Clinical Development Interview

The (pre)clinical development process is complex and risky. This is especially true for ATMP. Luckily, expert organisations are able to deliver strategic support as well as operational capabilities. We have invited at.las members Quality by Design and Venn Life Sciences to share their view on the ATMP development process and give insight into their experiences. A double-interview with Dominiek Rossillion (Quality by Design) and Bruno Speder (Venn Life Sciences).

When and why did ATMP become a topic of interest in your organisation?

"It grew on our organization. We first came into contact with the field when a production facility in Belgium reached out for support to become accredited around 2009. In 2016, we further strengthened our focus on ATMPs with the creation of a dedicated core team.", Dominiek starts off.

"Interesting, we also started working on the first projects for our clients in 2016.", Bruno joins in. "The development of ATMPs really requires an integrated approach, particular in the early stages of development. To successfully develop an ATMP product you need a very close collaboration between multiple disciplines: CMC, non-clinical and clinical. As an integrated drug developer these are the projects that are particularly appealing to us, as they allow to bring all our expertise around the table. In addition, as ATMPs are targeted to the treatment of unmet medical needs, we feel that these are projects where we can really make a difference for patients."

What lessons have you learned so far? What, in your opinion, are the main differences between ATMP and other pharmaceutical products?

"Due to the diverse nature of the ATMP field, we have had many different experiences. However, although ATMPs are very distinct from any other drugs and vaccines, the same principles for drug development still apply. Also there many technologies that share similarities with ATMPS, for example Adenovirus-based vaccines share aspects with adeno associated virus (AAV)-based gene therapy vectors.", Bruno explains.

"True.", Dominiek agrees. "At QbD specialists from multiple fields joined the ATMP core team and were able to add value. The team was further expanded with external cell and gene experts. It started with knowledge sharing and led to the creation of our ATMP development methodology: Cell by Design. Together with partners we have supported ATMP companies in assessing their current production process for feasibility, compliance, and automation level. In the last few assignments, we have included cost of goods assessments to paint a picture of the investment versus scalability and compliance costs. For me the most important lesson learned is that there are wonderful projects ongoing with life-changing possibilities for patients suffering from horrible diseases. Many of these projects start based on a purely manual open process and, due to funding limitations, need to move to clinical evidence as soon as possible. This makes it really difficult to scale up afterwards, impeding a swift trajectory to patients."

"I definitely agree that that ATMPs require a thorough multi-disciplinary approach. Small changes in for example the manufacturing process can have a significant influence on the (non)-clinical development; therefore it is critical that there is a very close collaboration between different disciplines. Other lessons we have learned is that early interaction with regulators to validate the (early) development plan is an essential part of the successful development of an ATMP. And last but not least, we have found that the classification of the product is crucial as well. For both the European Union and the United States, ATMPs fall under the regulatory framework of biological products, which determines the legal basis for their development. Sub-classifications of advanced therapies are different between regions: while in EU, there are four major groups, i.e., gene therapy, somatic cell therapy, tissue-engineered therapies, and combined advanced therapies, in US, the sub-classification covers two major groups of products, i.e., gene therapy and cellular therapy. In Europe it is advisable to have an early interaction with the Committee in Advanced

Therapies (CAT) to obtain feedback on the classification of the product. The ATMP classification procedures are valuable to address questions on borderline classifications, commonly raised for combined ATMPs, to confirm the medicinal product framework and determine what type of ATMP a product is, and therefore, develop the product under the specific dossier requirements and quality guidance.", Bruno concludes.

It is often stated that each ATMP product is unique. Standards, however, are needed to streamline processes, make them more efficient and reduce costs in the long run. Do you see standards emerging? Do you see overlap between products and processes?

"Compared to traditional pharmaceuticals, ATMPs are indeed unique in nature. The starting material varies per donor. And even more importantly, to obtain a personalized medicine, the endpoint – the product specifications of the final product – will have to be tailored to the needs of the patient and will therefore vary.", Dominiek explains. "For a product to become widely available, there must be evidence and confidence that it works consistently and can be produced that way, which is challenging for a personalized product. The only way to achieve this is through a high level of understanding of the biology and biochemistry in and during the production process. It is necessary to truly master the process. In order to demonstrate robustness and evidence to regulators, there must be pathways for these therapies to be produced without mishaps. To be marketed globally, there must be standards for how that evidence must be presented so that it is acceptable to many different competent authorities worldwide.", he elaborates.

