# Good manufacturing practice in Europe

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Compliance with good manufacturing practice (GMP) is an important regulatory requirement to demonstrate that adequate facilities, utilities, manufacturing practices, trained personnel and quality management systems are in place to consistently produce a biological product with desired quality attributes.

BIOLOGICAL manufacturing is a complex process involving multiple steps and factors that can influence the quality of final product. These include: establishing cell banks; quality control, storage and usage of raw materials; control of TSE/BSE risks associated with biological origin materials, clean room and containment issues, man/material movements, use and cleaning of production equipment, campaign changeover procedures, etc. GMP requirements also vary for different types of biological products. For example, manufacturing live attenuated viral vaccines requires well-designed clean rooms, biosafety cabinets and decontamination procedures to avoid product contaminations and the risk of virus particles escaping into the outer environment.

The most important step in the entire process is the interpretation and understanding of region-specific GMP requirements for a biological product, and preparing an appropriate compliance plan as per future commercialisation goals.

Prospective planning for GMP compliance with optimal utilisation of investment and resources can help in assuring a high degree of compliance. Inadequate planning may end up with a manufacturer complying with all regulatory requirements for marketing authorisation but failing to demonstrate GMP compliance.

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## EU GMP regulatory perspective

- The principles and guidelines of GMP for medicinal products for human and veterinary use in the European Union were laid down in the Commission Directives 2003/94/EC and 91/412/EEC respectively.

- Detailed guidelines in accordance with the principles mentioned in the above EU directives were published in the Guide to Good Manufacturing Practice (EudraLex Volume 4).
- EudraLex Volume 4 is used to assess applications for manufacturing authorisations and as a basis for manufacturer inspections. It is organised into three parts and supplemented by a series of annexes:
    - Part I covers GMP principles for the manufacture of medicinal products as defined in Directives 2003/94/EC and 91/412/EEC
    - Part II covers GMP for active substances used as starting materials. This part was established on the basis of ICH Q7A guidance (GMP for active pharmaceutical ingredients)
    - Part III contains GMP-related documents, which clarify regulatory expectations, but which are not detailed guidelines on the principles of GMP laid down in Directives 2003/94/EC and 91/412/EC
    - Annexes: this series of annexes provide details about specific areas of activity like sterile preparations, biological medicinal products, and radiopharmaceuticals and so on. The Annexes provide guidance which supplement Parts I and II of the EU Guide to GMP.

The regulatory expectation is that biological active substance manufacturers must comply with Part I, II and all related annexes of EudraLex Volume 4 that are applicable for their product type and the manufacturing activities under that scope.

In addition to the EU Basic GMP requirements (Part I), Part II and Annex 2 are the primary requirements for biological active substance GMP compliance. The scope of Part II begins from the maintenance of working cell banks, whereas the scope of Annex 2 includes the establishment of seed lots and cell banks. However, these early manufacturing steps within Annex 2 do not imply that they will be routinely subject to inspection by the authorities. In addition to the above GMP requirements, European agencies also expect manufacturers to follow EudraLex Annex 1, which sets requirements for aseptic operations and manufacturing activities of a product or substance that is claimed to be sterile.

Facility design, clean room practices, operating procedures, personnel training, process equipment design, and performance qualification for intended process significantly influence product quality. While a validated manufacturing process ensures production of a biological product with pre-determined quality attributes, GMP compliance with all these other factors is essential to reach this goal.

## Quality risk management

Regulatory agencies insist on an adequate quality risk management process for biological product manufacturers. A quality risk management process consists of two main parts – risk assessment and risk mitigation.

Risk assessment includes a detailed assessment of the impact of various manufacturing factors like the facilities, utilities, equipment, materials, personnel, etc, on the quality of the biological product.

Risk mitigation involves setting up mitigation plans that will help in either eliminating identified risks or reducing risk factors to an acceptable level. For example, after identifying and categorising risks associated with the manufacturing of a certain biological product, the appropriate risk mitigations can be implemented by setting up adequate controls over the process, materials, procedures, personnel, clean rooms and environmental conditions, etc.

## The Brexit effect

On 29 March 2017, the United Kingdom notified the European Council of its intention to withdraw from the European Union in a process known as Brexit. When the UK leaves the EU on 30 March 2019, it will become a 'third country', but until that time all EU primary and secondary laws apply to the UK.

As the UK's exit from the EU is expected to be drawn out, it is of utmost importance to decode how quality and standards will be maintained for medicinal products, ie, how EU GMP will be adopted and amended. It is expected that manufacturing sites for finished products in the UK cannot release their products to the EU market unless a new site is nominated in the European Economic Area, for which a qualified person is required to take the responsibility.

In addition, Brexit is expected to affect how the quality of active substances that are manufactured in the UK are recognised. Post Brexit, substances manufactured at UK plants are expected to be considered as imported active substances and require MHRA certification that the manufacturing plant is following an equivalent to EU GMP.

On the other side of the story, it is assumed that any post-Brexit changes to EU GMP will not improve the medicinal products' safety and efficacy. Moving too far from existing systems may not satisfy the holistic purpose, ie, harmonisation of GMPs. So it is expected that EU GMP and UK regulations may not differ greatly. But in this uncertain scenario, it is suggested that organisations adopt a wait and see approach and investigate and invest in intelligent regulatory partnership.

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BIOGRAPHY

**SURESH MODUGU** is Senior Manager at Freyr solutions, handling the biologics portfolio. He has extensive regulatory experience in the development and registration of more than 20 biological products, including recombinant therapeutic proteins, monoclonal antibodies, vaccines, blood and sera products for US, EU and ROW regions. His expertise includes regulatory and GMP requirements for marketing authorisation, and the commercial manufacturing and lifecycle management of biological products produced from recombinant expression systems.