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European regulatory landscape: Demystifying new Qualified Person (QP) requirements for supplying medicine in the EU and UK

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Abstract

Under European Union (EU) law, QPs are legally responsible for certifying that every batch of a medicinal product meets all required provisions when it is released from a manufacturing facility within the EU or imported into the EU. The evolving regulatory environment in Europe has added a layer of complexity to QP processes. The United Kingdom's withdrawal from the EU has introduced regulatory oversight and compliance obstacles that threaten to increase supply chain risk, disrupt clinical trial plans, and impede delivery of medicines to patients. To ensure full compliance and timely and efficient batch release processes, drug sponsors pursuing clinical trials and commercialization in the EU and UK require a deep understanding of European GMP requirements and the roles and responsibilities of the EU and UK QPs in this new environment.

Executive summary

Qualified persons (QPs) play an essential role in the European clinical trial supply chain. Under European Union (EU) law, QPs are legally responsible for certifying that every batch of a medicinal product meets all required provisions when it is released from a manufacturing facility within the EU or imported into the EU. An already complex undertaking, QP release has added another layer of complexity in the shadow of Brexit.

The withdrawal of the United Kingdom (UK) from the European Union (EU) has brought with it major changes to the way medicinal products are tested, analyzed, and regulated in the UK and European markets, along with many questions about the impact these changes might have on the pharmaceutical supply chain, clinical trials, and commercialization efforts in the respective regions.

Because Great Britain is no longer included within EU regulations for release and distribution of medicinal products, certain regulatory activities, such as batch testing and QP certification, conducted in the UK will no longer be recognized in the EU. In addition, expectations are soon to be altered when supplying medicines into Great Britain and Northern Ireland from the EU. If not understood and carefully planned for, the extra layers of regulatory oversight and compliance obstacles can increase supply chain risk, disrupt clinical trial plans, and impede timely delivery of potentially life-changing treatments to patients. To help drug sponsors understand and overcome the regulatory hurdles and expedite time to clinic, this paper provides critical direction and support for the following activities:

- Maximizing the chances for seamless and effective interactions with QPs
- Anticipating QP requirements
- Understanding the impact of Brexit on QP processes
- Navigating the QP landscape to facilitate timely and efficient batch release of commercial and clinical drug product supply

For drug sponsors pursuing clinical trials and commercialization in the EU and UK, achieving a deep understanding of European GMP requirements and the roles and responsibilities of the EU and UK QPs should be a strategic imperative from the project outset to ensure full compliance and facilitate timely and efficient batch release processes.

Introduction

European Directive 2001/83/EC issued on Nov. 6, 2001 required that a single individual known as a Qualified Person (QP) be responsible for commercial and investigational medicinal product certification and release at manufacturing sites.[1] A QP certification attests to the integrity of the chain of documentation provided by other QPs upstream in the process, perhaps via a QP-to-QP agreement. It provides the final release and allows a finished clinical or commercial batch to enter the market or clinic for use.

In addition to final certification of a batch, a significant supply chain role of the QP is to sign a "QP Declaration" for active pharmaceutical ingredient (API) in commercial drug products or for the entire supply chain for investigational medicinal projects (IMPs). In essence, the QP declaration states that medicinal products have been manufactured according to standards of Good Manufacturing Practice (GMP) at least equivalent to those applied in the EU. The QP declaration is part of the regulatory submission for a clinical trial application or for an EU Marketing Authorization Application (MAA) and stands as evidence that an audit(s) has been performed and that the requirements of the marketing authorization have been met.[2] This may include confirming that medicinal products from external countries undergo qualitative and quantitative analyses and any other quality checks and balances have been completed.

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QPs abide by a code of practice and possess the extensive qualifications, knowledge, and skills required to perform their legal and routine duties. In line with the Brexit timeline of January 2021, these roles and responsibilities changed dramatically. The EU and UK now function as separate legal and regulatory jurisdictions, and drug products must meet the relevant requirements for the market in which they will be sold. This added layer of complexity brings with it substantial planning implications and documentation requirements that must now be considered. The burden of understanding falls heavily on the QPs themselves. Much of this learning occurs through professional development opportunities directed specifically to QPs, but any entity involved in manufacturing or development (including clinical trial sites) in the EU and/or the UK should have a working knowledge of the changes to ensure requirements are being met and legal or other challenges are avoided.

