ISSUE
02
NOVEMBER
2019

Venn Rapporteur

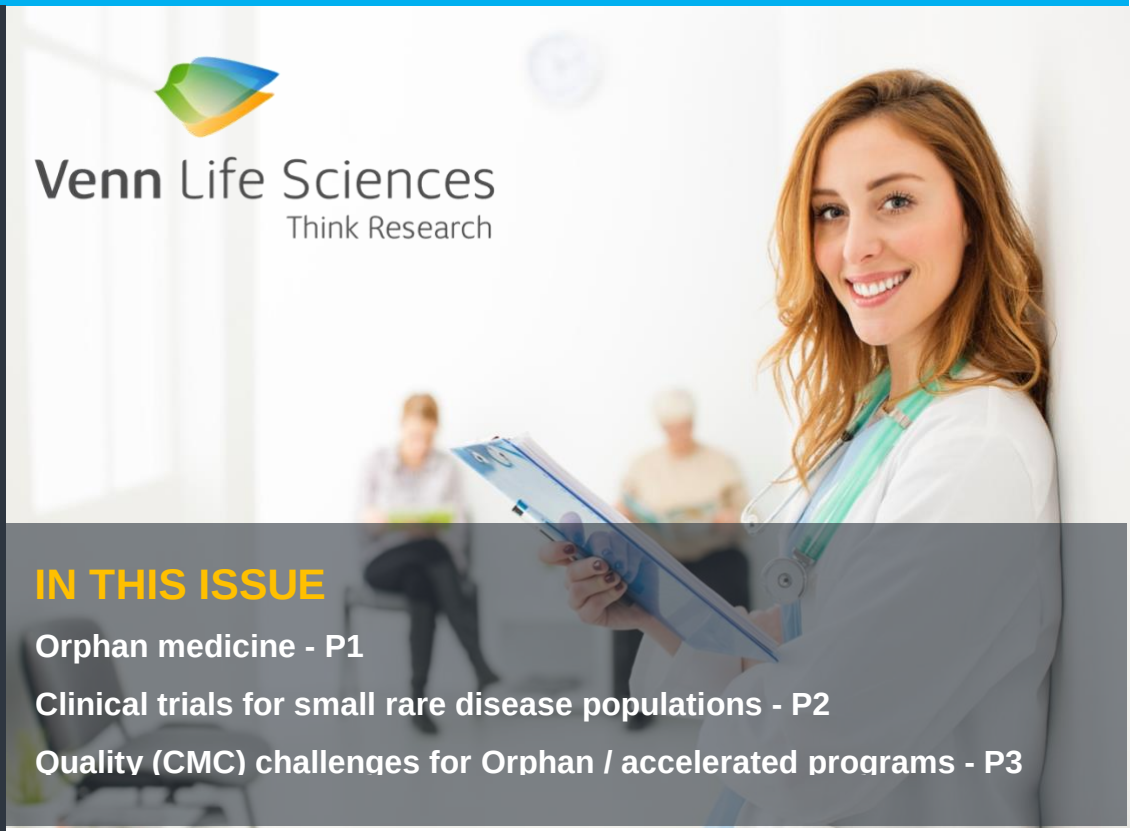
Update on EMA relocation

On 20 November 2017, European Union (EU) Member States decided to relocate the European Medicines Agency (EMA) to Amsterdam, the Netherlands, as a result of the United Kingdom's (UK) withdrawal from the EU. The Agency immediately began working with the Dutch authorities to prepare for the move and take up its operations in Amsterdam by 30 March 2019.

EMA left its London premises on 1 March 2019 to relocate to Amsterdam to its temporary premises in the SPARK building in the Sloterdijk area of Amsterdam. From 4 March 2019, the official address of the Agency is that of its permanent building in Amsterdam Zuidas.

Permanent location

In October 2019, EMA's Management Board was informed that the building will be handed over to the Agency on 15 November 2019. EMA plans to move equipment to the new building and configure and test IT systems from mid-November to January 2020, allowing staff to move in during the week starting 13 January 2020.



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Orphan Medicine Development

Developing therapies for rare diseases requires often specialized, innovative and costly techniques. As the patient population is small, development and marketing of medication would not generate sufficient return on investment to justify the investment without extra incentives that apply for this type of medicines. To promote and regulate development for rare diseases orphan legislation was developed and laid down in Regulation (EC) No 141/2000, which refers to drugs developed to treat rare diseases to as "orphan medicinal products" (OMPs) in the EU. Similar guidance exists in other regions e.g., in the US Orphan Drug Act (21 CFR 316).

Criteria

It is noted that the criteria for orphan designation are not internationally harmonized. Although a single clear global definition of 'rare' does not exist, orphan status is based on the size of the patient population. Additional criteria may apply depending on the region concerned.

For example in the EU the disease must be life threatening and there must be a significant benefit over existing treatment.

Incentives

Incentives for OMPs differ per region. In the EU Sponsors who obtain orphan designation benefit from a number of potential incentives, including protocol assistance, market exclusivity and fee reductions. Further incentives may apply for micro, small and mediums sized companies (SME). These incentives can include administrative and procedural assistance from the Agency's SME office and further fee reductions. US potential incentives comprise of financial incentives and increased assistance from the FDA's Office of Orphan Product Development. In addition, the Pediatric Research Equity Act (PREA) does not apply to OMPs, and OMPs may be made available to patients before marketing approval.

Venn Life Sciences

Venn Life Sciences is an Integrated Drug Development Partner offering a unique combination of drug development expertise, clinical trial design and execution services including regulatory services. This enables us to create, plan and execute drug and medical device development programs effectively and seamlessly for our clients. We have dedicated operations in Ireland, France, Germany, the Netherlands, the UK, the US, and Europe-wide representation.

