the product. This approach also allows for a random

[9] IFPMA (2019), Considerations for effective regulatory reliance – an Industry perspective

[10] Mature NRAs refers to Stringent Regulatory Authorities, SRAs [2-4]. Specifically, if an NRA is: a) a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway. A list of SRAs has been published by the WHO here. Once the WHO listed authority, (WLA) system is fully implemented the term WLA will replace the term SRA

[11] IFPMA (2019), Position Paper on Assessment Reports as a Tool for Regulatory Reliance.

[12] S. Roenninger, J. Garbe (2016) Import Testing Turned into an Unnecessary Limitation of Patient Access to Medicines as Risks are Managed Effectively. *International Pharmaceuticals Policy and Law.* 18 (1-4):141-156.

assessment of the product quality at the pharmacy level and the detection of falsified and/or substandard products[13].

Real data[4] suggest that import testing does not add significant benefits to the quality or safety of products if above conditions are met. The batch rejection rate of import testing was determined to be 0.005%. Alternatively to import testing, PMS may help to detect counterfeited, substandard, or diverted product from illegitimate channels. Consequently, it shows higher batch rejection rates (e.g., centrally authorized products sampled from the European Economic Area: 4.3%)[6] and thus more added value to NRAs and to patients

Testing programs can be organized in networks across countries to reduce costs and efforts by avoiding duplication of regulatory sampling and testing. The European Centrally Authorised Product (CAP) program, which yearly involves product sampling across all member states of the EU/EEA, is an example of work-sharing in practice. In a similar fashion, WHO's National Control Laboratory Network for Biologicals (WHO-NNB) provides a platform for exchange of quality and technical information between relevant stakeholders on prequalified vaccines. Another approach to also maximize product surveillance and anti-counterfeiting activities would be to explore random sampling of products in the market and strengthen work-sharing around these activities.

- Provisional approaches for better managing samples & testing requirements

If waiving sample requested for visual inspection or quality testing cannot be immediately implemented, IFPMA has additional recommendations that include:

- **Implementing risk-based approach**

A risk-based approach may be adopted to foster a simplified and consistent scheme when assessing the need for samples. Adopting this scheme ensures that sample requirements are proportionate to their impact on the quality, safety, and efficacy of a medicinal product. For example, accepting the testing results from the manufacturer or a trusted NRA. For changes that have none to minor/moderate impact (e.g., administrative changes or "name changes") on the product, a notification to NRA without samples should be acceptable. If the NRA requires the review of a physical sample for approval there should be clear justification and guidance on its use and impact in the regulatory decision-making process[14,15].

- **Implementing a Focused Method Scope**

Registration/surveillance testing should not comprise the full specification testing but focus on key quality attributes of the respective product category/dosage form (e.g., ID and content). This allows a more efficient and faster assessment of the product quality without compromising the overall conclusion. For temperature-sensitive products (e.g., biologicals), the focused scope may be extended to key stability indicator methods.

- **Ensure transparent co-ordination between NRAs and Industry**

Making regulatory guidelines or requirements transparent and available online or through other communication streams would be useful in ensuring compliance. NRAs may also benefit from addressing cumbersome administrative processes by organizing regular and consistent

[13] J. Garbe, S. Rönninger (2015), The Value of Import Testing versus Surveillance Testing, Infographic. PDA Letter, LI(8):34.
[14]WHO (2016), Guidelines on procedures and data requirements for changes to approved biotherapeutic products.
[15] IFPMA (2016), Position Paper on the Handling of Post-approval Changes to Marketing Authorizations.

dialogue around the specific issues so that guidelines and procedures remain proportionate[16], adequate, and achievable. One other challenge observed is the limited sample traceability in some countries, often resulting in multiple sample requests. There may also be instances where there is a lack of transparency on the whereabouts and/or destination of samples in case these are not tested (e.g., if these are used, stored, destroyed, returned, etc.). A less stringent chain of custody for test samples may increase the risk for samples to be lost or diverted. This risk is minimized when robust GDPs are not interrupted[17].

