QP release in the EU in 2022 and beyond: Your questions answered

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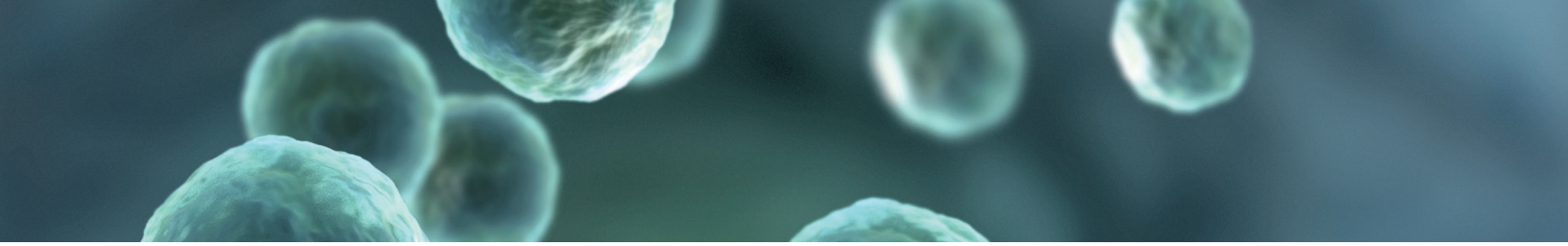
Introduction

With the rules on Qualified Person Certification undergoing significant change, it is important to discuss and maintain an ongoing understanding of Good Manufacturing Practice (GMP) and new legislation in order to successfully navigate the global clinical trials market and ensure the timely supply of your Investigational Medicinal Products (IMPs).

In the European Economic Area (EEA) and in the UK, the Qualified Person (QP) plays a crucial role in bringing safe and timely products to the market and/or supplying them to the clinic. There have been interesting regulatory developments in Europe—most notably the EU Clinical Trial Regulation 2022—and it is critical that pharmaceutical companies stay abreast of them. The UK has also recently issued proposals to overhaul its clinical trial framework.

In a recent webinar titled "QP release in the EU in 2022 and beyond: Your questions answered," two clinical QP experts from Thermo Fisher Scientific, Harry Berlanga, Senior Director of Quality, and Naomi Wilmer, QA Manager and Qualified Person, discussed the expectations and responsibilities of the UK and EU QPs in ensuring supply of clinical and commercial drug products between the UK and the EU. Their observations and responses to key questions are shared here.*

*Responses have been edited for clarity and brevity.



Q: Has there been progress toward formal recognition of UK QP activities by EEA QPs? Are QP-to-QP agreements helpful?

NW: This question is pertinent due to Brexit. The answer is no. There has been no progress with the EU/UK Mutual Recognition Agreement (MRA). The UK is currently deemed a third country, although it is anticipated that there may be a MRA in place in the future.

With regard to QP-to-QP agreements, these are essential when relying on a QP for part of the supply chain. However, agreements between an EU QP and UK QP now have no legal standing in EU GMP, as the EU QP can only delegate responsibilities to another EU QP (which no longer includes UK QPs).

Additionally, from a legal standpoint, the EU QP has no legal standing in UK either. However, as the MHRA are accepting EU QP certification in the UK, there is a rationale that if the EU can provide full QP certification, they can provide confirmation for part of the supply chain, which can then be utilised by the UK QP in the form of QP to QP agreement.

TIP	Always consult with the certifying QPs to assess their comfort level and how much they are able to rely on other QPs in the supply chain.

Q: Is the QP release for a commercial drug product, which is then exported to the UK as bulk and then secondary packaged in the UK, accepted by the UK QP? Is there any intermediate period for acceptance of EU QP release for UK market?

NW: In this scenario, it is assumed that the UK QP is the final certifying QP. In this instance, either the UK QP would need to assume responsibility of the whole supply chain, or they could rely on the EU QP for the bulk drug product, with an appropriate QP-to-QP agreement as required. The UK QP is only able to certify for UK or Rest of World (ROW) countries. To supply back into the EU, the finished product would need to be imported into the EU and then certified by an EU QP.

Regarding the intermediate period for EU QP release acceptance, EU QP certification is continuing to be accepted in the UK. As of January 2022, this is subject to UK QP supply chain oversight to confirm IMPs have been QP certified in the EU. Required documentation needs to be supplied to the UK QP and added to the technical agreement, and the Clinical Trial Application (CTA) must include the UK site where UK QP oversight is taking place.

Q: The new regulation appears to require the expiry date to be placed on all components (Annex VI, A2.2). This will cause issues for expiry updating supplies at clinical sites. Do you see any way around this?

