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M.A.R.S.: A process for establishing consistent standards

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Multinational companies face an increasing number of challenges when deploying a common standard across different affiliated country offices or sites (referred to as affiliates in this article). This is particularly relevant in the pharmaceutical industry where standards of quality and expectations are high. There is often a path of destruction that results when a regulatory agency such as the U.S. Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, or European Medicines Agency routinely conducts inspections across international borders, companies fail to effectively deploy a common global standard.

From a country affiliate office perspective, it is also difficult. They are usually restrained by resources and have local country requirements to accommodate, apart from an international and global standard required by the company. The benefits of a flexible, local quality management system (QMS) are recognised as positive reinforcement for a mature QMS and have already been discussed in a previous publication.[1] This reference discusses the impedance of implementing consistent messaging to reinforce compliance to policy intent. The process described in this article is at an even deeper level of operationalization where consistent compliance is required to various operational standards.

To add to the complexity, there are often different levels of required standards, depending on whether there is manufacturing and/or testing at the country level. This leads to a requirement for cross-functional governance. There may also be different cultural implications that can affect the levels of understanding or effectiveness of deployment, and the different levels of available resource between large and small country affiliates also cannot be underestimated. Somewhere between everyone having good intent and the effective delivery of policy and actual procedures and processes, there is a disconnect. The end result is that global functions think they have deployed the intended standard adequately, and the affiliate assumes they have implemented it satisfactorily. Sadly, the reality can be that neither has occurred.

Many regulatory agencies have over the last decade made inroads to take a more holistic approach for compliance to standards, quality, and risk assessment for good manufacturing practice (GMP). Good practice (GxP) guidelines (synonymous with best practice) were established in the U.S. by the Food and Drug Administration. The "x" stands for a particular field, whether that's GMP, or good distribution practice (GDP), for example. In 2006, the U.S. released its *Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations*,[2] and the European Medicines Agency also released the "ICH guideline Q10 on pharmaceutical quality system" in 2008.[3]

Similarly, compliance standards of best practice issued by the Foreign Corrupt Practices Act[4] and the

Department of Justice[5] also call for consistent deployment of policies and practices.The Department of Justice, for example, emphasizes the importance of a compliance program "implemented, reviewed, and revised, as appropriate, in an effective manner" versus simply having a "paper program" in place.[6]

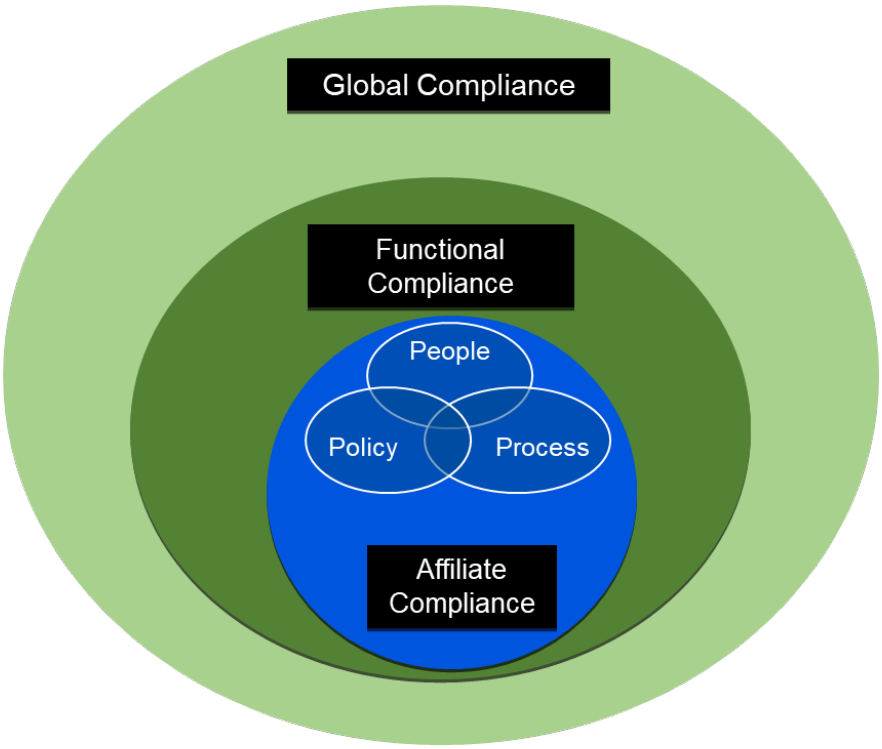
Two years ago, we began creating a process of minimum affiliate reference standards (M.A.R.S.) to address this issue. We introduced a controlled process that established the agreed standard from a global perspective and guidelines on how to implement this at a country level across more than 30 different countries. The basis for the process was that one size does not fit all and each affiliate could implement the process as best suits their environment, providing the intent of the standard was reached and could be demonstrated.

