QP Essentials: Your EU Gateway to Clinical and Commercial Distribution of Cell-Based Therapeutics

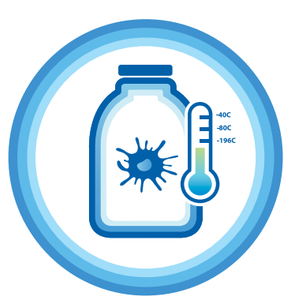
By Colin Grant, Quality and Regulatory Manager, Fisher BioServices

Fisher BioServices

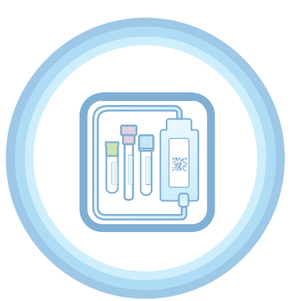
this "eBook"

Biobanking &
Biorepository

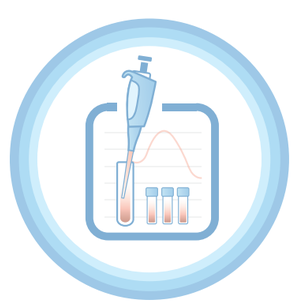
**Cell Therapy
Solutions**

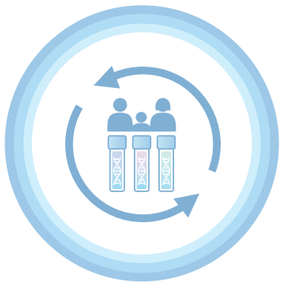


Clinical Trial
Kit Production

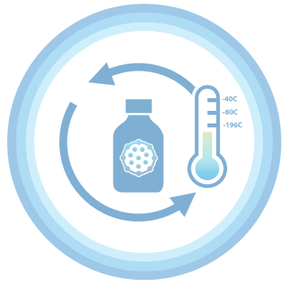


Laboratory
Processing





Clinical Trial
Sample Management



Biologic-API
Management

Qualification /
Validation Services

Cold-Chain
Logistics

Share this ebook!

About the Author

Colin Grant is the Regulatory and Quality Manager for Fisher BioServices UK, and has more than 17 years of experience in a Quality role, including overseeing QP release of Small Molecule, Herbal, and Advanced Therapeutic Medicinal Products (ATMPs). Currently, his role also includes serving as a Human Tissue Authority Designated Individual, Responsible Person (RP) for the Human Fertilization and Embryology Authority, and the RP for the Medicines and Health-care product Regulatory Agency. Colin manages a number of QPs within his role in Fisher BioServices UK.

5 Key Insights

Overview

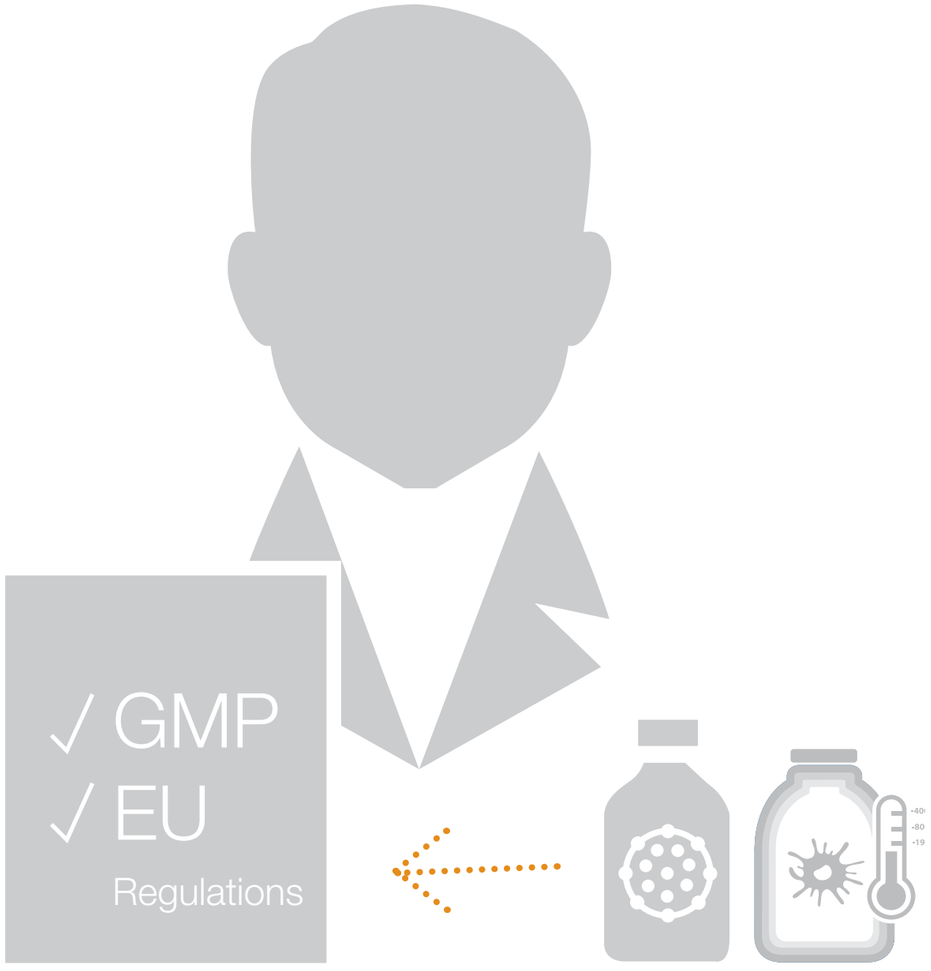
1. The Qualified Person's Responsibilities and Licensable Activities
2. What a QP Does
3. The Documentation Required by a QP
4. What You Should Know About Working with a QP
5. Lost in Translation