Overall, a more streamlined journey through the process can alleviate worries among many about the availability of adequate and timeline medication supplies, particularly in the UK.[3] The following are some important points offering critical direction for successfully navigating the complexities of the EU-UK regulatory environment post-Brexit.

Maximize chances for seamless QP interactions

In an EU multi-stage medicinal product batch release, QP-to-QP agreements are required documents that help delineate where one QP's responsibility ends and another QP's responsibilities begin.[4]

For non-EU sites ("Third country") which now also includes the UK, it is extremely important that extensive data on manufacturing, testing, storage, and transport are communicated to the QP. Without the assurances gained from another QP, the QP has to ensure compliance as if they were present at these sites. This often involves regular audit, communication, and document flow from these sites.

As discussed previously, all these sites will need to be listed on the QP declaration and signed by the QP as complying with 'standards equivalent' to EUGMP Communication, and a joint under-standing of processes is critical to avoid delays. This can be accomplished in part by ensuring that all appropriate information is listed in any application, including each site of QP release, and that the application mirrors the supply chain so that no critical steps are at risk of being forgotten.

Anticipate QP requirements

Understanding the various requirements for QP certification according to the types of products, phase of study, and countries/regions involved can make for a smoother, more efficient progression through the batch processing and certification stages.

The "best" course of action can vary substantially depending on the specific scenario. The multitude of possible scenarios validate the need for highly experienced QPs with extensive knowledge across multiple aspects of the development process (See "The complex landscape of QP involvement in drug development on p. 6").

QP to QP agreements

A robust supply chain will typically involve multiple QPs engaged at different stages in the manufacturing process. When multiple QPs are involved, a QP to QP agreement is required.[5] These agreements are essential whenever 2 or more QPs (within EU) are involved in the batch certification process (both commercial and IMP) and when there are two or more QPs within the same organisation, but at different sites. To avoid potential roadblocks, the agreements should:

- Delineate the responsibilities of each QP around medicinal product batch releases, considering a stepwise manufacturing and testing process
- Ensure responsibility about compliance to MAA/CTA sections are clearly reported and the final certifying QP is well identified
- Include process flow diagrams and tables detailing tasks, including shipping and warehousing

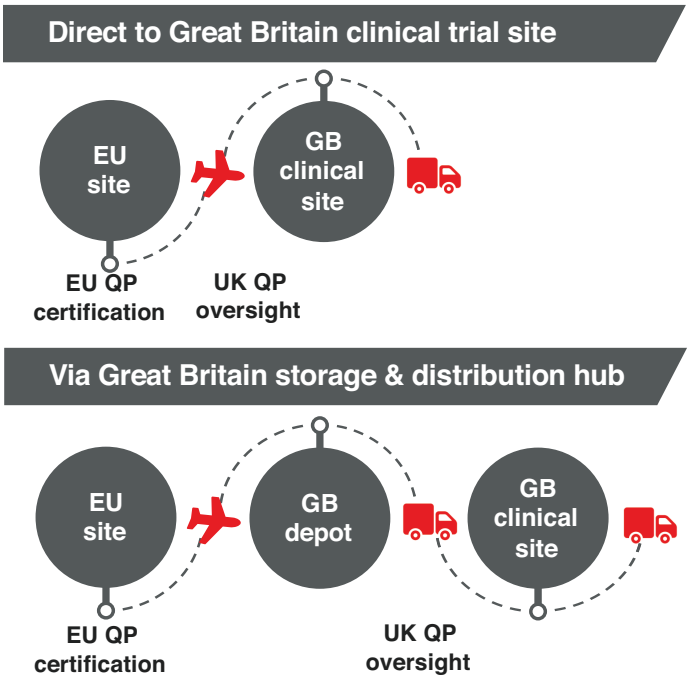
Brexit's effect on QP process

Changing regulations as the UK leaves the EU have far-reaching effects on drug production, authorization, regulation, trade, health and safety monitoring, and research.[6,7,8] Perhaps the only significant, reciprocal agreement between the UK and EU in terms of medicinal product development with Brexit was the mutual acceptance of EU GMP inspections. Importantly, QP certification in the UK is no longer accepted in the EU; however, EU certification is accepted by the UK until January 1, 2022.[9] After this time, a UK QP will have to provide oversight for shipments coming into Great Britain. Additional changes with varying grace periods have an impact on decommissioning for non-investigational medicinal products before export to the UK, testing equivalence, and other functions which may be of interest or concern to those responsible for managing supply chains.

