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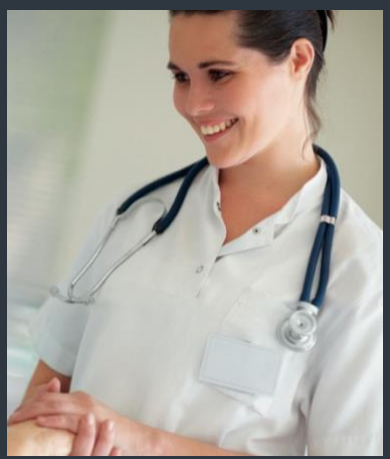
Venn Rapporteur

Update on FDA form 1572

Sponsors and CROs are reporting that Investigators are increasingly refusing to sign FDA form 1572. This has become a particular issue for US Sponsors who have been used to investigators raising no issue. The Danish Medicines Agency have stated that Investigators should not be signing this form as they cannot guarantee compliance with US legislation.

FDA Advice

The concern focuses on clinical trials conducted under an IND. The FDA state that there are two options; apply for a waiver of any Institutional Review Board requirements or conduct the study as a non-IND trial. Non-IND must be conducted in accordance with 21 CFR 312.120: Foreign clinical studies not conducted under an IND.



IN THIS ISSUE

The Clinical Trials Regulation (CTR) will significantly alter the delivery of clinical trials within the EU impacting almost every process involved. The CTR has developed out of necessity to ensure the EU remains a competitive option for drug development. Although now universally accepted as having stifled the number of clinical trials conducted in the EU, the Clinical Trials Directive (CTD) was initially viewed as a positive initiative for clinical research. Unfortunately, it was negatively impacted by the differing interpretations of the CTD by Member States to create complex and administratively cumbersome approval processes. Some common causes of confusion for clinical studies involving several EU Member States include:

- inconsistent grounds for non-acceptance of Clinical Trial Applications;
- different approaches to consent;
- variable definition of the Legal Representatives role;
- contradictory positions on label text, NIMP dossiers;
- the review process for low risk clinical trials.

To resolve this variability the new legislative framework is dictated by a regulation which is binding across EU Member States. In contrast directives set out a series of goals that Member States must develop their own laws to achieve. The biggest change that could be transformative for clinical trials in the EU is the creation of a central submission portal and the switch to a single opinion for all Member States involved in the trial. Technical issues along with the Brexit-related move of the European Medicines Agency to Amsterdam has resulted in substantial delays in the applicability of the CTR. This is now on a rolling deadline that will be fixed to six months after the release of the CT Portal.

Whilst the CTR will introduce a significant number of changes and require considerable resources to review and change procedures to comply the benefits will make this worthwhile. The ability to get a single decision for a clinical trial for the whole of the EU is expected to be a transformative change positioning the EU as an extremely attractive region to conduct clinical research.

FDA Priority Review Vouchers

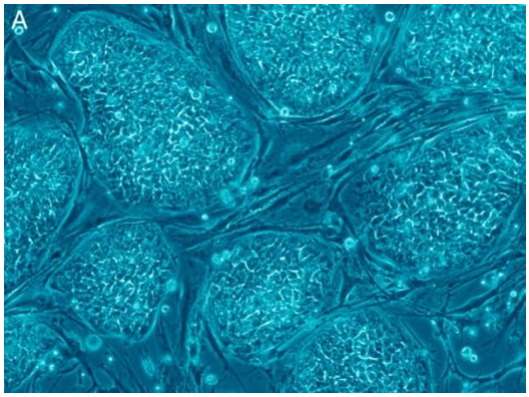
Priority Review Vouchers (PRVs) for rare paediatric diseases have come under scrutiny again following a publication from Harvard. PRVs are granted to encourage drug developers to produce treatments for diseases that would not be commercially viable without incentives. There are currently two types PRV available; rare paediatric diseases and eligible tropical diseases. Companies should request designation under the scheme and can apply for a PRV with the product submission package.

Whilst the impact of PRVs is difficult to ascertain, it remains one of the most interesting initiatives of any Regulatory Agency. It was reported by the authors of this study that there was no increase in the number of drugs being made available for these conditions or clinical programs being initiated. However more investigational drugs made it from Phase 1 to Phase 2.

As this initiative is essentially self-funded by Industry it must be worth continuing given that collectively 10 million children live with a rare disease in the US alone. RAPS have written a great summary article for anyone interested covering neglected tropical disease PRVs as well.

Cellular Products in Clinical Trials Common Challenges

The use of cellular products in clinical trials introduces a multitude of complexities in comparison to conventional investigations involving New Chemical Entities (NCEs). Whilst it is beyond the scope of this review to provide a detailed appraisal of valid regulatory and developmental strategies to de-risk these trials, it is worthwhile listing the fundamental issues into the early development of these innovative products.