Minimum requirements

M.A.R.S. have been implemented to develop a set of minimum reference standards for affiliates, which describe the operations for defined activities to assure compliance to the required standards. The aim was to achieve a consistent approach for routine execution of the defined activities.

They reflect global, functional, and local country minimum requirements in a cascading fashion, as shown in Figure 1.

Figure 1: Hierarchy for the holistic establishment of the Minimum Affiliate Reference Standards (M.A.R.S



Of highest precedence are the global standards. Within these, where there is a requirement for specific functional variation (that is of a higher compliance requirement), these are reinforced by the M.A.R.S. In some cases, countries have even more specific additional requirements to satisfy local country regulations in addition to any global or functional standard requirement. Provisions within the M.A.R.S. have been made for countries to execute these additional requirements in their implementation plans described in greater detail below.

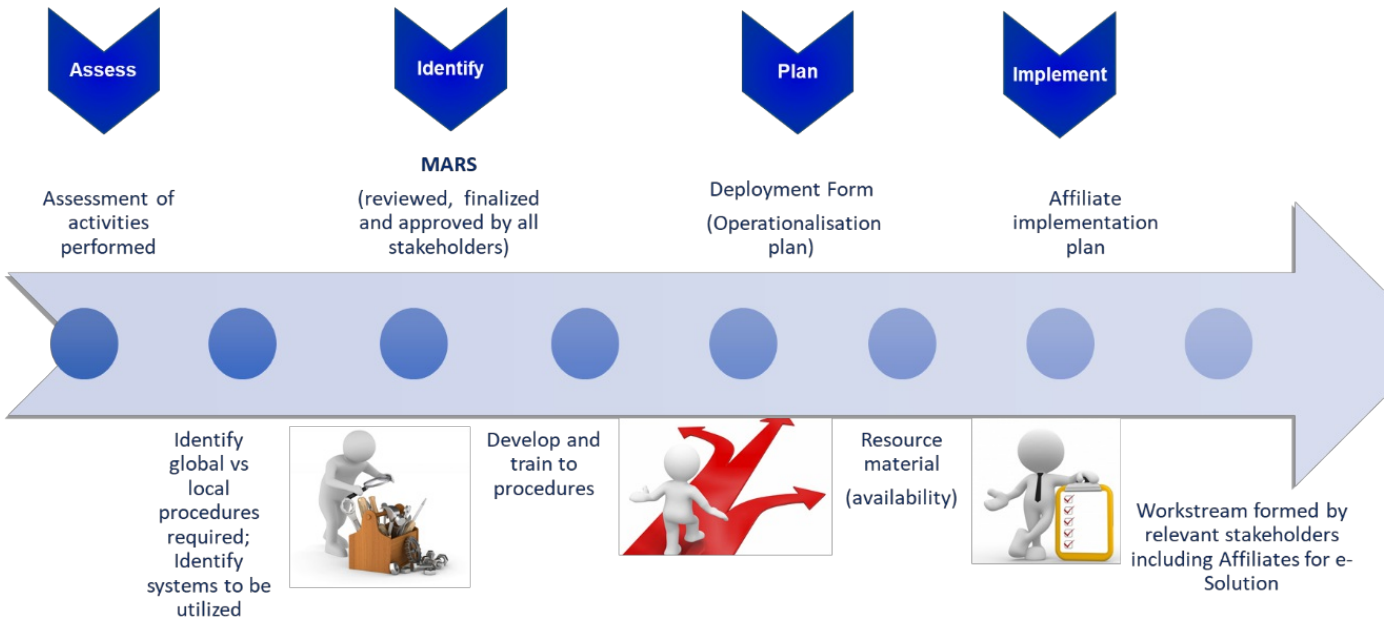
The M.A.R.S. process is holistic in intent, providing a quality system framework by which all standard requirements at a country level can be executed. Although they are biased toward GxP compliance (in the areas of