In review of anticipated changes, it is extremely important that sponsors begin the process of establishing and implementing necessary protocols to ensure compliance with portions of the Medicines for Human Use Regulations 2019 that will become effective January 1, 2022.[10]

There are essentially two routes for IMPs to be received into Great Britain—either direct to a Great Britain clinical trial or via a storage and distribution hub or depot (see Figure 2). Both of these routes require the oversight of a UK Manufacturing and Import Authorization [MIA(IMP)] holder and QP. QP oversight of the process will ensure that appropriate certification is performed, IMPs are only shipped to appropriate sites, up-to-date trial information is available to the QP named on the UK MIA(IMP) and the clinical trial is authorized by the Medicines and Healthcare products Regulatory Agency (MHRA) before IMP is made available to the investigator.

Figure 2: Two routes for IMPs to be received into Great Britain following grace period ending January 1, 2022



The complex landscape of QP involvement

Below are scenarios that sponsors have encountered when working with QPs to supply medications to trials and the market.

- A sponsor chooses to outsource QP services to a group with specific experience in injectables. In this scenario, a Quality Agreement is required between the QP and the sponsor. The QP services are provided by an experienced CMO who guides the development of the agreement including delineation of the roles of the outsourced QP and sponsor.
- A sponsor wishes to import gene therapy products from the US. The QP advises the Sponsor on existing restrictions to this type of import product and provides information on exemptions.
- A sponsor must submit API information to the Italian Medicines Agency. A QP advises that, under this Health Authority (HA), all APIs destined for commercial use are subject to an authorization process that can take up to 90 calendar days.

Advice for supply of medicines in the UK, EU

- Include appropriate information in study submissions
- Understand your supply chain strategy for QP oversight
- Plan for QP API and IMP declarations
- Review quality and technical agreements
- Prepare for new Clinical Trials Regulation
- Factor potential API import requirements into timelines
- Keep your QP updated at all times

QP oversight mitigates risk and protects timelines

QP oversight can protect timelines through numerous protocol-level, batch-level, and shipment-level checks. Notably, this process should be formalized in a technical agreement to be captured in the clinical dossier for the UK.

Northern Ireland QPs and supply into 2022

QPs in Northern Ireland (NI) will still be recognized by EU, and NI will continue to follow EU rules as part of the Northern Ireland Protocol.

It is also important that Northern Ireland supply is safeguarded. Northern Ireland has been subject to a reasonable level of political debate, with both the EU and UK expressing concerns of the supply parameters agreed under the NI protocol.

Each sponsor should review their process of establishing and implementing necessary protocols to ensure compliance that UK/EU agreement on NI supply of IMPs which could become applicable from January 1, 2022 (dependent on political decisions leading to this date).