"Again I agree.", Bruno chimes in. "Every ATMP product is indeed unique, however the same `drug development` principles as for other drugs apply to ATMPs. It is therefore important to keep the general principles in mind. With the experience regulators have accumulated in the past years we see more targeted guidance / guidelines being developed. Although the development of ATMPs is still case-by-case and tailor made, we certainly see overlap between processes and products, particularly in non-clinical safety testing, where the same principles as for other drugs / vaccines apply."

Is the demanding regulatory framework imposed on ATMP developers justified? Could an argument be made for the case of showing more lenience when terminal or end-treated patients are involved?

"ATMPs are – like any other drugs – administered to humans. They have to be as safe as possible and to the applicable quality standards. The discussion related to use different standards when treating terminal patients, or patients with no treatment options, is not specific to ATMPs, but also emerges related to other drugs used in oncology or other life-threatening diseases. Besides a scientific and medical discussion, it is also an ethical one.", Bruno states.

"I have been active in the pharmaceutical industry for quite some time and in my opinion a rigid framework is part of the business.", Dominiek is clear. "The end goal of the competent authorities is to balance the risks and benefits of a therapy, taking into account variations in the production process. Protecting patients from harm is the heart of the matter, but also enabling them to get the best treatment they can. For patients whose prospects are bleak, that balance between risks and benefits tilts. Risks perceived in these cases will typically be considered less impactful. I agree with Bruno, this is more of a philosophical or ethical discussion than a scientific one."

How do you see the future?

"ATMPs represent a fast-growing field of interest with a lot of potential in diseases with a high unmet medical need. Although most of the products are in a relatively early stage of development phase, there is a clearly an enormous therapeutic potential. We see a bright future for ATMPs, however there seems to be a big `conversion gap` between the clinical trials run and the number of ATMPs that are reaching the market. Even though over 500 clinical trials were performed with ATMPs in the EU between 2009 and 2017, this led to only 19 market authorization applications to EMA (European Medicines Agency). A well designed and executed development strategy might allow to close that conversion gap.", Bruno concludes.

"Correct, the future of ATMPs does indeed look bright, while also being a challenge. By now, the technology has proven itself. The benefits to patients are enormous. There is a big difference in the impact of the treatment and the effect of the therapy compared to more traditional treatments. Think of an oncology patient, who might see the same results from one or a few injections, as compared to radiation treatment or chemotherapy with an enormous impact on the quality of life. The future is challenging, however, because we see the potential on the horizon, but also struggle to automate and close production systems. Many therapies are extremely labour intensive, use a lot of medium and are not scalable. I firmly believe, we need to build automation into our products to scale beyond a production capacity of a few hundreds or thousands of patients annually. The WHO states that 1 in 6 deaths is related to cancer. If we truly want to make a difference in cancer treatments, we that means the production of billions of therapies.", Dominiek looks ahead.

Thank you both.

Bruno Speder
Bruno Speder is VP, Regulatory Affairs & Consultancy at Open Orphan plc (of which Venn Life Sciences is a fully owned subsidiary). He holds a degree in Bio-Engineering (Ghent University, Belgium) and a degree in Health Economics (EHSAL Management School, Belgium). He is currently advising a broad range of organisations (non-profits, biotechs, large pharma) on the regulatory aspects of their drug development. He has been actively involved in the development of the regulatory strategy for a number of ATMP products, including cell therapies and the regulatory strategy for the development of novel gene therapy delivery vector.

Dominiek Rossillion
Dominiek Rossillion is an industrial engineer biochemistry by training. He spend his active career within the life sciences scene. Learning about qualifications, validations and overall quality and regulations in sterile manufacturing environments. He broadened his focus and started building and supporting customers in obtaining accredited quality managements systems statuses (for pharma, Medical devices and distribution). As a member of QbD's ATMP core team he co-developed a quality by design framework for Cell Therapies. Since two years his focus shifted towards a more commercial role, connecting to parties in need of support within the industry.