GMP or GDP), the process is intended to satisfy the requirements across all areas of compliance where operationalization of a common standard is required. In our case, these included regulatory and medical affairs and healthcare compliance. By design, the process is also flexible enough to accommodate affiliate offices in different countries with a developed QMS through those affiliates without a defined QMS structure. By providing different levels of support documentation (M.A.R.S. tool kits), corresponding different levels of guidance for the implementation are possible.

M.A.R.S. structure

M.A.R.S. are deployed to the country affiliates by the global quality affiliate function. The corresponding implementation and adoption of the M.A.R.S. followed four key phases: assessment, identification, planning, and implementation (see Figure 2). The four levels of M.A.R.S. implementation (Assess, Identify, Plan, and Implement) are shown above the implementation line in Figure 2. The actions required at an affiliate level are shown below the line.

Figure 2: Four phases of M.A.R.S. implementation



Assess

Each country affiliate is required to identify whether the M.A.R.S. have applicability to the activities performed at their affiliate. For the seven critical M.A.R.S. identified above, it was expected that these were common elements for each affiliate process. However, in some countries, requirements may dictate a higher standard of compliance than indicated in the M.A.R.S., and as such, a more detailed implementation plan that embraced the nature and extent of the enhanced requirements was required.

Identify

Once the requirements for the affiliate are identified, each affiliate is required to develop an implementation plan. Where the required elements of the M.A.R.S. were already in place, the implementation plan consisted of an assurance that those procedures were current and that all required employees have been trained on the content

of the M.A.R.S. and the corresponding procedures.

Plan

In situations where the affiliate does not have the required processes to meet the requirements of the M.A.R.S., the appropriate stakeholders are required to put together an implementation plan (a simplified version of corrective and preventive actions [CAPA]). The CAPA is required to detail what processes (standard operating procedure, work practice, or form) are going to be implemented, the function or stakeholder responsible for implementation, and an estimated timeline for completion. This may or may not require a workstream to be developed at the affiliate depending on the magnitude of the corrective action required and the extent of involvement by different stakeholders.

Implement

M.A.R.S. are considered to be successfully implemented (completed) when a process is in place and appropriate training has been conducted. Once the process is implemented and training conducted, all relevant stakeholders sign off the M.A.R.S form. It is expected that affiliates maintain appropriate document management for all aspects of the M.A.R.S., including unique identifiers for documents introduced, appropriate traceability and version control, and monitoring as required by the M.A.R.S. to the defined key performance indicators.

The structure and content of the M.A.R.S. did not, nor did it intend to, change the QMS structure at the global cross-functional level. Rather, it provides a prescription for a more harmonized and holistic QMS at the country affiliate that is intended to satisfy the business requirements of that country. Each affiliate was also required to appoint a central contact person referred to as the business management system coordinator. Their responsibility was to act as a central liaison between the global function and the country affiliate stakeholders to ensure the completion of the M.A.R.S. implementation.

In its simplest form, the M.A.R.S. process provides a formalised implementation schema.

The M.A.R.S. form template (a controlled document) is the central element of objective evidence used to define the requirements of the standard. In more advanced affiliates, the standard requirements can be traced to the global quality or compliance manual and policies and/or in the local country affiliate policies, where present. The complete set of M.A.R.S. is intended to address all areas of the business where there is a need for a controlled and demonstrable process of implementation—in our case, GxP activities, healthcare compliance, and regulatory affairs and medical (which includes aspects of pharmacovigilance and risk management associated with high-risk products).