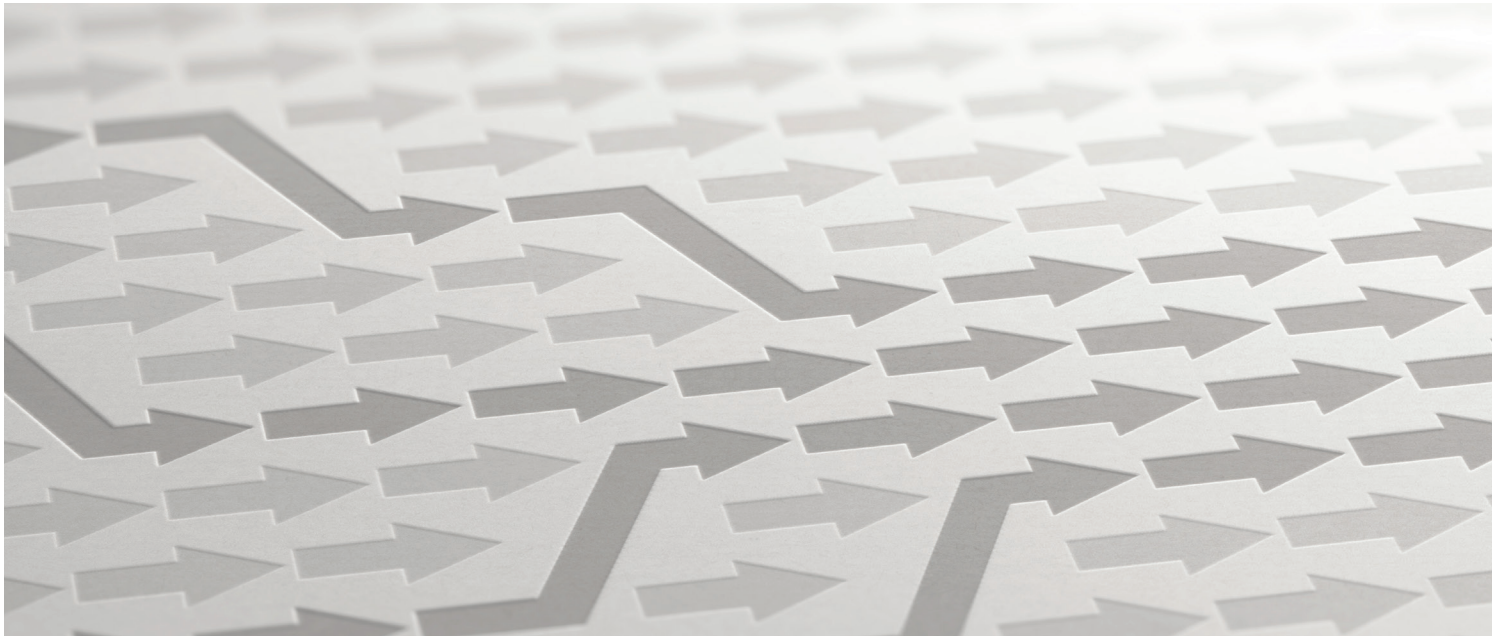
For Northern Ireland, the following supply chain considerations are essential.

QP expertise reduces delays associated with phase II GMP activities

An IMP Phase II supply started from an API imported to EMA from India, a non-MRA country. The drug product manufacturer, Thermo Fisher Scientific, purchased the API because the sponsor did not provide it. Only one API lot sufficient for the planned batches was available, thus it was booked. Because the drug product was to be exported to the US for secondary packaging, release, and clinical use, a QP/QP agreement was not required. The project did require the following:

- A quality agreement between the sponsor and Thermo Fisher for full contract manufacturing services
- A quality (supply) agreement with the API manufacturer
- API manufacture qualification through onsite general audit and API-specific process scrutiny
- Import notification application with EMA (AIFA), including mandatory API supply chain qualification and full API lot retesting

Successful completion of the project required navigating multiple challenges, including a complex interaction with the API manufacturer to achieve required API-specific information and the shutdown of the API plant due to the pandemic making it difficult for the QP to obtain needed information. Additionally, because only one lot of API was available, an agreement was made with the Health Authority to calibrate the import retesting demand on API lots. The entire process required coordinating the API import and retest timelines with the IMP batch manufacturing and clinical phase timelines.



- IMPs supplied from Great Britain to NI will require importation via a MIA(IMP) holder in NI or a European Economic Area (EEA) state and certification by a QP named on the MIA(IMP). There are other supply chain options that will not require importation controls to be performed in NI or an EEA state. These include supplying IMPs to NI directly from the EEA and changing the location of QP certification activities.
- Effective January 1, 2021, facilities in Great Britain will no longer be able to supply clinical sites in NI. Again, subject to political decisions, all supply to NI will need to be routed through an EEA facility or be imported into an MIA holding facility based in NI. This may have an impact on interactive response technology (IRT) set up and clinical trial application (CTA) compliance as facilities and depots may change as a part of a sponsor review.
- The "safety features" elements of the EU Falsified Medicines Directive (FMD, 2011/62/EU) and Delegated Regulation (2016/161) ceased to have effect in Great Britain from December 31, 2020. End users in Great Britain were disconnected automatically from the UK National Medicines Verification System. However, under the terms of the Northern Ireland Protocol, part of the UK's Withdrawal Agreement with the EU, FMD will still apply in NI. End users should ensure they are registered with SecurMedUK.