- Simplify approaches

NRAs may consider accepting samples from the production site having the same medicinal product specifications with no specific local pack requirements (and local language) as long as the outer pack and language are compliant with the local guidance.

Adopting digital tools can further simplify regulatory procedures, facilitate the submission and accelerate review process. For example, requests for variations/mock-ups or artworks can be provided using an electronic format, a secure USB key, or a secured cloud service, in place of physical commercial samples (e.g., EMA requirements).

Conclusion

In-country market surveillance testing of pharmaceutical products provides NRAs with additional assurance of the product quality in the local supply chain and helps preventing the distribution and supply of substandard and falsified medicines.

The experience of IFPMA members shows that in many cases that current practice applied to in-country testing does not provide additional benefit to patients. Extensive sample requests and redundant testing can represent a serious burden for NRAs, their NCLs, as well as manufacturers and increase the risk of supply interruption/drug shortages, which can ultimately have a negative impact on health systems. Implementation of reliance and work-sharing can be a smarter approach to focus available testing capacity and reduce physical sample requirements.

IFPMA supports increased focus of in-country testing capacity on local market surveillance testing to ensure patient safety.

[16] WHO (2020), WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medicines and vaccines.
[17] WHO Technical Report Series 957, Annex 5 - Good distribution practices for pharmaceutical products (2010).

Annex: Samples Management of Medicinal Products in Africa

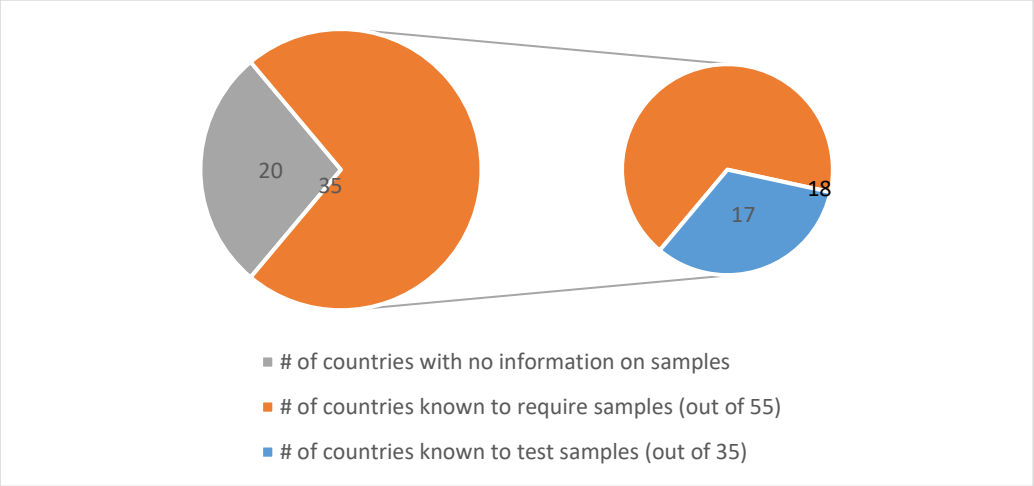
Background

In Africa, sample requirements may differ across regional groups and countries. Depending on the regulatory jurisdiction, these can be required for registration, renewal, post-approval changes (PACs), and/or import testing, with varying procedures, timelines and volumes. This annex provides specific information on samples management practices in Africa, including some best practices from selected National Regulatory Authorities (NRAs) in ensuring timely access of medicinal products for patients in Africa.

IFPMA survey on samples management in Africa[18]

In 2019, IFPMA conducted a survey across regional industry associations members and identified around 35 NRAs in Africa that require samples for a regulatory review. Out of the 35 countries, around 17 of these are reported to require samples for testing (Figure 1).

