EMERGING TRENDS IN REGULATORY EXPECTATIONS

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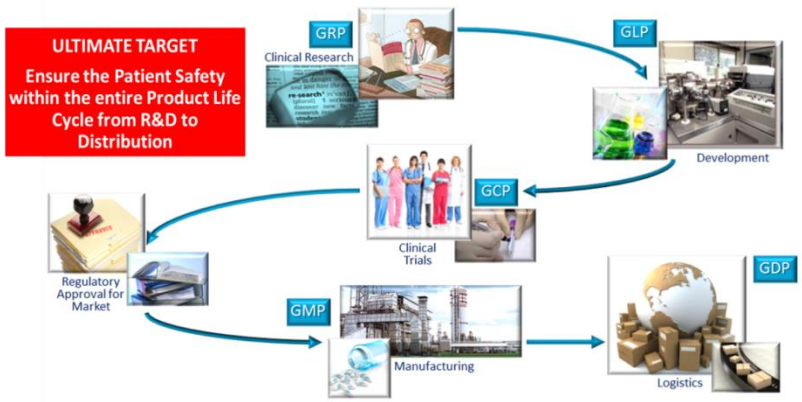
Introduction

The Ultimate Target in the Pharmaceutical and Medical Device industries is to ensure Patient Safety within the entire Product Life Cycle, from R&D to Distribution



Quality of Medical Products (both drugs and devices) becomes a Social and Ethical Responsibility as products are developed, produced and distributed for preventing treating and reducing discomforts of diseases.

The final User/Patient trusts the medical products efficacy and simply relies on them. A continuous commitment from manufacturing companies and from those involved in the product life-cycle is in need to continue gaining the Patient Confidence.

Together with the principles and guidelines that the regulatory authorities are laying down for the industry (i.e. Regulatory Requirements) we can say that **Quality of Medicines** is not "only" mandatory by law, but also a **Social and Ethical Responsibility.**

Responsibility implies the importance of the human factor when considering regulatory requirements: people are at the heart of doing, and it is the failures of people—often the combined failures of a number of people—which result in non-compliance in most of cases.

Globalization has fundamentally altered the economic and security landscape and demands a major change in the way Regulators/Medical Products Manufacturers, Distributors and Suppliers fulfill their mission.

Globalization processes, characterized by longer and more complex Supply Chains, and greater risk of **Counterfeiting** problems, have been forcing the industry and inspectorates/enforcement Agencies to challenge their current practices.

Regulatory Expectations nowadays focus on Harmonization of global regulations in the sense of giving guidelines to address the following:

⇒ **Overall Process Oriented approach**. Since Quality should be built within the product, testing alone cannot be relied on to ensure product quality. Increasingly Validation of Computerized Systems is

processes oriented, to ensure both the reliability of GxP/Business Processes and the Integrity of Data managed by each System, including Laboratory and Manufacturing. Many manufacturing sites have multiple systems from multiple vendors and different release versions: integration of manufacturing applications often takes 50% - 80% of a project cost. An effective integration of business logistics systems and manufacturing operations (production, maintenance, laboratories, material handling, storage etc.') suggest Corporate validation approach as a cost/effective opportunity.

⇒ **Quality by Design (QbD)** with an understanding of the product and the relevant development and manufacturing process along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. Quality by Design principles have been adopted recently by the regulatory authorities as the initiative attempts to provide guidance on pharmaceutical development to facilitate design of products and mitigate the risk through Design. Increased utilization of Risk Management and Change Management, that become paramount important for understanding where to buy, which supplier and sources need to be more controlled and how changes impact Product Registrations.

⇒ **Increased Reliance on Suppliers and Outsourced processes.** The rising complexity in controlling larger Supply Chains with raw materials, components, sub-assemblies, Finish Goods and Packaging Materials coming from different sources from around the world. Businesses players need to be aware of the supply chains they participate in and to understand the roles they play. As the environment becomes more complex in terms of Products and Technology and due to the fact that Business Margins are more and more limited, companies are forced to rely more on Suppliers and Outsourced processes. Leveraging Suppliers Knowledge, sharing and applying it in supply chains can promote the business performance and efficiency.