1

The Qualified Person's Responsibilities and Licensable Activities

The Qualified Person's Responsibilities and Licensable Activities

A Qualified Person (QP) is an individual who is responsible for ensuring that drug products that are manufactured in or Imported into the European Union (EU) were manufactured and handled according to GMP and EU regulations. The concept of the Qualified Person was first established in 1975 and is a unique regulatory requirement that currently applies only within the European Union, but is being extended into other countries, such as Israel, in 2013.



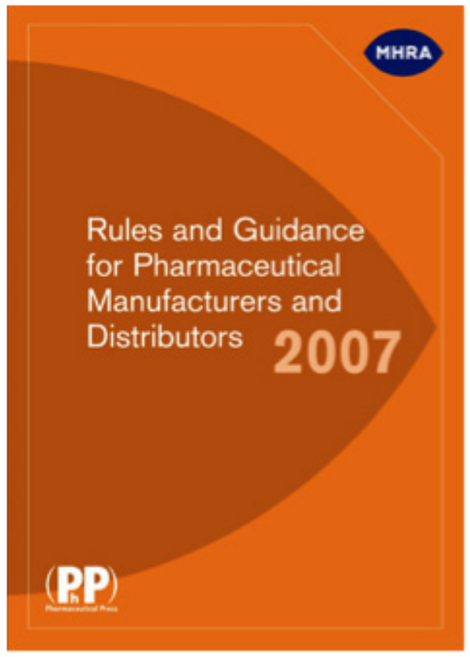
The Qualified Person's Responsibilities and Licensable Activities

Specifically, a QP must release, or certify that each batch of product, whether investigational medicinal product (IMP) or commercially approved drug for human use, was produced according to EU Directives. The critical Directives concerning QP release include 2003/94/EC, which specified that all medicinal products for human use that are manufactured or imported into the EU must be manufactured in accordance with cGMP; 2001/20/EC, which extended QP oversight to materials for use in clinical trials; and 2001/83/EC, which dealt with disparities between national provisions in the internal market of the European Union. Advanced Therapeutic Medicinal Products (ATMPS) are covered under EU Regulation 1394/2007 and Veterinary Medicinal Products are addressed in Directive 2001/82/EC. It should be noted that these Directives are expected to be updated shortly.

The Qualified Person's Responsibilities and Licensable Activities

Companies importing IMP must be licensed by the country of import, and all companies holding a license to manufacture or import medicines in the EU must have a QP named on their license. The identified QP, although employed by (or contracted to) the company holding the license, in effect serves as the eyes and ears of the Regulatory Body. As a company that provides biorepository storage, labeling, secondary packaging, and distribution services for IMP and clinical agents, Fisher BioServices holds a license for the UK. I am the Responsible Person (RP) for the MHRA license at our Bishops' Stortford site, allowing us to release ATMPs into Europe. All Fisher BioServices QPs report to the MHRA as well as to me.

The Qualified Person's Responsibilities and Licensable Activities



The Orange Guide is the ultimate reference regarding the manufacture and distribution of medicines in the EU. QP oversight was extended to material used in clinical trials by the Clinical Trials Directive (Officially Directive 2001/20/EC of 4 April 2001), and EC Regulation 1394/2007 called for QP release of cell-based therapies (Advanced Therapeutic Products).