Structure of the M.A.R.S. form

Each M.A.R.S. follows a standard format of eight sections, described in Table 1. Where applicable, additional requirements for functional enhancements are detailed as part of the "Standard Requirements" section. Standard requirements define the expectations required to satisfy the M.A.R.S. and the nature and extent of different approaches that are acceptable.

Country-specific requirements are not defined in the M.A.R.S. form, as these are required to be stated as part of the country's response and implementation summary described in the next section. The "Output" section references the nature of the required output without being prescriptive. For example, a common output for the country affiliates was to have a written procedure to define the process applicable to the implementation of the standard. Depending on the country, this could either be a formal standard operating procedure, a work practice or equivalent, or, in its simplest format, a form. Providing the requirements were satisfied, it was at the

discretion of the country affiliate to determine the most effective method.

Key performance indicators were more prescriptive to provide a structure that would allow consistency of reporting back to senior management and the collation of consistent statistical trends.

The "Oversight" section contained standard wording across all M.A.R.S. and reflected the independent assessment afforded by the corporate auditing function. Not only does this provide an independent assessment of the implemented processes but also enables a consistent comparison across the different affiliate approaches.

Table 1: Standard sections of the M.A.R.S. form

1. PURPOSE	Defines the intent of the M.A.R.S. and the standard.
2. SCOPE	Defines the scope of the standard and the 'high level' expectation to be satisfied. It also lists all relevant global standards, policies and procedures that apply to the M.A.R.S.
3. DEFINITIONS AND ABBREVIATIONS	Lists definitions and abbreviations or (as in our case), references the global glossary of terms.
4. STANDARD REQUIREMENTS	Defines precisely the expectations for each component of the M.A.R.S. that is to be satisfied and provides commentary on the rationale for the requirement.
5. OUTPUT	Defines the minimum expected output in terms of procedures (SOPs), Forms or Logs required together with any expectations for Key Performance Indices (KPIs).
6. OVERSIGHT	A standard statement reflecting that the oversight of the M.A.R.S. process is the responsibility of the corporate auditing function.
7. REFERENCES & ASSOCIATED DOCUMENTS	List of referenced or associated guidance documents
8. REVISION HISTORY	Revision history of the M.A.R.S.; part of the requirements for a controlled documentation that expresses changes to the M.A.R.S. and rationale for changes.

Country affiliates have the option to use existing documentation where it satisfies the standard requirements, implement new forms or equivalent procedural guidance documents, or draw on predefined templates provided as part of the supporting M.A.R.S. tool kits. M.A.R.S. tool kits were a set of pro forma procedures and accompanying forms that provided a template to satisfy the basic requirements of the M.A.R.S. They were available to all subsidiary affiliates and were particularly useful for smaller affiliate offices with limited resources.

In each case, the actual M.A.R.S. and implementation form were accompanied by the M.A.R.S. tool kit, which contained:

- A template or example standard operating procedure (if existing),
- Template form, where appropriate (e.g., GxP deviation handling form/CAPA management form, training attendance form), and

- Template tracker or log (if required).

The tool kit provided an immediate resource to be implemented that would satisfy the standards required where the affiliate lacked the required resource to self-implement the required processes and forms to drive compliance. Similarly, although management of processes and associated documentation through an electronic document management system was preferred, a manual process in smaller country affiliates was acceptable.

To date, seven M.A.R.S. (listed below), the critical components of the document management system, have been deployed. This is the culmination of both the required quality elements and the compliance elements to provide an overall satisfactory level of compliance to meet and maintain the business needs.

1. Documentation management (document management system),
2. Training management,
3. Self-inspection,
4. Vendor management,
5. Deviation management,
6. Corrective and preventive action management, and
7. Change control management.