⇒ **Growing focus on Data Integrity** as key evidence of Supply Chain reliability and ultimately of the Product Quality. In order to achieve these targets through a feasible and cost-effective strategy, an harmonized approach is required to create Validation Common Standards not only for the traditional owned IT applications, but also for stand-alone Laboratory and Production systems usually managed by the Engineering/ maintenance department.

Globalization Impact

Globalization can be described as: rapid flows of goods, capital, services, labor and information around the world. Integration of national industries into global ones is becoming a commonplace and it is increasingly unhindered. One of the strongest driving forces of this globalization is the revolution in Information and communication Technologies, which are now reaching some of the poorest and most remote locations in the world. A big concern for medical products companies occurs due to high costs for research and development, international competition, reduced life time of products and measures of health policy, cost saving, considerations. This pressure in pricing and competition leads to development and manufacturing at lower costs. It is mostly relevant in innovative developing countries like India, China and Brazil.

While the various functions of the industry were traditionally all located within the same company, now the vertically integrated supply chains are breaking apart into component activities that can be outsourced.

The challenges for the Quality of medical products which are triggered by globalization include the assurance of Good Manufacturing & Distribution Practice compliance, new impurities in drug substances induced by alternative manufacturing routes, long lasting transports of medical products passing through various climatic zones, complex supply chains and product transfers. All these factors make the changes in Global Supply Chain inevitable.

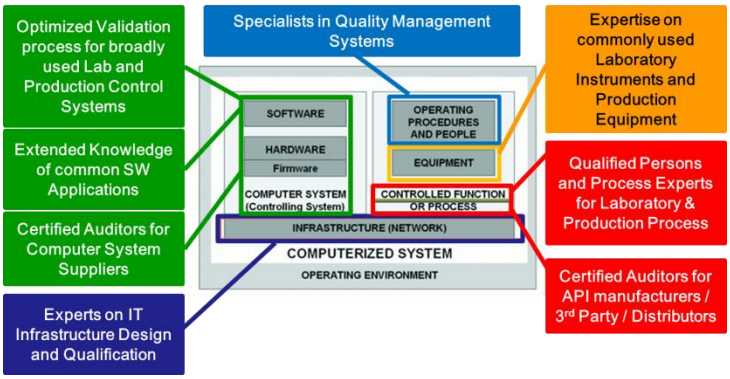
Regulatory systems of all kinds – whether dealing with flows of finances, goods or information - find it difficult to keep up with the pace of change. World-Wide recognized Regulators (EU & US) together with other active Regulatory Authorities like (Japan, Brazil, Canada, Australia) have gradually evolved to respond to the increasingly global challenge of medical products development and distribution.

Risk based approaches, Decision making techniques, Global Cooperation and Harmonization initiatives, Validation Common Standard are valuable tools to deal with the uprising challenges to ensure that safe, effective and high quality medical products are developed, registered, manufactured and distributed in the most resource-efficient manner.

Global Compliance

A model for Global Compliance is the challenge currently faced by all global regulated companies.

In order to design an effective strategy and tactic, it is recommended to create teams including all the skills required to implement a feasible and scientifically sound approach.



Such approach has to be supported by a centralized organization since a Regulated company shall ensure a uniform level of compliance across its sites and its suppliers.

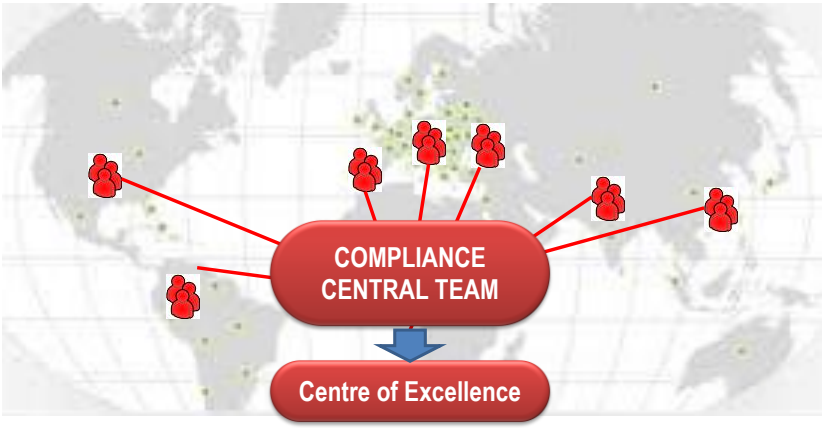
The best solution is to establish a central organization for Data Integrity in order to create standards and support the sites to assess, correct and monitor the Compliance level.