A QP is typically a licensed pharmacist, biologist, chemist, or person with other appropriate academic qualifications who has several years of experience working in pharmaceutical manufacturing operations, and who has passed the required examinations. The QP responsibilities are spelled out in the Rules and Guidance for Pharmaceutical Manufacturers and Distributors, published by the UK Medicines and Healthcare Products Regulatory Agency, also known as the "Orange Guide." In addition, QP's have a Code of Practice which was updated in February 2013.

Companies planning to conduct clinical trials in the EU must have a QP Declaration stating that the QP is satisfied that the manufacturing and storing sites are compliant with GMP, from an EU perspective, as part of their Clinical Trial Application.

The QP is on the front line, protecting the patient by ensuring that Medicinal Products are safe and fit for their intended use. The QP's legal responsibility focuses primarily on the safety of a product, i.e., whether it was manufactured according to GMP and meets all applicable regulations. However, QPs also consider the larger picture of patient safety, including quality and efficacy issues, in fulfilling their obligations.

The Qualified Person's Responsibilities and Licensable Activities

Table 1: Complexity of the Manufacturing Process Involved with Biopharmaceuticals & Small Molecule Drugs

Complexity (Metrics/Lot)	Small Molecule Drugs	Biopharmaceuticals
Numbers of Batch Records	<10	>250
Product Quality Test	<100	>2000
Critical Process Steps	<100	>5000
Process Data Entries	<4000	>60000

Source: Sharma B. Immunogenicity of therapeutic proteins. Part 3: Impact of manufacturing changes. Biotechnol Adv 2007; 25(3): 325-31, Kuhlmann M. Covic A. The protein science of biosimilars. Nephrol Dial Transplant 2006:21 Suppl 5:v4-8

This is especially important where biopharmaceuticals and cell therapeutics are concerned, as biological manufacturing processes are far more complex compared to that of the small molecules (table 1). Protein based biologics often involve multiple highly technical steps between cloning the target gene and the end product, and biological preparations can vary significantly; for instance, glycosylation, which significantly influences the isoform of manufactured erythropoietins, is highly sensitive to cell growth conditions. Even autologous therapies, where the batch size is minimal and immune response to foreign proteins is not a primary concern, require intensely controlled manufacturing and temperature conditions for therapeutic efficacy. You can read more about these challenges from my colleague Dan O'Donnell's eBook *"Commercially Successful Cell Therapies : Navigating the Ultra Cold Chain Minefield".*

