



Policy Position

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Good Manufacturing Practice Inspections and the Provision of Batch Records¹ in Sub-Saharan Africa

Good Manufacturing Practice (GMP) inspection by National Medicine Regulatory Authorities (NMRAs) coupled with industry internal audits is a fundamental way and accepted practice to ensure patient safety and well-being by verifying that medicines are manufactured to high quality standards.

As such, the research-based biopharmaceutical industry² supports regulatory oversight through inspections of their manufacturing and supply sites.

GMP inspections of the Finished Product (FP) manufacturing sites are a requirement of many African countries prior to product registration. The pharmaceutical industry has noticed that there has been an increase in the number of GMP inspections carried out for registration purposes, conducted by African NMRAs for FP manufacturing sites.

An ARN survey³, recently conducted across IFPMA member companies, showed that some NMRAs enforce this inspection requirement; some perform *ad hoc* inspections whilst others provide for a GMP Inspection waiver. The survey also found intercompany variability with regard to country-specific inspection requirements relating to manufacturing sites which had already been inspected by a Stringent Regulatory Authority (SRA)⁴ and for which valid GMP Certificates are available. Also, countries within the same Region, e.g. the East African Community, do not accept GMP inspection reports issued by the NMRAs of other member countries within the Community, despite the fact that the applicable Guidelines in these countries provide for the recognition of such prior inspections by other NMRAs.

Multiple inspections of one international site within a short time period results in duplication of effort and the inefficient utilization of resources by the NMRAs of countries without necessarily improving quality assurance or product quality/safety. For greater efficiency, the ARN recommends that resources should be focused on areas of the regulatory process that add the most value and where patient access to high quality, safe, and efficacious medicines may be expedited.

Manufacturing and packaging documents are included in the submission dossiers. However, some African NMRAs, e.g. countries in East Africa, West Africa and the SADC region, also require Executed Batch Records (EBR) and Master Batch Records (MBRs) in addition to the evidence provided in the dossiers confirming that the manufacturer can produce uniform batches that meet established quality requirements and specifications. Again, member companies have experienced intercompany variation of this practice, and there is no notable harmonized or standardized approach. There is also an NMRA expectation that these documents should be translated into English if the original executed document is in a foreign language. Some companies noted that the provision of the MBRs did not exempt a site from GMP inspection.

¹ Batch Records includes Executed Batch Records and Master Batch Records

² IFPMA (International Federation of Pharmaceutical Manufacturers & Associations) member companies

³ ARN survey conducted in June 2015. Data on file

⁴ The national drug regulatory authorities which are members or observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are considered as Stringent Regulatory Authority (SRA) as per the Global Fund Quality Assurance Policy for Pharmaceutical Products from July 1, 2009

Manufacturing according to GMP requires that companies have written manufacturing formulas and processing instructions in place for each product and batch size to be manufactured. Such information is provided in a standard format: the MBR.

The MBR is basically a recipe for manufacturing a product at the manufacturing site(s). It contains the detailed stepwise processing instructions, including information on the principal equipment to be used as well as the equipment settings. The MBR also describes or refers to the methods to be used for preparing equipment, e.g. cleaning, calibrating, sterilizing, and the required checks of the equipment to ensure that it is clear of previous products, clean, and suitable for use. These instructions are intended for the personnel in the manufacturing facility and therefore have to be written in the local language. Depending on the manufacturing process described, a MBR can be several hundred pages long. The structure of the MBR varies between manufacturing sites and companies. The MBR is very detailed instruction to personnel to run the process and provides for each individual processing step, such as granulation, compression, or filling, a hands-on description, including equipment settings, and as such may be fragmented. Therefore, the complete MBR is difficult to read and understand as one document to non-site personnel.

For the research-based biopharmaceutical industry the MBRs are viewed as intellectual property (manufacturing know-how) documents and should not be a prerequisite for product registration, in particular when no confidentiality agreement is in place. Provision of a valid GMP Certificate issued by an SRA or a positive inspection (reference below) should counter this requirement and confirm that the product is manufactured in compliance with GMP requirements.

For registration purposes therefore, an easy to read manufacturing process description is provided in the submission that is derived from the MBR. This description contains all quality-relevant steps and controls (CTD section 3.2.P.3.3). The list of the components used in the manufacturing process, as well as their amounts on a per batch basis, is provided in the Batch Formula (CTD section 3.2.P.3.2). Furthermore, evidence is provided in the dossier in the process validation section (CTD section 3.2.P.3.5) that the manufacturer can produce uniform batches that meet established quality requirements and specifications. Therefore, the provision of MBRs to NMRAs, as part of the Marketing Authorization Application, does not provide additional valuable information for the dossier reviewer.

