quality brief

Quality Highlights Bulletin – Issue 1 March 2019

Pharma Quality Partners
Quality Excellence Through Partnership

No Deal Brexit

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Brexit! Is there going to be a "No Deal" situation for the UK? Will the UK become a true third country? The 29th of March looms ominously in the not too distant future. Uncertainty grips the nation and the pharmaceutical industry like many other industries is watching nervously as to what the final outcome may be. The MHRA has been publishing guidance as to what the regulatory landscape may look like in the UK in the event of a "No Deal" scenario. Here we look at the predicted future state for importation of medicines, importation of IMPs and export of APIs.

No Deal Brexit

When we turn on our TV news channels or pick up our favourite newspaper these days there is one story that dominates. Brexit! Whichever side of the debate you are on, you cannot help but notice that industry is calling for certainty in these uncertain times. For well over a year at Pharma Quality Partners Ltd we are seeing more and more of our clients and indeed many of their customers setting in place contingencies for a so called "No Deal" Brexit scenario.

"...within 6 months of exit day...must notify MHRA...intend to continue import..."

As the UK's competent authority, the MHRA have not missed the need to make ready for all possibilities. If you are a regular visitor to their webpage or keep up to date with developments on their blog, then you will already be aware that much guidance has been published in this regard. This article is not intended to discuss in depth the full scope of that guidance but will look briefly at some key points by way of an overview.

Importing Medicines...

The MHRA published guidance on importing medicines from countries within the EEA on the 11th March 2019. It sets out a number of provisions that the UK intends to invoke to assure the continued supply of medicines and to facilitate a smooth transition to the post Brexit regulatory framework that will come to exist in the UK should "No Deal" become reality.

Firstly, the UK's exit from the EU in the case of any form of Brexit will see the Human Medicines Regulations 2012 amended. Under national requirements any entity undertaking importation and wholesaler activities must hold a Wholesale Dealers Authorisation (WDA). Will that change? Simply put no, entities that currently have a WDA will retain their authorisation after the UK's departure from the EU. Importation of medicinal products will still be permitted if the source country is on a list of countries the MHRA will define. Initially it is intended that this will be all countries within the EEA (the remaining 27 members states of the EU along with Liechtenstein, Iceland and Norway).

Within six months of exit day a WDA holder must have notified the MHRA that they intend to continue importation from a listed country. Within two years of exit day an RPi (Responsible Person (Import)) must be named on the relevant WDA. The RPi is a new entity that the MHRA has defined but the role of this individual will not be discussed in this edition of Quality Brief.

So, what if your organisation does not hold a WDA prior to exit day? In this case you will need to apply for a WDA

to carry out import and wholesale dealing activities. For such new applications an RPi must be named on the WDA immediately.

Medicines already authorised within the UK may be imported from listed countries provided the WDA under which they are imported includes importation as a licensed activity. This will also apply to any "specials" being imported.

Medicines that are not already authorised in a listed country may still be imported provided the WDA allows this activity. In this event an RPi will not be required, but an RP will be.

Medicines imported for export purposes will require a WDA allowing both import and export activities. The medicines status in the listed country (authorised or not authorised) will dictate the need for an RPi versus RP respectively.

Medicines destined for the UK parallel import market will require a WDA for import and an authorisation in the source listed country.

Importing IMP's...

The MHRA indicates that in the event of a "No Deal" Brexit the requirements relating to importation of IMP's from third countries outside of the EEA will not change.

That said some changes will occur for IMP's imported from a listed country (the same list of countries as for commercial medicines will apply to IMP's). A clinical trial sponsor will need to have an MIA (IMP) holder in the UK verify that the imported IMP has been QP certified in the source listed country. An assurance system must be overseen by a UK QP, but the IMP will not need to be re-certified by the UK QP. The UK QP may delegate their duties under an appropriate assurance system. The MHRA is indicating a one-year transition period will come into effect enabling clinical trial sponsors to transition to a state of compliance with these requirements.

IMP's coming from another country typically arrive in the UK either:

1) Direct to the trial site
2) Via a UK based distribution centre

"...must be overseen by a UK QP ..."

Irrespective of the mechanism of arrival the MHRA will expect:

- IMP is not released for use in the clinical trial until such time as the verification of QP certification has occurred
- IMP is not shipped to any clinical trial site that is not listed in the UK clinical trial application and ethics application
- The Sponsor makes available up to date trial information and Product Specification File (PSF) to the UK QP
- The MHRA has approved the clinical trial before the IMP is released to the Investigator

Agreements between relevant parties should be put in place. These may be necessary between:

- Trial Sponsor and UK MIA (IMP) holder
- Trial Sponsor and source listed country MIA (IMP) holder
- UK MIA (IMP) holder and UK distribution centre
- Trial Sponsor and UK distribution centre

The UK QP must have access to relevant information and documents to fulfil their role. Such documents may include:

- Details of the supply chain
- UK Clinical Trial Application
- Evidence that the certifying site in the listed country is appropriately licensed and holds a current GMP certificate for the IMP dosage form and operational activities undertaken
- Details of the approved UK trial sites as per the ethics application
- Details of each shipment of IMP to the UK
- Details of any excursions from the stated storage conditions during shipment
- Details of the responsibilities described in any written agreement

So, what can be considered as evidence that QP certification of the IMP in the listed country has taken place?

- A batch certificate confirming QP certification as per 2001/20/EC
- A statement of certification confirming QP certification as per 2001/20/EC
- Data from an Enterprise Resource Planning (ERP) system that confirms batch certification has occurred
- Any other form of evidence that can be justified as fit for purpose

It will be permitted for IMP's to be imported to a distribution centre in the UK prior to the UK QP verifying their QP certification in the source listed country. In such cases controls must be in place to assure the IMP is not released to clinical trial sites before all requirements to do so have been met.

Exporting API's...

The Falsified Medicines Directive enacted new requirements with respect to API's entering the EU. These have been in place for some time and are nothing new to the industry at this stage. A number of countries from which API's are imported into the EU qualify for exemption from the requirement to be accompanied by a Written Confirmation. These countries appear on the EU's White List which (at time of publication) includes USA, Japan, Brazil, Australia, Israel and Switzerland. The MHRA intends to continue to accept Written Confirmations from these countries and EEA member states where a "No Deal" Brexit occurs.

But what if you are an exporter of API's. what does "No Deal" Brexit mean for your operations? Well the UK would be considered a third country and will not be a White List country, at least initially. So, shipments of API's moving from the UK to the EU will need to be accompanied by a Written Confirmation. The MHRA are keen to highlight however that this is anticipated to be a temporary measure as the UK intends to apply to be added to the EU's White List in time.

Will API exporters have to request these confirmations each time they need them? Breathe a sigh of relief. The MHRA has pre-empted this and is using information about API exporters held within the agency's information systems to generate online Written Confirmations for each exporter. The

exporter can download their own document as and when required. Online Written Confirmations will be valid for three years from the date of last inspection. There are two exceptions:

- Written confirmations will not be published online for API's with confidential GMP Certificates. Such entities will be sent their Written Confirmation by the agency
- API Distributors exporting API's they have not manufactured will have to obtain a Written Confirmation from the manufacturer or the relevant authority

In Summary...

Where do importers and exporters stand? Well in truth very much in a state of continuing uncertainty. By the end of March, it will hopefully at last be clear where the UK finds itself and what relationship it is to have with our nearest neighbours. But your organisation cannot afford to be unable to function. Preparation for all possibilities is the only sensible option albeit the costs may never provide a satisfactory return on investment. We still watch nervously…

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