We have teams across both early and late phase development. Our late phase teams specialize in multi-site cross cultural clinical trials with unique knowledge of local and EU regulations. Over our 25 year history we have built up substantial therapeutic and study experience, contributing to the efficient management of sites, budgets and communication channels with all parties involved. Venn is renowned for its hands-on approach and consistent delivery of high quality work on budget

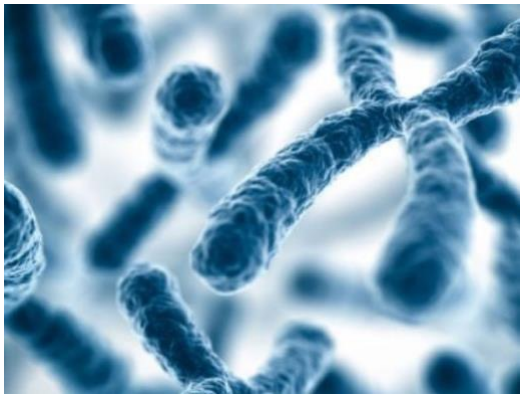
Clinical trials for small rare disease populations

One of the challenges of clinical trials for rare diseases is the limited evidence that can be obtained during the process due to the small populations. In addition to the already small populations, further challenges arise when pediatric considerations need to be dealt with and/ or regional differences in prevalence exist. EU and US guidelines describing the regulatory perspective on clinical trials for small populations / rare diseases are available. These guidelines describe e.g., choice of endpoints, methods and statistical considerations in obtaining sufficient evidence.

Despite the small population, according to the EMA guidance document most orphan drugs and pediatric indications submitted for regulatory approval are based on randomised controlled trials that follow generally accepted rules and guidance. Deviation from such standards is, therefore, uncommon and should only be considered when completely unavoidable and would need to be justified. However, it may be that in conditions with small and very small populations, less conventional and/or less commonly seen methodological approaches may be acceptable if they help to improve the interpretability of the study results. Key here is early interactions with the regulators to discuss the preclinical and clinical program.

Challenges

There are specific challenges related to the development of treatments for rare diseases. E.g. design of the clinical trials may be hampered by poorly understood mechanisms and potential heterogeneity of the disease across the population. Other potential issues are related to the small patient population and potentially limited number of available specialist centers, which may prove the recruitment to be challenging.



Interact early and frequently

Both EMA and FDA encourage early and frequent interactions. EMA states that it is strongly recommended that scientific advice/protocol assistance be sought during all phases of development to guide sponsors as to the acceptability of their planned approaches for later marketing.

FDA similarly encourages sponsors to discuss their overall plans for maximizing the quantity and quality of safety data in early drug development meetings with FDA.

Venn regulatory services for clinical trials

- Determine the optimal regulatory strategy
- Regulatory process guidance
- Support in regulatory agency meetings, e.g., FDA, EMA, EU National
- Compilation and authoring of investigational applications (IND, IMPD/CTA)
- Manage regulatory submissions and procedural timelines

Quality (CMC) challenges for Orphan / accelerated programs

As orphan drugs often address unmet medical need, orphan development programs can be eligible for accelerated development programs. In accelerated programs, clinical development moves quickly into patients and/or pivotal studies. As a result, quality developments adaptation to these time limited scenarios is becoming necessary, and CMC is more likely to be on the critical path than with normal development programs. For quality/ CMC the formal minimal requirements for market application files is the same as for normal programs. Amongst others, process validation (PV) and formal stability programs typically tend to be on the critical time path.

Process validation

PV can be approached in different ways. The Traditional PV approach can be reasonably straightforward in design and puts the emphasis on the PV itself. Enhanced development and validation approaches rely on more extensive development efforts (e.g. following 'Quality by Design' principles and continuous process verification e.g. using sophisticated process monitoring systems and could justify a more limited scope of the PV itself. For orphan drugs, Traditional PV approaches may be favorable since they are acceptable in combination with a smaller process development scope.

When manufacture of only a limited number of batches is anticipated, a leaner development effort in combination with a traditional PV approach may be sensible from a business perspective.

Stability

Meeting the typical stability requirements for licensure may be challenging in orphan programs as the number of batches may be limited. It is key to discuss and agree with the regulatory agencies on e.g., post-approval commitments. Solutions to be considered could be to provide pilot scale stability and commit to provide full scale formal stability post approval.

Rare disease funding in the EU

To date, a limited but increasing number of orphan drugs (drugs for rare diseases) are reaching patients. Funding opportunities for rare diseases research are available in the EU Horizon 2020 work program. Major investment, more than 1.4 billion euro, has been made to more than 200 research and innovation projects in the area of rare diseases. Funded projects cover nearly all fields of medicine. The EU funding facilitates the formation of multidisciplinary teams from universities, research organizations, healthcare providers, SMEs, industry and patient organizations from across Europe and beyond.

Recommended Online Resources:

Information on EMA location/ relocation
https://www.ema.europa.eu/en/about-us/uks-withdrawal-eu/relocation-amsterdam

Workshop report on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)
https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf

EMA Guideline on clinical trials in small populations.
https://www.ema.europa.eu/en/clinical-trials-small-populations

FDA. Rare Diseases: Common Issues in Drug Development Guidance for Industry.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry-0

EMA Orphan designation overview
https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

EU Horizon 2020 program:
https://ec.europa.eu/research/participants/data/ref/h2020/wp/2018-2020/main/h2020-wp1820-health_en.pdf

Get in Touch

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