MRAs streamline transfer of key information

Mutual recognition agreements (MRAs) with third-country health authorities allow the EU and counterparts to maximize efficiency by relying on each other's existing inspection systems (i.e. waiving pre-approval inspections) and to share information on inspections and quality defects which can speed up transfer of key information.

Additionally, these agreements allow for the waiver of retest of product batches on import into their territories (not including IMPs) and for the waiver of full retesting of API/DS imported lots. In short, the presence of an MRA can make it faster and less costly for the stakeholder countries to bring medicines to market. (Note: Currently, there is no MRA between the UK and EU and it is unclear whether there is a plan to sign up to any MRA outside the established Free Trade Agreement.)

Given the complexities of the European regulatory environment and the divergence between the requirements of EU, its member states, and the UK, successful completion of critical processes requires deep and broad QP expertise, as illustrated by the scenarios described at right (See "QP expertise reduces delays associated with phase II GMP activities on p. 7.")

Conclusion

With the rapidly changing regulatory environment, the QP plays an even more critical role than ever in bringing medications to market safely and quickly. Pharmaceutical companies and sponsors planning to supply the EU or UK must become familiar with the shifting legislation and manufacturing requirements, as well as the role and responsibilities of QPs in each region. Partnering with a CDMO that offers in-house UK and EU-based QPs may allow sponsors with less regulatory experience to successfully navigate the evolving landscape. Choosing a CDMO partner with the expertise to understand the unique issues associated with the product type, project phase, and geographic entities involved can reduce timeline and budget risks for clinical trials and commercialization and ultimately get much-needed medicines to patients more quickly.

Additional resources

On-demand webinar: EU Clinical Trial Regulation 2022 – impact on regulatory, labeling and QP

Blog post: Regulatory landscape in Europe: Key advice for meeting post-Brexit Qualified Person requirements

On-demand webinar: QP Release – expectations and responsibilities for clinical and commercial drug products in Europe

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A Chartered biologist, with a Masters in Pharmaceutical Sciences, Harry has over 20 years' industry experience in Steriles, Biologics & Solid Dose in both Commercial and Clinical Manufacturing and Packaging. Harry currently holds the position of Senior Director, Quality, EMEA, leading the EMEA Quality function at Thermo Fisher Scientific. Based in Horsham, UK, Harry oversees 6 sites specializing in the Manufacture, Packaging and Distribution of Investigational Medicinal Products (IMPs). Harry previously led Quality at the Thermo Fisher Scientific Horsham site for several years. Harry is an experienced Qualified Person (QP) for clinical and commercial products.

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Dr. Barbato has more than 25 years of experience in the pharmaceutical industry and has spent the last 18 years in the context of contract manufacturing operations with focus on sterile products, covering Quality Compliance/ Assurance and Quality Control roles, including experience in the Thermo Fisher UK site of at Swindon. During that period, the manufacture and certification of commercial and investigational products, with focus on biopharmaceutical preparations were extensively examined. He also expanded his area of interest to optimisation and qualification of inspection processes (manual / automated) for parenteral products, with focus on strategies for control of contamination of filling lines. Since 2015, Dr Barbato has held the role of Qualified Person at the Pharma Services Group Ferentino Site, for the certification of investigational and commercial medicinal products.

Dr. Barbato has received his degrees in Pharmaceutical Chemistry and Technologies and in Pharmacy from the University "La Sapienza" of Rome. He has been certified as Pharmacist in the Italy National Order. Prior to joining Patheon, Dr Barbato worked in Abbott Laboratories, Campoverde Site, as R&D formulation scientist, moving to Quality context for various roles in Quality Control and Assurance. He was accredited as Qualified Person by AIFA (Italy EMA) in 2007. Dr. Barbato is member of various international pharmaceutical professional organizations; has been a speaker on Quality Control/Assurance and QP batch certification topics in pharma industry seminars; and is the owner of an industry US filed patent for a soft-gel based anti-HIV formulation.

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