This organization (termed Center Of Excellence) will create the Validation Common Standard (Golden Packages) to be provided to the sites in order to facilitate the creation of Validation documentation for the Computer Systems used at the site.

The Global strategy of Regulated Manufacturers for Data Integrity shall be based upon the following key steps:

⇨ **ESTABLISH A CENTRAL TEAM TO ACHIEVE**

- ❑ Common Quality Approach Preliminary Agreed with Global Team
- ❑ Continuous Consistency between Central and Local Teams
- ❑ Centralized Control of Validation Deliverables
- ❑ A Tailored Team for Each Customer Need
- ❑ Dedicated Local Teams to Specific Geographical Area
- ❑ Allow a Timely Fashion Response



⇨ **ESTABLISH CENTRAL OF EXCELLENCE** (CoE), **ASSESS CURRENT STATUS AND PLAN REMEDIATION**

- ❑ Implement a Sustainable Model to ensure Compliance across all company sites
- ❑ Execute a feasible Assessment and Remediation based upon Global QA SOP, Site Risk priority and Risk associated to each Computer System
- ❑ Assessment to Verify the Validation Status of Site Control, Production and Computer Systems
- ❑ Assessment Outputs to be Evaluated to Mitigate Bias for Consistent Results Across Customer Network
- ❑ Remediation Plans to be Defined Centrally
- ❑ Approach to Ensure that Sites will not Deviate

⇨ **CREATE AND DEPLOY VALIDATION GOLDEN STANDARDS**

- ❑ Develop documentation packages for each type of systems mostly used in the Laboratory and Manufacturing environment
- ❑ Provide guidance and training to each site to create system specific
- ❑ Ensure harmonized approach for systems across sites

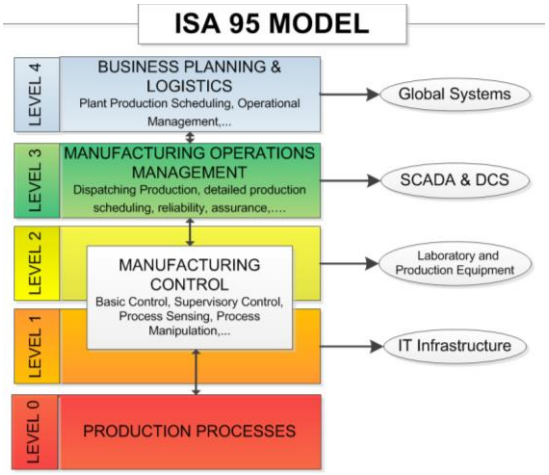
The rollout of this strategy allows Regulated Manufacturers to achieve sustainable and harmonized compliance of Computer Systems and, ultimately, to ensure the Integrity of Data where the Product Quality is built upon.

A Suppliers audit and monitoring program is another subject that receives great benefit from a centralized-tailored approach.

Process oriented approach

The classical company interpretation model based on ISA95 implies the need of creating common standards consistent and integrated in all the levels. These standards provide definitions around people, materials and equipment, as well as procedural models on how these are combined to make products.

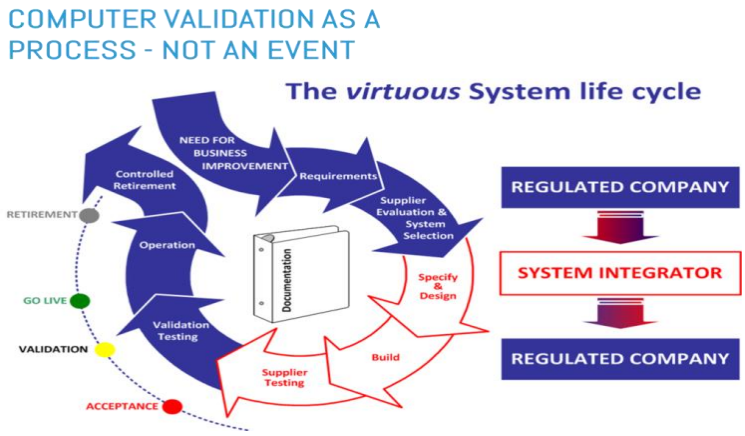
Validation common standards and templates can be considered one of the milestones for the implementation of the ISA95 model not only for the traditional owned IT applications, but also for the systems, such as stand-alone Laboratory and Production systems, traditionally managed by the Engineering/Technical Services department.