2

What a QP Does

What a QP Does

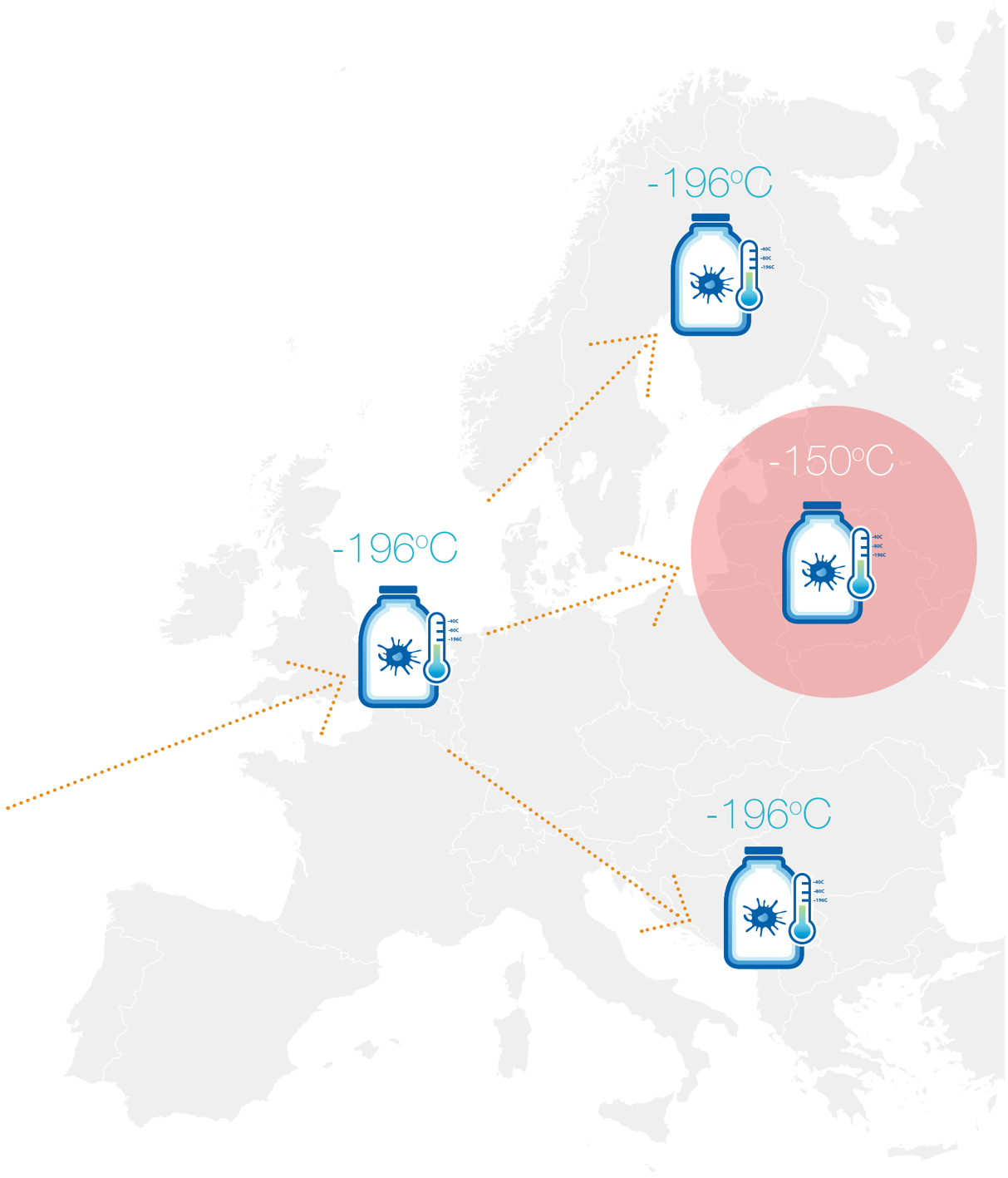
The QP must ensure that all documentation is correct and GMP compliant, that the product is manufactured according to the IMP Dossier, and is within product specifications. Manufacturers must provide all the documentation needed to allow the QP to make an informed decision (see the list on page 15). The QP will need access to all parts of the supply chain critical to the product, and may perform an audit of the sites of storage and manufacture.

As the eyes and ears of the MHRA, the QP must ensure that each batch is manufactured in compliance with GMP and EU regulations, including verifying that all the principle manufacturing and testing processes were validated, verifying that the production and quality control documentation was completed and signed by authorised staff, and that the sites involved in manufacturing and storage are EU GMP compliant, which is typically done through a QP audit. In addition, the manufacturer must report to the QP all deviations and out-of-specification events in the manufacturing process and supply chain that can affect the batch. The QP will then verify that the necessary checks and tests were performed and the batch can be certified.

What a QP Does

A number of factors may result in batch certification failure, particularly for ATMPs. Two main reasons are the sterility of the product at point of manufacture, and temperature excursions without suitable stability data. Without stability data, the QP cannot make a conclusive decision on the suitability of the product with regard to temperature variations.

Temperature control is the primary issue with cell based therapies. Manufacturers must ensure that the product was maintained within correct temperature specifications throughout the manufacturing and distribution process, and this compliance must be verifiable by the QP.