Figure 1. Countries known to require and test samples in Africa



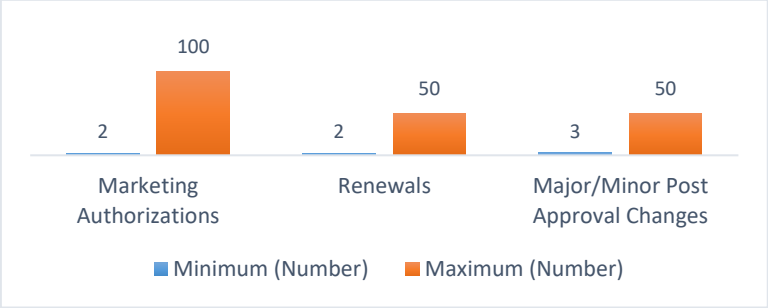
Source: IFPMA Africa Regulatory Network survey on samples management in Africa, 2019

Often, there is no fixed or predictable number of samples required by NRAs across product types or based on the criticality of change. The quantity of samples requested by each regulatory authority can vary across manufacturers. Even for a single manufacturer, the required quantity of samples can also vary for the same type of regulatory submission. This inconsistency in samples requirement makes it challenging for the manufacturer to predict and plan the required samples for submission.

[18] NOTE: The data and figures in this section were collected from 8 IFPMA member companies. Information was available for only 35 of the 55 countries, of which the companies have data. There is no information on how samples are managed in the remaining 20 countries not covered in the survey.

The quantities of samples requested can range from 2 to 100 samples for marketing authorizations, from 2 to 50 for renewals, and from 3 to 50 for post-approval changes (Figure 2). For variations, some countries may require the same amount of sample regardless of the classification of the change (minor or major classification).

Figure 2. Range of samples required for registration, renewals, and post-approval changes

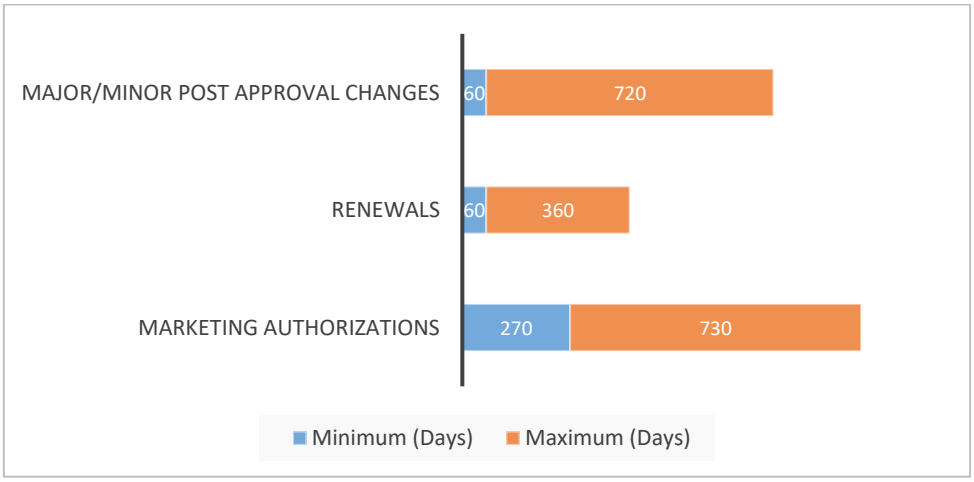


Source: IFPMA Africa Regulatory Network survey on samples management in Africa, 2019

Timelines for manufacturing and importing samples to regulatory authorities can also differ across regulatory processes. This could range from 60 to 180 days for marketing authorizations and 60 to 365 days for both major and minor post-approval changes. These lead times in providing samples (from the manufacturers) to the authorities to comply with the review/assessment requirements, have a direct impact on the approval lead times for new medicines as well as for post-approval changes.

In terms of review timelines, these fall within a minimum of 60 days to a maximum of 720 days. Our survey reveals that a review with samples can range from 270 to 730 days for a new marketing authorization, from 60 to 360 days for renewals, and up to 720 days for post-approval changes.