Justification and discussion

The M.A.R.S. process affords a consistent and auditable process for introducing common standards across country affiliates, subsidiary offices, departments, or branches of an organization. There are some similarities to a process for operationalization of corporate compliance policies discussed in a previous publication.[7] The process described here demands a higher degree of implementation (a more complex process of operationalization) to a higher set of standards and with a broader cross-functional range of stakeholders, which typically complicates the implementation of a consistent and agreed approach. This in turn achieves a higher expectation of standards to be attained, and the stakeholders associated with the M.A.R.S. need to be familiar with the requirements of quality systems.

The cascading process described here for process implementation provides a framework for the consistent implementation of procedural standards that are often associated with either quality or compliance operationalization.

M.A.R.S. provide a mechanism for deployment of a consistent message aimed at obtaining implementation with the flexibility for each country affiliate to create the correct level of implementation. In our deployment, several affiliates struggled with the extra level of complexity until they realised that they could retain their own systems with appropriate modifications to meet the required standard. Our aim was to provide a harmonised system of standard implementation across different countries that varied in both size of operation and culture.

An important aspect of acceptance is the independent assessment of the M.A.R.S. and the supporting process by the corporate auditing function. In our organisation, for many years, this function has been requesting a consistent approach across the QMS design and implementation at affiliate levels, and we see the M.A.R.S. process as a positive step toward this.

The intent of M.A.R.S. is to also try and develop a “quality backbone” for the overall compliance requirements at

a country level but maintain the flexibility in design to cater for all forms of business where the result is compliance to a standard. It also provides the opportunity for cross collaboration with quality functions to support and enhance compliance systems and programs in areas of the organisation that may be less familiar with structured implementation processes.

Too often the rigour of a structured QMS (often associated with GxP activities) remains specialized within those functions, and the benefits for the entire business are lost due to the insecurities or perhaps insufficient understanding often displayed by non-GxP functions. The success of M.A.R.S. implementation is heavily dependent on the buy-in from non-GxP functions together with the support of senior management. In both cases, there is a need to devote adequate resources to providing support to these areas for successful implementation.

There is no reason why the M.A.R.S. structured implementation could not be adapted to other forms of quality practice or compliance requirements in the medical or healthcare settings wherever there is a need to deploy a consistent standard across functional or geographical boundaries. Provided there is senior management endorsement and sponsorship for a robust business management system, the M.A.R.S. process can be a valuable tool in driving change from the archetypical QMS typically driven by quality to a broader-based, all-encompassing management system. The delivery of clear and consistent messaging around required standards is considered a key element for sustainable compliance.

Takeaways

- "Companies failed to effectively deploy a common global standard" is often a reported audit observation.
- Somewhere between good intent and effective deployment there is an absence of consistent process for deployment.
- The minimum affiliate reference standards process affords a consistent and auditable process for introducing common standards.
- It provides a "quality backbone" for compliance for aspects of business where the result is compliance with a standard.
- Implementation of such processes (deployment of policies or standards) is better referred to as a business process rather than a compliance or quality process.

1 Calvin London, Reyna-Chris Comeros, and An Nguyen, "Making your policies POP: A policy operationalization process," *Compliance Today*, April 2020, 52–55, https://bit.ly/2JxRPbm.
2 U.S. Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, and Office of Regulatory Affairs, *Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations*, September 2006, https://bit.ly/2QY5ufv.
3 European Medicines Agency, "ICH guideline Q10 on pharmaceutical quality system," last updated May 28, 2015, https://bit.ly/2QT1pJC.
4 15 U.S.C. §§ 78dd-1, et seq.
5 U.S. Dep't of Justice, Criminal Div., *Evaluation of Corporate Compliance Programs* (Updated June 2020), http://bit.ly/2Z2Dp8R.
6 Thomas R. Fox, "The 10 Hallmarks of an Effective Compliance Program: Still the Foundation," *FCPA Compliance & Ethics* (blog), November 16, 2017, https://bit.ly/3iLpz54.

7 Calvin London, "Making your policies POP: A policy operationalization process."