3

The Documentation Required by a QP

The Documentation Required by a QP

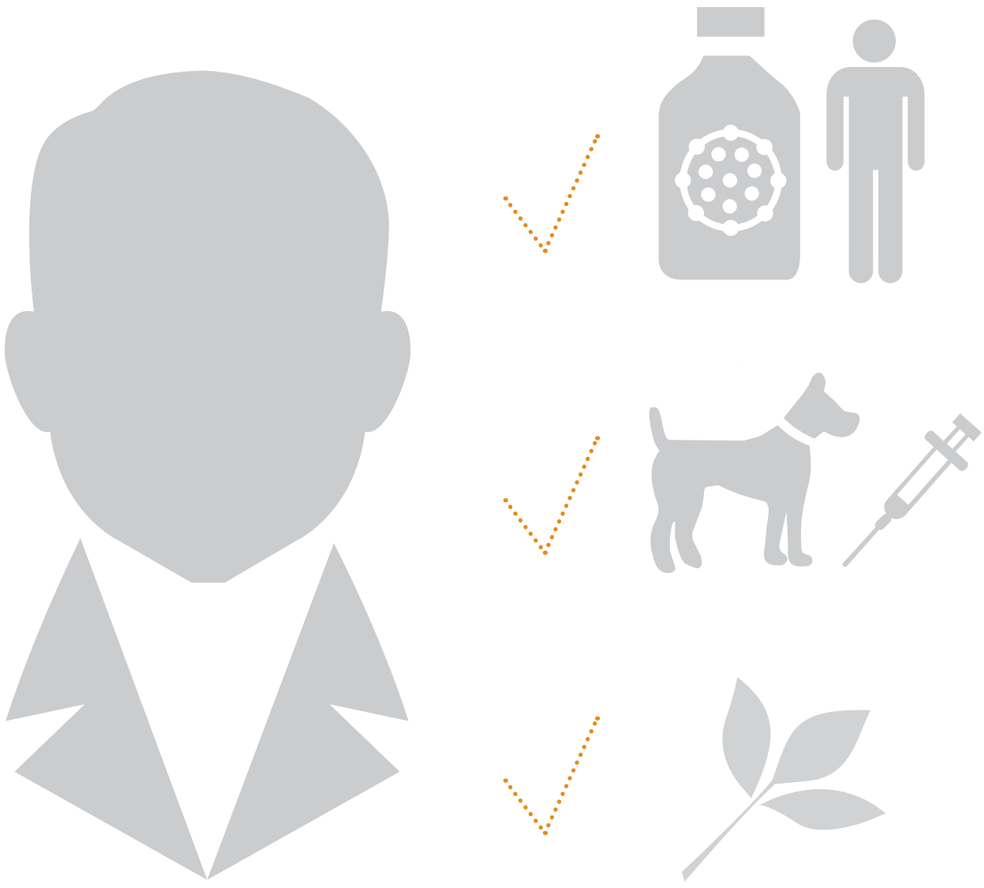
The documentation required by a QP includes but is not limited to:

- The country-specific acceptance letter with no remarks
- The Clinical Trial Application (CTA)
- Copy of the Final Letter from the Research Ethics Committee
- Final Study Protocol (Investigation Medicinal Product Dossier) and Protocol Amendments
- Investigator Brochure
- Import QP release declaration
- Service Level/ Technical Agreements
- IMPD - Product Specification File
- Stability Profiles
- Material Safety Data Sheet
- Manufacturer's GMP compliance letters
- Manufacturer's TSE (Transmissible Spongiform Encephalopathies) Compliance
- C of A / QP Release certificate
- Manufacturing Worksheet
- QC testing worksheet

4

What You Should Know About Working With a QP

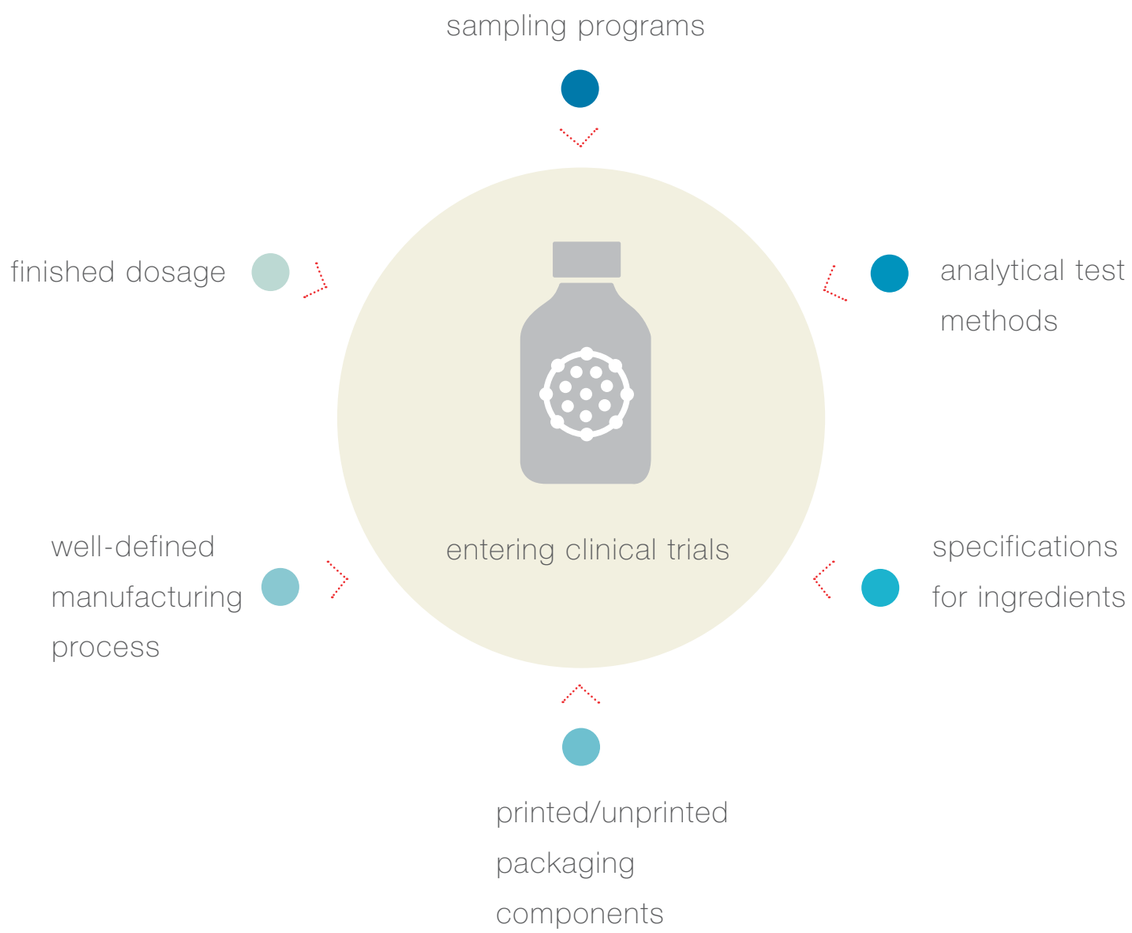
What You Should Know About Working With a QP