This is also reflected in the ICH guidelines on CTD, where the provision of MBRs is not required for the registration dossier.

MBRs are a GMP requirement and are typically viewed during GMP inspections conducted by NMRAs. In addition, the MBR is becoming increasingly part of the electronic systems in place at the manufacturing sites which are then viewed online during an inspection. The reports, which can be printed from such systems, are even more fragmented and difficult to read. Provision of a valid GMP Certificate issued by a competent Authority or a positive site inspection report confirms that the product is manufactured in compliance with GMP requirements. The confirmation of the GMP status includes the confirmation that appropriate MBRs and EBR exist at that site.

Currently, these requirements (GMP & MBR) are not widely implemented in the West African Economic and Monetary Union Regulations. However, we have recently noticed that some of these countries have started to request GMP inspections.

In order to harmonize and efficiently adjust the regulatory burden for NMRAs and the biopharmaceutical industry ensuring efficient utilization of resources, the ARN would like to propose a number of alternative, equally effective approaches to full GMP inspections whilst maintaining assurance of GMP compliance. These are:

1. Recognition and acceptance of GMP certificates issued by an SRA or Pharmaceutical Inspection Co-operation Scheme (PIC/S).

When a GMP inspection has already been conducted for a FP manufacturing site by an SRA or a PIC/S member authority and a valid GMP Certificate exists, there should be recognition of this GMP inspection and exemption from a GMP inspection granted.

2. Acceptance of GMP declaration based on a WHO Certificate of Pharmaceutical Product (CPP) issued by an SRA or a PIC/S member authority.

As the GMP declaration in the CPP refers to assurance of GMP for the product approved in the certifying country at the stated manufacturing site(s), there should be recognition of this statement. The decision to inspect should be based on a risk-based assessment of the manufacturing site, taking into account the GMP and inspection status from an SRA or a PIC/S member authority. ARN encourages NMRAs to become a member authority of PIC/S in order to ensure sharing of training, information, as well as audit reports with other PIC/S authorities.

3. Conducting risk-based assessments of the manufacturing sites.

NMRAs are encouraged to use a Quality Risk Management system for their processes, e.g. scheduling and conducting of inspections; risk-based ranking of sites; etc., aiming at:

- Assisting with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity;
- Evaluating the significance of, for example, quality defects, potential recalls and inspectional findings;
- Determining the appropriateness and type of post-inspection regulatory follow-up that may be required;
- Assessing the information submitted by industry including pharmaceutical development information; and
- Evaluating the impact of proposed variations or changes likely to have a significant impact on the quality and performance of a dosage form.

4. Mutual recognition of GMP inspections performed by African countries within the same Region which could, in time, extend to countries beyond this Region.

Harmonization between NMRAs is required so that the inspection report and GMP certificate provided by one NMRA is recognized and accepted by other NMRAs. This could be particularly effective within the existing established Communities and significantly reduce the regulatory burden across Africa. This is also in alignment with the key objectives of the African Medicines Regulatory Harmonization (AMRH) Program.

5. Joint inspections (twinning)

It is noted that the collaborative approach of NMRA's "twinning" to do joint inspections has started. Such practice will reduce the workload for both the industry and the inspectorates. It will provide capacity building by the sharing of scientific advances and current best practice between NMRAs, particularly those where medicines regulations are recent, or in the process of being implemented. Similarly, the Prequalification Program of the WHO can support capacity building for NMRAs when participating jointly in the inspection process.

Such collaborations meet the needs for regular inspections to ensure GMP compliance without duplicating the efforts of NMRAs. It thus maximizes the efficient use of regulatory resources that could be used in other areas to safeguard the patient.

Conclusion

Patient protection and access to high quality, effective, and safe medicines remain the primary focus of the research-based biopharmaceutical industry. It is well recognized that GMP inspections are one of the fundamental ways that NMRAs can ensure high quality product manufacture. Recognizing SRAs and the mutual recognition of African NMRA inspections and implementation of the above mentioned practices may be a more resource efficient way of providing assurance with GMP compliance. A positive inspection report or a valid GMP certificate from an SRA negates the requirement for MBRs and/or EBRs.

The challenge is to achieve a better understanding and implementation of regulatory requirements, allowing an appropriate level of regulatory insight. Co-operation to facilitate the best and efficient utilization of the limited resources within both the pharmaceutical industry and NMRA is to the advantage of patients in urgent need of high quality, safe and efficacious medicines.

It is possible to avoid major quality gaps in the supply chain without any impact on the quality of medicines provided to patients. To do so, there is a need to apply a risk-management approach and include Pharmaceutical Quality System elements for inspections and related processes, and optimize the global coverage. In this way, existing resources can be utilized efficiently, and alternative measures to safeguard the patient can be sought and expanded.
