pci CLINICAL TRIAL SERVICES

IN ASSOCIATION WITH MARKEN a UPS Company

Water Cooler Chat

EU Compassionate Use Programs - Where's My Drug?

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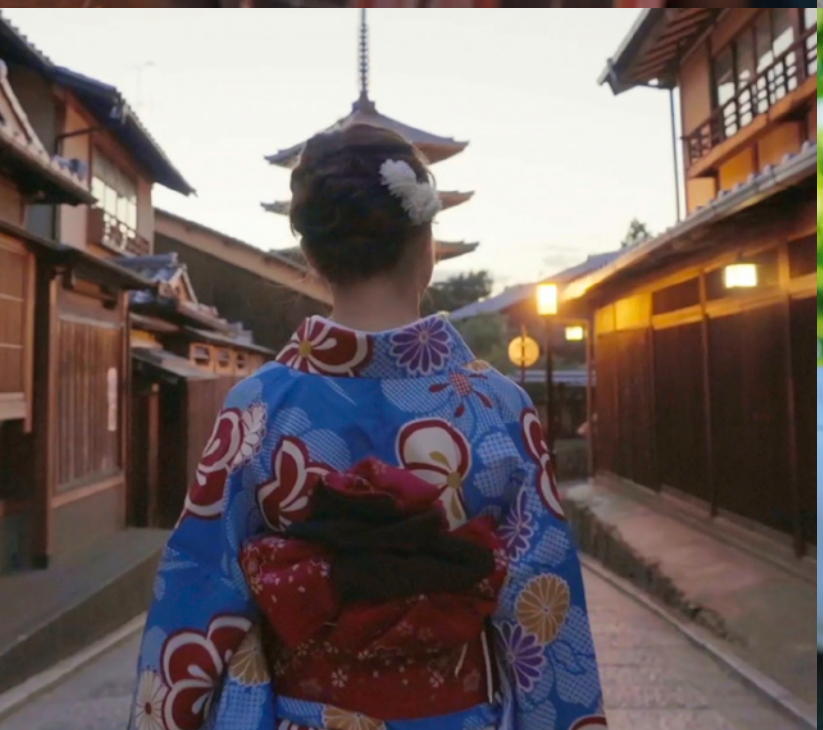

PCI Clinical Trial Services hosts a weekly virtual *Water Cooler Chat* series, where our subject matter experts host informal discussions around a number of clinical supply hot topics.

Distributing Clinical Supply in the EU for Compassionate Use Programs

In our previous Water Cooler Chat article, we introduced EU Compassionate Use clinical programs, and in this article, our experts – Gavin Morgan, Senior Manager of Global Logistics, Uday Pathapati, Senior Manager of Clinical Project Management and Tiago Mateus, Project Manager from Marken – describe the logistical and distribution risk management factors that need to be considered when planning an EU Compassionate Use Program.

By its nature, EU compassionate use supply is needed urgently. This means packaging, labeling, and distribution must be executed rapidly and efficiently. Trial sponsors must know what issues to manage and need to select the transportation routes carefully, especially during COVID-19.

Distributing compassionate use material within Europe has not been historically challenging, but the COVID-19 pandemic has created logistical obstacles including a decrease in transportation options and closed borders.

DISTRIBUTION SET-UP

What needs to be in place for an EU compassionate program distribution process?
There are four key items that are needed prior to initiating an EU compassionate use shipment request. Bringing these to your clinical trial service provider's attention early allows them to set up all the required activities and documentation ahead of time in preparation for the shipment request.

Four Key Pieces of Information to Initiate a Shipment Request for an EU Compassionate Program

1. **The number of sites and which EU countries are involved.**
   During COVID-19, transit times to certain countries may be longer than expected due to commercial flights occurring less frequently or shipping route requirements changing. Each country has varied transit routes with different conveyance times, as such your courier will identify the best route for your needs. Knowing which countries and how many sites up front will help you identify when drugs need to be shipped to be received by the sites on time.