Figure 3. Timelines for reviewing applications with samples



Source: IFPMA Africa Regulatory Network survey on samples management in Africa, 2019

It is clear from these findings that some current practices in samples management delay the review and approval of medicinal products in African countries. These delays can ultimately impair access to

new and innovative medicines for patients in the continent or delay access to improved versions of a medicinal product.

Opportunities to improve samples management in Africa

IFPMA identifies opportunities to mitigate concerns with in-country testing/sampling and recommends waivers based on clearly defined conditions to phase out samples requests.

Reliance[19] upon testing and/or approval decisions conducted by other regulatory authorities avoids duplication of regulatory efforts, reduces lag time in patients' access to medicinal products, and prevents shortages to ensure supply continuity. It is based upon trust, regulatory network collaboration across NRAs, and the sharing of analysis conformity results either from a mature Health Authority's control laboratory or coming from manufacturer-approved and GMP-inspected results by a mature Health Authority.

In case waiving of samples through application of reliance principles is not yet feasible, below are some best practices on samples management in Africa.

- Developing clear sampling plan guidelines
  Ghana's Food and Drug Authority (FDA) provides clear and transparent samples requirements to manufacturers, including appropriate sample schedules and number of samples in volume and dosage forms by product category (small molecules and/or biologics) for new marketing authorizations, renewals, and/or PACs.

- Adopting a risk-based approach
  The Ghana FDA and the Egyptian Drug Authority (EDA) have adopted a risk-based approach when handling post-approval changes, where samples are not required for minor variations or are waived if no test is to be performed by the regulatory authority.
  In Morocco, samples are not required for renewals or post-approval changes but are required for new marketing authorizations.
  Similarly, the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria is accepting some major PACs such as manufacturing site changes to be reviewed through the submission of listed documentations, without the additional need for samples.

- Facilitating the importation of medicinal products, including samples
  The EDA withdrew registration samples management to expedite approvals for major post-approval changes. This is done by checking all administrative documents, such as application forms, and relying upon GMP certificates, CPPs, and other approval/authorization letters granted by the country of origin, under conditional post-approval commitments. These post-approval commitments include:

  An analysis that is undertaken on the first 3 batches at the time of commercial shipment,

[19] IFPMA (2019), Considerations for effective regulatory reliance – an Industry perspective

Stability studies that are submitted within 30 months from its approval.

Through this risk-based and reliance approach, import of medicinal products could be facilitated, through taking samples from commercial shipments.

- Flexibility in the artwork of the sample pack
  The EDA has also adopted some flexible approaches for samples artworks, such as allowing the use of an international pack in English language, with the commitment that the authorized product follows country-specific requirements at the time of its release or first commercial shipment.

- Flexibility in testing samples
  The EDA samples review and testing can be done before or after a marketing authorization has been granted, as long as it is done before it is released in the market. However, this practice is currently being applied to products imported from reference-approved countries (e.g. mature NRAs) which ultimately is still leading to redundant testing.
  To reduce burden on review and testing, the Ethiopian Food and Drug Authority (EFDA) and the EDA conduct random routine sampling instead of systematic import testing for all batches.

Conclusion

NRAs in Africa are taking significant steps to improve samples management – by waiving or phasing out the need for samples and adopting reliance and work-sharing or, when not possible, using pragmatic approaches to simplify processes and reduce regulatory burden for all involved stakeholders. In adopting reliance, we recommend NRAs to refer to WHO practices[20]. The increasing use of regulatory reliance and work-sharing demonstrates a collective approach in improving and strengthening regulatory systems across NRAs and fosters greater international cooperation in ensuring availability and access of high-quality, safe, and efficacious medicinal products for patients in the continent.

[20] WHO (June 2020), Good reliance practices in regulatory decision-making: high-level principles and recommendations, Working document QAS/20.851