1. QPs are eligible to certify only the materials for which they are qualified, which are divided into human medicine, veterinary medicine, and traditional herbal medicine products. According to the Code of Practice, QPs “have a professional duty to decline to act as Qualified Persons in the release of product types for which they do not possess the relevant experience and knowledge.”

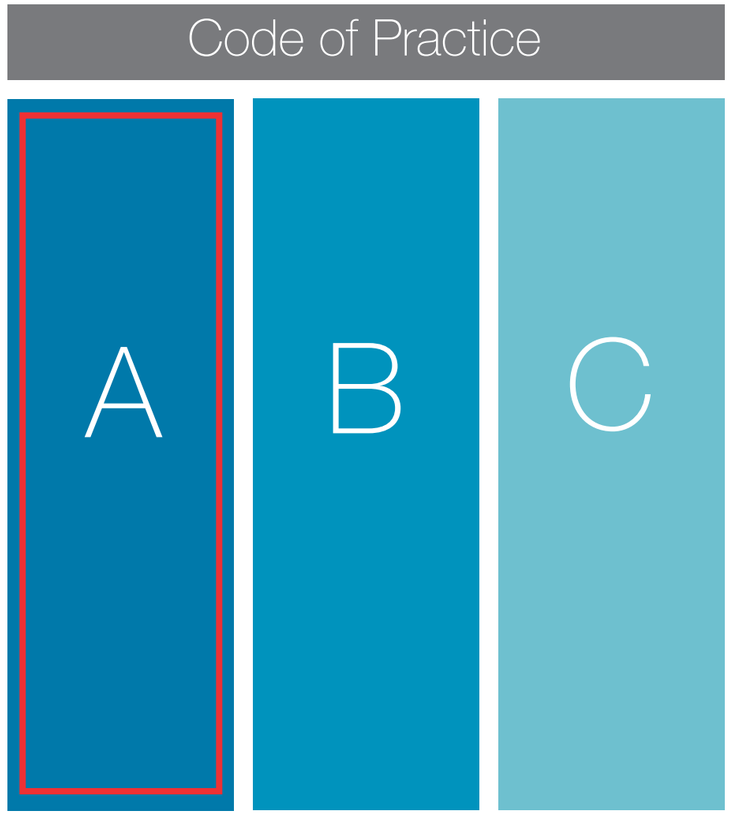
What You Should Know About Working With a QP

2. QPs apply the same quality criteria to the manufacture of medicinal products for use in clinical trials to as to batches of commercially approved products. For products entering clinical trials, the QP will also consider original product design, development, and formulation. This includes the establishment of sampling programs, and analytical test methods, appropriate specifications for ingredients, printed and unprinted packaging components, and finished dosage forms, as well as well-defined manufacturing processes.