The relevance of assuring the validated status of compliance is emphasized not only in projects implementation, but also during the on-going phase.

This new vision considers the medical product during its whole lifecycle, starting from development through technical transfer to routine manufacturing and decommissioning. Risk management tools and a robust Quality System are the pillars for building a more systematic approach to validation. All data and information should be secured, accurate, and reliable and only those personnel required viewing, adding, or updating a given piece of data are in fact allowed to access it.

Reliable Data Collection shall be in place: any delay in releasing a batch of product is not only costly but cost of non-compliance consumes additional resources of the company. It is therefore crucial that during the manufacturing phase analytical data be collected, compiled, and submitted in a timely, accurate and reliable manner



Need for Data Integrity

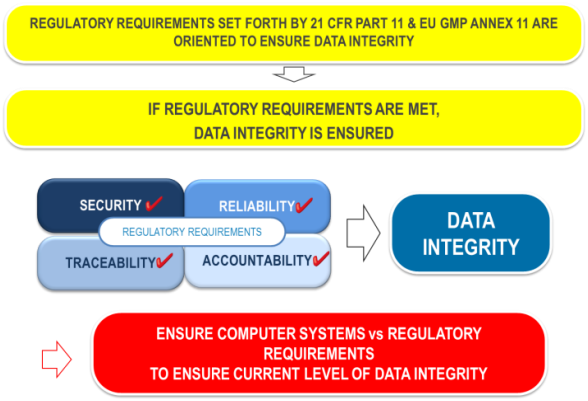
In the last 2-3 years, regulatory authorities became focused more on Software and Computerized Systems. The agencies detected problems in the Computer Compliance such as: incomplete or faulty recordkeeping; repeated and undetected errors in critical data; reduced capability to recall drugs and medical devices; release of contaminated blood and components. The numbers of US/FDA's Warning Letters related to Data Integrity has strongly and consistently increased in the last twelve months. This Regulatory pressure together with the technology and environment complexity shall be

counterbalanced by: Validation, Quality Risk Management, Record Management and Supplier Management.

Data Integrity became one of the highest priorities and can be described as "The condition existing when data is unchanged from its source and has not been accidentally or maliciously modified, altered or destroyed". [National Information Assurance Glossary]

Reliability of Data defines consistency also referred to as: repeatability, method precision or system precision. It is imperative to demonstrate that:

- **Regulated data** collected through Logistics, Laboratory, Production, Distribution and other systems have been generated and maintained with care, are technically and procedurally protected against manipulations.
- **Documentation and Result Reporting** have been done in real time (action), can be clearly identified, have been standardized, predefined, authorized (and Person who recorded must be clearly identifiable).
- **Data integrity Control** ensures the chain of evidences backward from the final documents; the Audit Trail Review process is required to ensure that data show no violation patterns



Each Regulated Company is required to assess the level of compliance to regulations (e.g. 21 CFR Part 11) and to correct any deficiency in order to reach the required compliance level.

Conclusions

- ❑ Quality of Product (raw materials, components, sub-assemblies, packaging materials) rely upon integrity of Laboratory and Production Records and is the ultimate responsibility for Market Authorization Holders (MAH)
- ❑ New Challenges are triggered by Global Supply Chain Process
- ❑ A number of different Enforcement measures have been defined by Regulatory Bodies to mitigate Risk to Product Quality
- ❑ Compliance to new Regulatory Requirements is ultimately based upon Data Integrity
- ❑ Outsourcing can be used by Regulated Companies provided that an effective Provider Qualification/Monitoring process is in place

Validated Technology might be the only chance MAHs may have to face the current challenges for medical products industry (globalization, cost reduction, data integrity)

Applicable Rules and Guidelines

Analysis described in this document has been executed according to the following rules and guidelines:

Rules:

1. US Food & Drug Administration – Code of Federal Regulations, Title 21, part 210, "Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General"
2. US Food & Drug Administration – Code of Federal Regulations, Title 21, part 211, "Current Good Manufacturing Practice (GMP) For Finished Pharmaceuticals"
3. European Community – Guide to Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in the European Community, Volume IV)
4. US Food & Drug Administration - Code of Federal Regulations, Title 21, part 820: "Medical Devices Current Good Manufacturing Practice"
5. US FDA Code of Federal Regulations, Title 21, Part 803, "Medical Device Reporting"
6. US Food & Drug Administration – Code of Federal Regulations, Title 21, part 11: "Electronic Records; Electronic Signatures; Final Rule"
7. European Commission, The Rules Governing Medicinal Products in the European Union – Volume 4: Good Manufacturing Practices Medicinal Products for Human and Veterinary Use, Annex 11 – June 2011
8. European Commission – The Rules Governing Medicinal Products in the European Union – Volume 4 – Part III: Quality Risk Management – March 2008 (Adoption as ICH Q9 guideline Step 4)
9. European Commission – The Rules Governing Medicinal Products in the European Union – Volume 4 – Part III: Pharmaceutical Quality System – June 2008 (Adoption as ICH Q10 guideline Step 4)
10. Resolution – RDC N° 17, of 16/04/2010:Union Official Gazette Section 1 "Provides for the Good Practices of Medicament Manufacturing" (Anvisa)
11. NOM-059-SSA1-2013, "Buenas prácticas de fabricación de medicamentos", Mexican GMP
12. Resolution - 2013019704, of 05/07/2013, "Por la cual se adopta el Sistema Integrado de Gestión de Calidad del Instituto Nacional de Vigilancia de Medicamientos y Alimentos INVIMA"
13. Reglamento Sustitutivo del Reglamento de Buenas Prácticas de Manufactura (BPM) para Laboratorios Farmacéuticos - Acuerdo Ministerial 00000760 Registro Oficial 359 del 10 de enero del 20
14. RESOLUÇÃO - RDC Nº 59, DE 27 DE JUNHO DE 2000 - Agência Nacional de Vigilância Sanitária - BOAS PRÁTICAS DE FABRICAÇÃO DE PRODUTOS MÉDICOS
15. DIGEMID (Direccion General Medicamentos, Insumos y Drogas) - Manual de Buenas Practicas de Fabricacion RM n° 055-99-SA/DM
16. Russian Ministry Of Industry And Trade Of The Russian Federation – Appendix N 11 to Regulation Good Manufacturing Practices – June 2013
17. Chinese Annex 1 of Good Manufacturing Practice for Drugs – May 2015
18. Guidelines:
19. US Food & Drug Administration – Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2006

20. US Food & Drug Administration – Guidance for Industry Process Validation: General Principles and Practices – Revision 1, January 2011
21. US Food & Drug Administration – General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002
22. US Food & Drug Administration – Guidance for Industry: 21 CFR Part 11 – Electronic Records and Electronic Signatures: Scope and Application, August 2003
23. PIC/S Good Practices for Computerized systems in regulated "GxP" environment, Pharmaceutical Inspection Co-operation Scheme guidance, September 2007
24. PIC/s Guidance Draft August 2016 PI-041-1 "Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments"
25. GAMP Forum – GAMP Guide, A Risk-Based Approach to Compliant GxP Computerized Systems – Ver. 5.0
26. GAMP Forum – GAMP Good Practice Guide: The Validation of Legacy Systems
27. GAMP Forum – GAMP Good Practice Guide, Testing of GxP Systems
28. GAMP Forum – GAMP Good Practice Guide, IT Infrastructure Control and Compliance
29. GAMP Forum – GAMP Good Practice Guide: Validation of Process Control Systems
30. GAMP Forum – GAMP Good Practice Guide, Global Information Systems Control and Compliance
31. GAMP Forum – GAMP Good Practice Guide, A Risk-Based Approach to Compliant Electronic Records and Signatures
32. GAMP Forum – GAMP Good Practice Guide, A Risk-Based Approach to Operation of GxP Computerized Systems
33. MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)
34. Agência Nacional de Vigilância Sanitária - Guia de Validação de Sistemas Computadorizados
35. WHO Annex 5 Guidance on Good Data and record management practices May 2016
36. FDA-Data Integrity and compliance with CGMP (Draft, April 2016)
37. ICH E6(R2) Good Clinical Practice Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (2014)
38. OECD Series On Principles Of Glp And Compliance Monitoring Number 17 Application of GLP Principles to Computerised Systems
39. ISPE GAMP Guide_Records and Data Integrity
40. CFDA Drug Data Management Standard