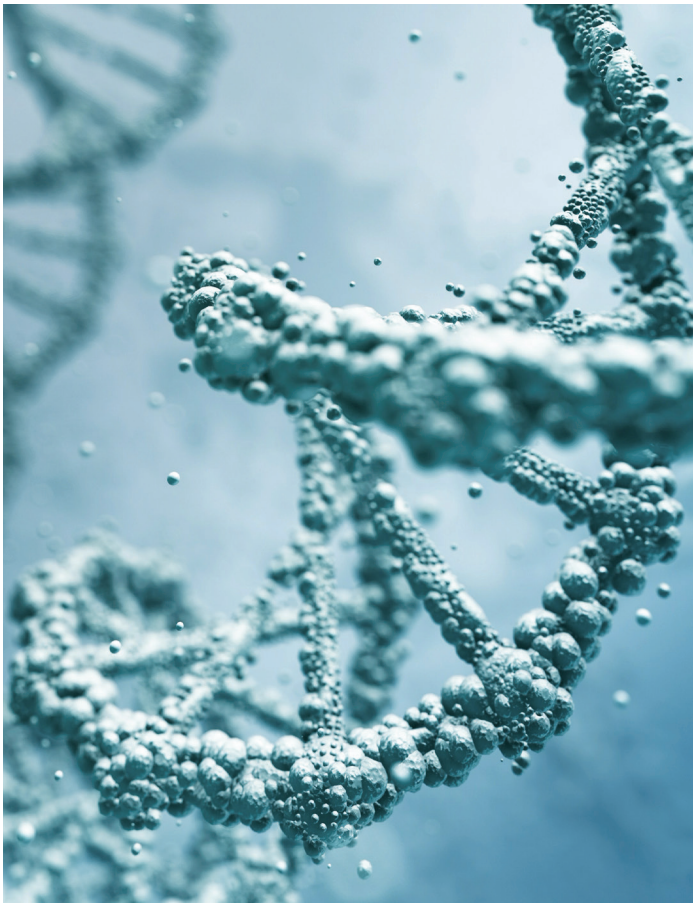
HB: The regulation requires that the expiry date is put on the primary pack, even on the small ampoules and blisters. It needs to be labelled and, more critically, re-labelled in the event of an expiry update. My advice would be to take full advantage of the one-year transition period. It is possible that industry pressure may cause the European Commission to react to this new regulation requirements. In fact, the European Commission is looking to amend the legislation to allow some products to return to the old arrangement of secondary packaging. If this does not happen, I would suggest a redesign of primary pack label to encompass enough real estate for the expiry update.

Alternatively, if this is not possible, a Just-In-Time (JIT) solution could effectively apply the expiry at a later date, limiting the need for costly expiry updates. However, if this alternative labelling solution introduces any perceived risk to product quality, the issue should be discussed with a competent authority. I also recommend consulting the European Federation of Pharmaceutical Industries and Associations (EFPIA) website for updates. The EFPIA appear to be making some progress with engaging with certain EU member states on how this law should be changed.

Of course, for trials outside the EU/EEA, including the UK, there will be no new requirement re expiry date labelling.

Q: Should QP release be expected for commercially available medication being used within a clinical trial as standard of care or supporting medications?

NW: Auxiliary medicines that are used in clinical trials but are not the investigational product are called non-investigational medicinal products (nIMPs) also known as auxiliary medicines. The clinical protocol and the clinical trial application can be used to determine if the product is an IMP or a non-IMP. Ideally, products with a marketing authorisation in the member state should be sourced. This would indicate that the nIMP had already been QP certified for its intended use with no further certification required. If this is not possible, it may be necessary to import the product as an unlicensed medicine as per local requirements. In the UK, for example, there is a requirement to notify the MHRA prior to importation. The product would also need to be identified in the Clinical Trial Application (CTA) as an unlicensed medicine, along with appropriate justification for its use in that trial. Often, sponsors include a nIMP dossier as part of the application. Finally, the product should be released under the unlicensed medicines arrangement for that member state.



Q: With respect to the Clinical Trial Regulation, will the UK follow the same processes?

HB: Now that the UK has left the European Union, there is no longer a need to align to the same legislation. In an attempt to improve the smooth running of clinical trials in the UK, a public/industry consultation has been issued with the following proposed changes:

- Inclusion of patient and public opinion on how trials should run
- Trial transparency and a WHO trial registry for easier access
- A combined Ethics and MHRA approval process (these were previously separate)
- A streamlined appeals process for shortening the 30-day approval timeline and an expedited 'further information' process to replace the straight rejection/approval process
- Streamlined safety reporting to limit the burden on the annual safety updates especially for Suspected Unexpected Serious Adverse Events Reporting (SUSARs)
- Adoption of Good Clinical Practice (GCP) into UK law
- Maintenance of existing definitions and terminology, including nIMP (vs. auxiliary medicinal products)

The presumed intent of these proposed changes is to adopt risk-proportionate labelling, which aligns well with the approach proposed by the EFPIA.