What You Should Know About Working With a QP

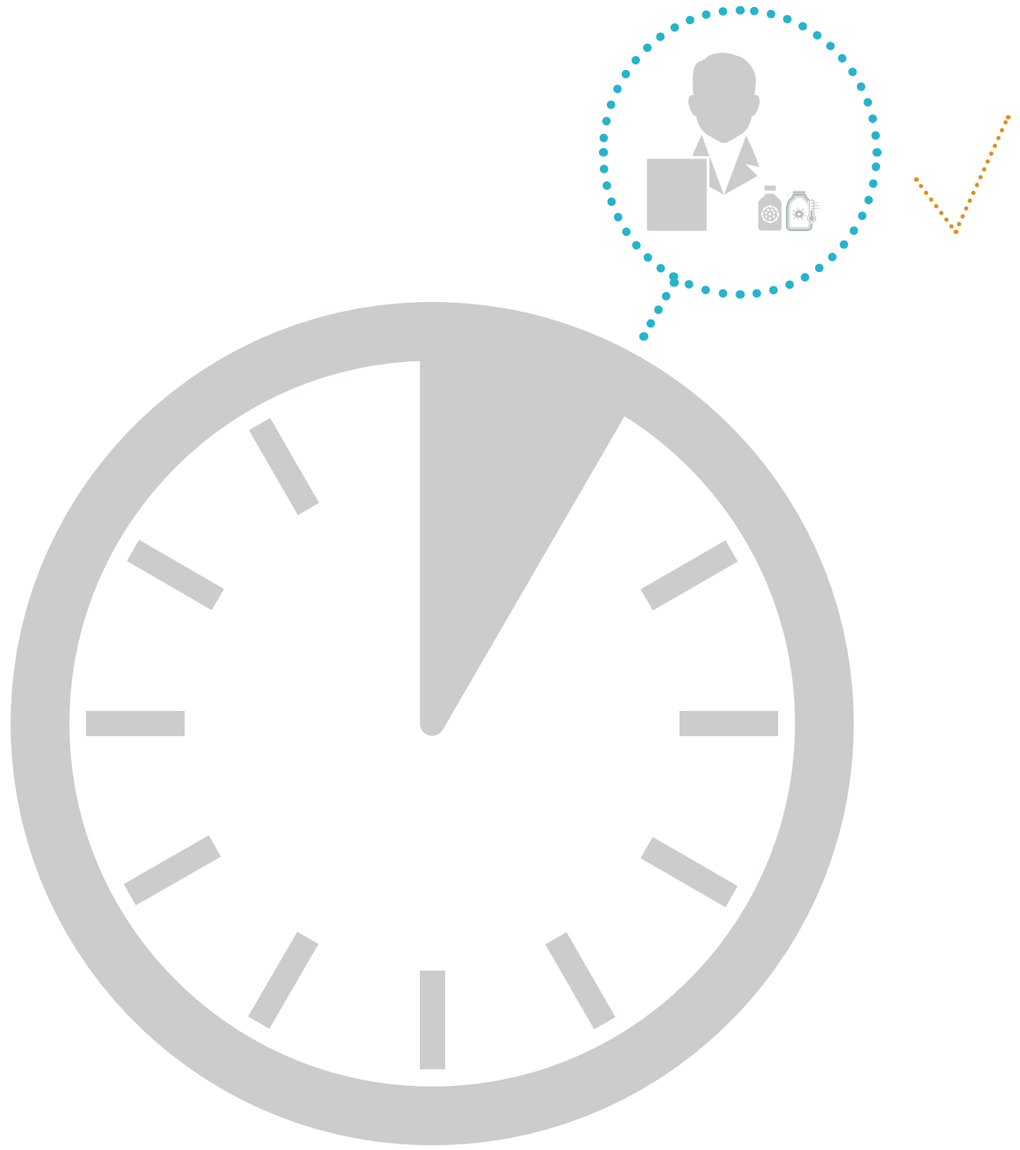
3. Some QPs have QP status as a permanent provision (Category A), while others are under the transitional provision (Categories B, C, D, and E). The eligibility requirements and tenure of the QP certification vary between the different categories. However, the Code of Practice applies equally to QPs certified under the transitional and under the permanent provisions.



What You Should Know About Working With a QP

4. According to the Code of Practice, QPs are required to keep their knowledge and experience up to date, including staying current with changes in quality management in the pharmaceutical industry, changes in regulations and GMP guidelines, innovations in product manufacturing and control technology, and general work practices. QPs must maintain records of Continuing Professional Development as part of their continued performance of professional duties.

What You Should Know About Working With a QP



5. The QP is responsible for patient safety, and by performing his or her job, also helps ensure the commercial success of the therapy. Companies developing new therapies and considering conducting clinical trials in the EU are advised to get the QP involved early in the planning stage, particularly companies developing cell-based therapies. Because the manufacturing of biopharmaceuticals is highly complex and to produce a single batch can require many months, and even minor variations in one of the manufacturing stages can lead to clinically relevant changes in the end product, the involvement of a QP from the very beginning of commercial production is critical. This will prevent your product from failing certification due to poor manufacturing practice.