2. **The temperature range for the product.** Understanding the temperature ranges for your product's stability will allow your clinical trial services provider to transport your shipment using the most cost-effective and efficient shipping system.

3. **The correct shipment addresses and operating times** – Avoid shipment delays by ensuring you have provided the correct addresses and receiving hours of the sites, hospitals, or hospital pharmacy departments. At the time of delivery, make sure the named consignee is present, and if not – it is good to have an alternate name such as another pharmacist or investigator. This additional information could be the difference between an on-time and a delayed delivery.

4 **The list of documents needed to accompany the shipment**. Each country requires different documents. For example, in Scandinavian and UK countries, even though there are no QP requirements for compassionate use programs, they do request a QP release statement for the received lot. This may be in the form of a certificate of analysis (C of A), QP release, or GMP release. The C of A is the one key document that the receiving hospitals request consistently in the EU.

SHIPMENT PROCESSING & DISPATCHING

EU Compassionate Use programs usually involve tight timelines. From a logistics point of view, what do sponsors need to be aware of?

Compassionate use supply is typically needed urgently. The material is packaged, labeled, released, and imported under a Manufacturer's Specials License and redistributed under short timelines. Timelines can be expedited by having shipment sizes and temperatures ready prior to shipping, allowing the material to be placed into a temperature-controlled shipping system ready for dispatch.

BE AWARE

Compassionate use supply is typically needed urgently. The material is packaged, labeled, released, and imported under a Manufacturer's Specials License and redistributed under short timelines.

Goods that have either been produced within the European Union (EU), or imported into an EU country with any applicable duties and taxes paid at that time are then considered to be in "free circulation" within the EU. With this in mind any movement of compassionate use material between EU countries can be completed with minimal or zero customs requirements. For example, shipping from the UK to Germany or Sweden presents no logistical or import challenges with delivery and can often be completed within 24-48 hours from time of dispatch.

If a consignee is identified as being located outside of the EU, for example Switzerland or Norway, a customs invoice detailing the Importer of Record and Incoterms will also be a requirement. Although the shipper will be responsible for providing this document, a draft invoice – detailing all required information – should be reviewed and approved by all relevant parties prior to the shipment initiation to ensure there are no delays with obtaining the approval to ship or issues at the time of customs clearance.

What type of site contact information is required for a smooth delivery?

To avoid delays, it is important to have as much site contact information as possible – there is never too much information in these situations because the specialist couriers will typically be delivering to a named consignee, and you need to ensure that consignee (or a consignee back up) is going to be available on the day of delivery.

The suggested site contact information to ensure a smooth delivery is:

- Consignee name (Pharmacist name or Investigator's name)
- Back up consignee name
- Phone numbers
- Opening hours (including delivery hours in case there are specific days and times they accept deliveries)

SPECIALIST COURIER INTERACTION

Which EU countries have strict regulations in place for compassionate use material?

Italy requires companies with compassionate use material to follow either the 2017 or the 1997 directive (see below for details about both directives). Generally, within the EU, you will be given an umbrella approval for a specific timeframe, for example 6 months, or you will be given an approval for a specific number of shipments as per your request. This approval can be easy to obtain within most countries, including Italy, but Italy does require different steps to be taken in order to ship compassionate use supply.

Compassionate vs non-compassionate classifications in Italy

In the EU, Italy's management of compassionate use supplies has additional complexities.

Compassionate medication in Italy is considered to be a pharmaceutical product not yet registered in the National Sanitary Service by the Sanitary Authority. This requires Nulla Osta release.

Experimental pharmaceutical products are not subject to Nulla Osta release if the protocol pertaining to this pharmaceutical product is registered in the National Sanitary Service database and approved by Sanitary Authority (AIFA).

Ministerial Decree 2017 directive vs. 1997 directive

These directives are slightly different and typically the ethic committee of the clinic will know which directive they will need to follow, but if there is any doubt, check with the destination country's Ministry of Health for confirmation.

ITALIAN EXCLUSION

Experimental pharmaceutical products are not subject to Nulla Osta release if the protocol pertaining to this pharmaceutical product is registered in the National Sanitary Service database and approved by Sanitary Authority (AIFA).