Q: Is UK QP oversight required for shipments from other countries such as the US and Canada to clinical sites?

HB: This is a frequent question, most likely stemming from the assumption that the UK is going to allow release of products coming into clinical sites in the UK and from the EU and EEA. But the simple answer is no. UK supply chain QP oversight is not applicable from these countries. The UK supply chain QP oversight process can only be utilised where the sending country is on the 'Approved list,' which for now is the EU/EEA. It's possible that other countries might be added to the approved list in the future, but this would mean that the MHRA would have to accept the assurances that are aligned to the UK, which may be a larger gap to cover for countries without QPs.

Q: What is the latest on Northern Ireland arrangements for supply of clinical medicines from GB and EU and ROW?

HB: Northern Ireland supply has been ever-changing. Since the Northern Ireland protocol required the country to stay in regulatory alignment with the EU, there has been some cause for concern. In December 2021, the UK government provided clarity under the current published statement, as follows:

"Medicines can be supplied from the Great Britain market to Northern Ireland without requiring additional regulatory importation controls, manufacture and import authorisation, batch testing, and QP certification that would have been done in Northern Ireland or an EEA state)."

This means that wholesale dealers can continue to supply medicines from Great Britain to Northern Ireland and apply that to authorisations for the manufacture/importation of investigational medicinal products for human use (MIA IMP holders) as well.

TIP	As with all changes, further negotiations are continuing, so please check the UK government website for the latest updates.

Q. Do we need to officially release the IMP for Phase I and Phase II? Do we need to fill the proposed data for QP release according to Annex 16?

NW: For the release of IMPs within the EU or the UK, the GMP requirements don't differ between different phases of clinical trials. Whether the batch is for Phase I, Phase II, or Phase III, the QP will still need to certify that batch for use within the EU and UK, which means compliance with all of the routine and legal duties.

Q: Do the labels of submissions done after the 31st of January 2022 need to be compliant to the new Annex in the EU and in the UK?

HB: It depends on the submission strategy of the sponsor company. If the sponsor has submitted under the regulation, then Annex 6 would apply and the expiry date would have to be on the primary pack. But from the 31st of January 2022, until the 31st of January 2023, the sponsor can submit under the old directive, under which Annex 6 would not apply.

TIP For updates on the labelling guidance, check the European Commission website.

Q. Does the material being assessed by the QP, either in the EU or UK, need to be physically located within that country or region to allow for physical inspection of the product, or can it be assessed via documentation exclusively?

HB: It is crucial to understand the importance of the material's physical location. The legislation does point toward it being physically present in the country for a legal decision to be completed. For example, in the EU, the product needs to be physically imported into the EU before a certification can be carried out. Of course, the EU QP can get ahead and gather information and review the data electronically. However, the legal certification must be completed when the product is physically present in the EU.

A different scenario emerges when the material is in the EU but will be shipped to the UK. In this instance, the UK supply chain QP oversight process can be applied, whereby, although the product is in the EU, there is a process outlined within a Quality Technical Agreement and a strategy for oversight agreed with the UK MIA and QP.

Q. If a clinical trial is being run in both the UK and EU, would QP release in the EU be accepted for distribution in the UK, or would separate QP release be needed by EU and UK facilities?

NW: If material is being packed within the EU, it could be certified by the EU QP in that location for clinical trials, both in the EU and in the UK. If the material is intended for UK clinical sites, it would be subject to the UK QP supply chain oversight process. In this instance, the clinical supplies could be imported into a UK depot with an import license or sent directly to a clinical site, where UK QP oversight would be needed. In the latter scenario, no additional QP certification in the UK would be required.

Q: How will this work for products where real-time stability is being performed and thus expiry is being updated every few months? Is over-labelling acceptable?

NW: With early phase clinical trials, there usually isn't a lot of stability data available. Expiry updating shelf-life extension is very common for those early phase trials and needs to be managed by the sponsor.

It is true to say that the new Clinical Trial Regulation adds complexity to this, due to the additional labelling requirements. I would advise being smart with your labelling strategy. Obviously, the requirements must be met, but there are innovative ideas circulating in the industry for overcoming labelling hurdles. One example is a dose pack that does not have a primary component inside, thus only requiring one expiry date on that component that is very visible. Another example is a tab that can be viewed from the outside but is also visible when the inner component is taken out. The design of the kit will dictate the labelling decisions, which will need to be submitted as part of the Clinical Trial Application.