Cells make unique drug products

A population of cells cannot be precisely characterised to the range that a low molecule weight chemical can be. The cell population of product will not be entirely homogenous and may even change in vivo depending on the specific microenvironment they are placed. Furthermore, the exact therapeutic and toxic effects of the cellular product will not be fully understood, and the development of a viable potency assay is difficult at an early-stage.

Logistically the product will be more complex with both allogenic and autologous treatments adding distinct challenges. The use of autologous cells or patient specific allogenic batches; stability of the final product measured in hours and long production times coupled with the limited volumes of product that can be produced are stressors on the production and supply chain that can frequently result in study participants missing their dose(s).

Limitations of non-clinical testing

In many cases it will be difficult to generate reliable data from animal models. The extrapolation of cell numbers used in an animal model to a clinical dose in humans is relatively unreliable and there may simply be a lack of comparable animal models. Species specificity and tumorgenicity are obvious problems with little solutions available now or in the future. Engagement with regulators is a necessity will the involvement of an assessor experienced in this area.

In the Clinic

Inclusion criteria for participants is dictated by the unknown risks inherent with cell therapies. Healthy volunteers are typically excluded because of these uncertain risks along with early stage diseases. There is also more pressure to collect data that is not just related to safety at an early-stage in comparison to NCEs. The route of administration must be feasible in the standard clinical environment and this should be evaluated. Investigation of the pharmacological activity and the fate of the cells in the participants body with factors such as cell engraftment being especially important. One of the most prominent concerns is the formation of ectopic tissue. A robust risk-management approach and steps such as full traceability from donor to patient is mandatory along with a records retention period of 25 years.

This is a very simple look at cellular products and some of the complicating factors for delivering a successful clinical trial

Brexit & Clinical Trials

The protracted withdrawal of the United Kingdom from the EU continues to trigger concerns in the pharmaceutical industry. Most of the focus is on the availability of marketed product in both the EU and UK in the event of a no-deal Brexit. The fear of a disruption in the supply chain as a result of no-deal has already resulted in supply shortages and price rises. Whilst there are always shortages and price-rises most stakeholders attribute the increase to Brexit.

Clinical research and specifically the conduct of clinical trials across the EU will also be impacted should a no-deal be the eventual outcome of Brexit.

In a no-deal situation can Sponsors' proactively reduce any impact on their clinical trial(s). As clinical trials are approved on a national basis this will fundamentally reduce the extent of the disruption in theory. Regulatory and ethical approval is provided by each Member State so there will be valid approvals in place. There are however some obvious areas that will be affected.

Sponsor location

The UK will require sponsors to either be located or have a legal representative in the UK or from a list of approved countries that will initially include the EU/EEA.

IMP Management

The UK will recognise QP certification from other countries on an approved list which again will initially include the EU/EEA. Importation of IMP require a Manufacturers Licence (MIA) and Importers must develop an assurance system overseen by a QP to ensure certification has occurred in the EU/EEA. IMP shipments directly to site will be possible.

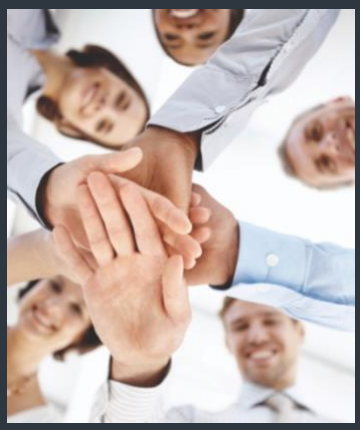
Safety Reporting

Remains the same except that SUSARs can only be reported through UK-based IT systems and not through the EMA systems that are currently active.

Professional Development

Our regulatory team have written a review article on Orphan Drug development in the EU available from our website.

This is an area of substantial growth over the past few years and one that will continue to grow especially as investment builds and public awareness drives the development of satisfactory treatments for those living with a rare disease.



Recommended Online Resources: Clinical Trials

In this edition we would like to suggest some online resources that we think might be of use

Clinical trials country requirements
https://www.nihcollaboratory.org/sites/CbyC/Pages/SnapshotDrug.aspx

Revised Brexit advice from MHRA
https://www.gov.uk/government/publications/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-theres-no-brexit-deal

Tips on using ClinicalTrials.gov
https://www.bmj.com/content/361/bmj.k1452

UK Clinical Trials Toolkit
http://www.ct-toolkit.ac.uk/

Online Regulatory News https://www.raps.org/news-and-articles

Get in Touch

Our Regulatory staff are always eager to talk, feel free to contact our Regulatory Team:

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