THE 2017 DIRECTIVE requires hospital or clinical ethics committee approval. Once the approval is received, it is then sent along with the airway bill, the master airway bill of the shipment and the invoice showing a $0 value along with a statement on the invoice indicating "for compassionate use only". This package of documents is sent to the Uffici di sanità marittima, aerea e di frontiera (USMAF), which is a governmental body belonging to the ministry of health, who would then give the approval to release the shipment once it has reached the country.

THE 1997 DIRECTIVE requires a copy of the Ministry of Health correspondence and their approval. This approval can typically come in the form of an email stating "I grant the permission for that particular medication to come into the country", but recently the Ministry of Health have been issuing statements in a stamped A44 form. With the 1997 directive, the commercial invoice is required to have a monetary value of the product and is sent along with the airway bill and the master airway bill. The Ethics Committee approval is not required.

COVID-19 SOLUTIONS & CONSIDERATIONS

COVID-19 has decreased the frequency of transit routes available, which can lead to drug supply concerns. If there is enough supply and no concerns about overloading a particular pharmacy, try shipping your material in various ways. For example, ship the same material, in the same quantities, at the same time utilizing 3 different routes – such as using 3 different couriers or 3 different transit lanes.

This will avoid challenges and delays in the case that the airline is cancelled or there are border delays/closures.

What are some work-arounds in the case a connecting flight is canceled due to COVID-19?
A delayed connecting flight can prove costly. If the shipment is stalled, the courier will issue a master airway bill correction and recover the material. If there is another airline in which they have a flight contract with, the material will be scheduled for that flight. In the EU, driving the material to its destination is also an option.

Is compassionate use material given more leniency at border crossings compared to a standard consumer goods shipment?
Yes, because compassionate use and clinical trial materials are considered part of a critical business. A standard compassionate use shipment's documents will emphasize the importance of this medication reaching its destination.

Many countries initially locked down due to COVID-19. If countries lock down again, how can a sponsor company deliver compassionate use material to that country?

In the case of a lockdown, some specialist couriers will reach out to local authorities and request a permit to transport compassionate use or clinical trial material into the country. This will help grant access to your compassionate use shipments.

*If you are interested in learning about PCI's **Water Cooler Chat** series where our experts answer questions in real-time, please visit us **here** to see the schedule and register for this complimentary series.*

ABOUT OUR EXPERTS AT PCI CLINICAL TRIAL SERVICES & SPECIAL GUEST FROM MARKEN

Gavin Morgan
Senior Manager, Global Logistics - Clinical Services, PCI Pharma Services
Since 2009, Gavin has been leading the clinical distribution team at PCI's Bridgend facility. His main responsibilities include the overseeing of all activities associated with UK imports along with supporting the full supply chain of clinical trial supplies including the selection and management of 3rd party couriers and depots. Gavin has over 20 years of experience within the clinical trial industry, with a focus on the distribution of clinical materials globally.

Uday Pathapati
Senior Manager, Clinical Project Management - Clinical Services, PCI Pharma Services
Uday currently leads one of the Clinical Project Management teams at PCI Bridgend, responsible for training and mentoring Project Managers and Associate project managers to ensure they are providing the industry leading customer experience. Since joining PCI in 2011 Uday has worked for 9 years on clinical projects from early Phase I to Phase III with a key focus on management of Compassionate Use (CU), Named Patient Supply (NPP) and Early Access Programs (EAP) in the EU.

Tiago Matheus
Project Manager, Marken
Tiago started as a project manager in January 2018 at Marken UK based in the Feltham office, responsible for an extensive list of UK and US customers, primarily focusing on implementing new projects from general clinical trials to cell and gene projects as well as direct to and from patient projects. Tiago is also responsible for supporting clients on technical requirements and following up on projects to ensure completion in compliance with the original setup. Tiago has over 11 years of experience in the logistics industry primarily focused in pharmaceutical and biological distribution to patients and clinics across the globe.

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