TIP Check the European Commission website for updates on labelling requirements.

Q: What are the important points for QP release of pooled supplies for IMPs?

HB: Producing IMPs that may be used in a number of clinical projects is a good strategy for optimizing the supply chain. The pooled supplies are customized to the specific trial through late-stage customization or Just-In-Time labelling. The labelling approach must be flexible enough to support ongoing updates.

From a QP perspective, a pooled supply isn't necessarily a finished product, because it doesn't have all of the expectations detailed on that label, and therefore cannot be certified. In this scenario, QP release can be approached in a couple of ways. One way is through a technical release of the pooled supplies, which is a partial confirmation of the supplies, then following up with full certification once the expiry date or protocol number has been applied to the label. Another option is to certify everything at the end, once the supplies have been fully labelled and are ready for release for that protocol.

It very much depends on the numbers of products that are going into your clinical trial, the QP support that you have, and how cost- and time-effective it is to certify supplies in large batches versus lots of smaller batches.

Q: Any commercial drug product having a manufacturing step done in the UK will need a full EU QP release for EU release. What about release testing?

NW: Previously we were talking about IMP specifically, so where any of the manufacturing steps are done in the UK, the requirement for the EU QP would be to include that site on the EU QP declaration.

HB: It is important to note that importation and testing requirements differ between IMPs and commercial products. If there's a UK manufacturing step on a product, and it is then going to be exported or imported into the EU and finished, it would need full testing and QP certification if it is a commercial product. Fundamentally, there's more flexibility with IMP versus commercial, which would have to be tested within the EU EEA before certification.

Q: Will the QP now certify against the Regulation exclusively, or is it acceptable to differentiate and release under the Directive for those still operating under the older Directive?

HB: The Regulation is now in place. However, everything depends on the submission strategy. If the submission was approved under the Directive, QPs are certifying under the Directive. If the submission was made under the Regulation, QPs are certifying under the regulation. Whatever the scenario, the QP needs to be fully aware of whether the submission was made under the Directive or the Regulation.

Q: What training needs are arising from these changes, if any?

NW: Certainly, for any QP, there is a requirement to keep up to date with changes in legislation and there are continual professional development requirements. In terms of how this impacts individual sites and locations, it is important that they are compliant with current GMP and any new legislation. An assessment should be conducted prior to any new legislation implementation to identify gaps and outline how they should be addressed and what the changes would be for the site's quality management system. Training following the gap assessment should be conducted to ensure compliance with the new legislation.

Q: Does the Clinical Trial Regulation 536/ 2014 apply to the UK? It was adopted initially waiting for the software to be available and up and running?

HB: Clinical Trial Regulation 5362014 does not apply in the UK. Rather, the UK statutory instruments (The Medicines for Human Use [Clinical Trials] Regulations 2004) apply. Effectively, we are certifying currently under the old statutory instruments for clinical trials in the UK. This is the legislation for which the MHRA is seeking industry and public input.

Q: Regarding GDP and IMP, is that transport of active substances and products expected to be temperature controlled or is temperature monitoring adequate? Is this something a QP may review as part of the certification process?

NW: This was introduced in latest update to Annex 15. There is certainly an increased expectation that there would be monitoring of active substances during transportation. This is reviewed by the QP to ensure that when transported from one location to another, products are maintained at the correct temperature. Certainly, for finished product, compliance during transportation with any labelled storage conditions is required.

Q: Under what circumstances are QP audits needed to support certification for the testing of drug product by contract labs that are qualified by the drug product manufacturer?

HB: If the testing facility is completing GMP release testing of the drug product and is therefore going to be named on the QP declaration, audit evidence will likely be required, whether that is the QP going out physically auditing or leveraging other available audit information. If that particular testing facility has a pharmacopeial test, it might be quite easy to establish its compliance. All of these considerations would impact whether a QP audit or other audit information might be applicable.

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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 across clinical services sites at Thermo Fisher Scientific. 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.

Naomi Wilmer BSc (Hons) PGDip CBiol MSB

QA Manager & Qualified Person, Thermo Fisher Scientific

Naomi currently holds the position of QA Manager & QP supervising the client liaison and auditing functions at the Thermo Fisher Scientific clinical services site at Horsham, UK. She has in-depth experience of clinical packaging and distribution of Investigational Medicinal Products (IMPs). Naomi qualified as a Qualified Person (QP) in September 2019 and has been supporting the site in various roles, including clinical project management for over 13 years. Naomi holds a Batchelors degree in Medical Biochemistry and a post graduate diploma in pharmaceutical studies. She is a full charted member of the Royal Society of Biology.

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