5

Lost in Translation

Lost in Translation

Here are some important terminologies you may find helpful in planning and developing your product for clinical trial in the EU.

USA

- IND
- IND Summaries
- IND Number
- FDA
- IRBs
- Country
- Federal Regulations

EUROPE

- CTA
- IMPD
- EudraCT Number
- Competent Authority
- Ethics Commity
- Member State
- EU Directives National Legislation

Additional Resources

As a worldwide provider of ultra cold chain management and distribution of cell-based therapies and biologics, Fisher BioServices can assist companies looking to import therapeutic products and conduct clinical trials in the EU.

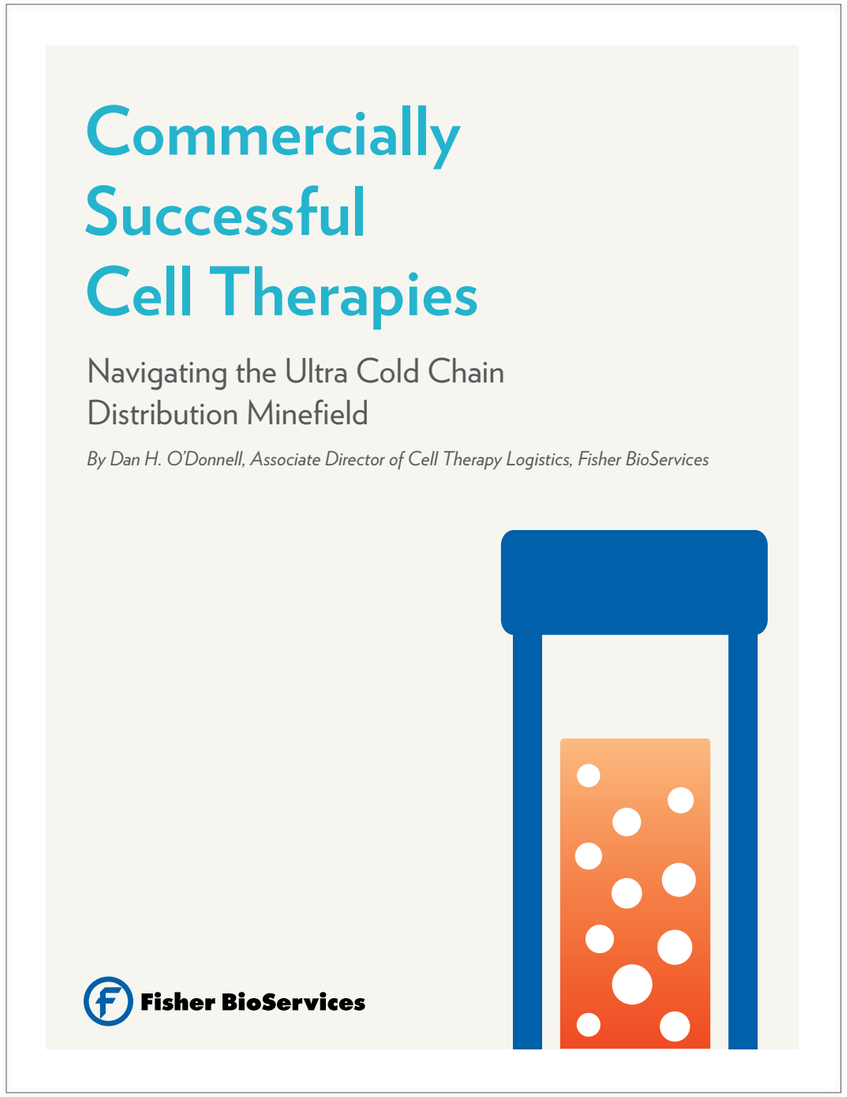
- QP Declaration for Clinical Trial
- QP Release: Biologics & Cell Therapeutics
- EU Biobanks for Ultra Cold Clinical & Commercial Storage and Distribution

▶ Explore Your Solutions

Additional Resources

You may also like our ebook

Cell Therapy: Commercially Successful Cell Therapies



Contact Us

www.fisherbioservices.com

info.fisherbioservices@thermofisher.com

301.315.8460

subscribe to our blog

blog.fisherbioservices.com

US | UK | CH | CN | SG

follow us on Linkedin

Explore strategies for your clinical & commercial development of biologics & cell therapeutics in the EU

Request more information and talk to our specialist

Share this ebook!

Part of Thermo Fisher Scientific