REGULATORY FOCUS

Advanced therapies: ‘Trip hazards’ on the development pathway

By Kirsten Messmer, PhD, RAC, Richard Dennett, PhD

This article concerns the development of advanced therapies and the challenges and complexities of getting them through the developmental pathway, which the authors call “the trip.” The authors examine at strategic levels the importance of some of the fundamental building blocks for the development program and highlight some commonly encountered challenges (trip hazards) for cell and gene therapies and offer “bench-to-bedside” and chemistry, manufacturing, and controls (CMC) considerations and advise on nonclinical and clinical investigations. They conclude that early contact with regulators can help avoid “trip hazards.”

Introduction

The advanced therapy sector has grown rapidly, reflecting the tremendous interest for these complex biologic products with potentially curative effect. Advanced therapy products, including cell and gene therapies, as well as tissue-engineered products, have shown great promise for addressing medically unmet needs, particularly for orphan diseases and in oncology. The Alliance for Regenerative Medicine reported a 32% growth in clinical investigations of regenerative medicine products from 2014 to 2018.[1] Currently, there are more than 2,000 product candidates under development. Although forecasts of

compound annual growth rates and predicted market values vary among different reports, the cell and gene therapy market was valued at more than US$1 billion in 2018 and by 2025, is likely to exceed US$10 billion.[2]

However, product development for advanced therapies still poses a number of potential "trip hazards," even though supporting guidance has matured to a good level. Potential challenges may occur at all stages of nonclinical, process, and clinical product development. These hazards include, but not limited to, technology transfer; CMC; clinical investigations; and stage-appropriate good practice considerations. It is paramount to be aware of trip hazards before they occur because they can equate to time- and cost-related program impacts.

In this article, we will highlight, at a strategic level, the importance of some of the fundamental building blocks for the development program and highlight some commonly encountered challenges (trip hazards) for cell and gene therapies, in which things frequently go wrong, and sometimes critically so. For simplicity, tissue-engineered products are not covered in the scope of this article but share certain commonality with cellular-based products.

What makes advanced therapies different?

It is imperative to understand the product itself for the successful development of any therapeutic product. Small molecules are very well understood because they are a single molecule of low-molecular weight and produced through a defined chemical synthesis that yields mathematically identical copies. As such, they can be straightforwardly characterized. Biologics, such as monoclonal antibodies, cytokines, and other recombinant products, can also be generally well defined but they have higher structural complexity and posttranslational modifications. The fact that these are manufactured in living producer cells also reduces the ability to control production of identical copies. There is, therefore, inherent heterogeneity in the product, making biologics generally more sensitive to external conditions and stability. Many of the "traits" associated with biologics also apply to advanced therapies. So, what makes them so different?

Advanced therapies add an additional layer of complexity to the "traditional" biologic product. These definitions are paraphrased from the European Medicines Agency (EMA)[3] and US Food and Drug Administration (FDA)[4] definitions for cell and gene therapies:

- Cell therapies are substantially manipulated cells that treat, prevent, or diagnose a disease.
- Gene therapies introduce genetic material into humans to regulate, repair, replace, add, or delete a genetic sequence. Gene therapies are typically facilitated by in vivo vector-based delivery (plasmid, viral vectors) or can be facilitated via ex vivo cell-based transduction.

Advanced therapies are significantly different from other biologics as in general, they introduce either new genetic material and/or cells into the human body as opposed to the activity of small or large molecule therapies. Traditional biologics have a mechanism of action mostly at the molecular level, whereas

gene therapies aim to change the disease-causing gene in the patient to cure the disease. Cell therapies aim to insert cells with changed biological characteristics for potential curative or preventative effect.

Bench-to-bedside considerations

The development of advanced therapies is still a relatively "new kid on the block" in the overall span of pharmaceutical history. In addition, most technologies are borne out of academia, hospitals, and small-to-medium biotechnology enterprises. Frequently, and more so in the case of cell therapies, the manufacturing process that becomes transferred to good manufacturing practice is effectively still a bench-top process that produces small quantities of the product. This may be sufficient for first-in-human trials using very few patients. However, for later-stage development, larger quantities are required to be manufactured to defined specifications. An inherent trip hazard is that companies often do not think with the end in mind, by asking: "Can I readily scale up/scale out (see later) my process to meet sufficient market demand and without potential product impact changes/comparability issues en route, and what is the market access strategy once I get there?" An essential start-to-finish thought process should get underway as soon as possible to avoid later time- and cost-intensive pitfalls (**Figure 1**).

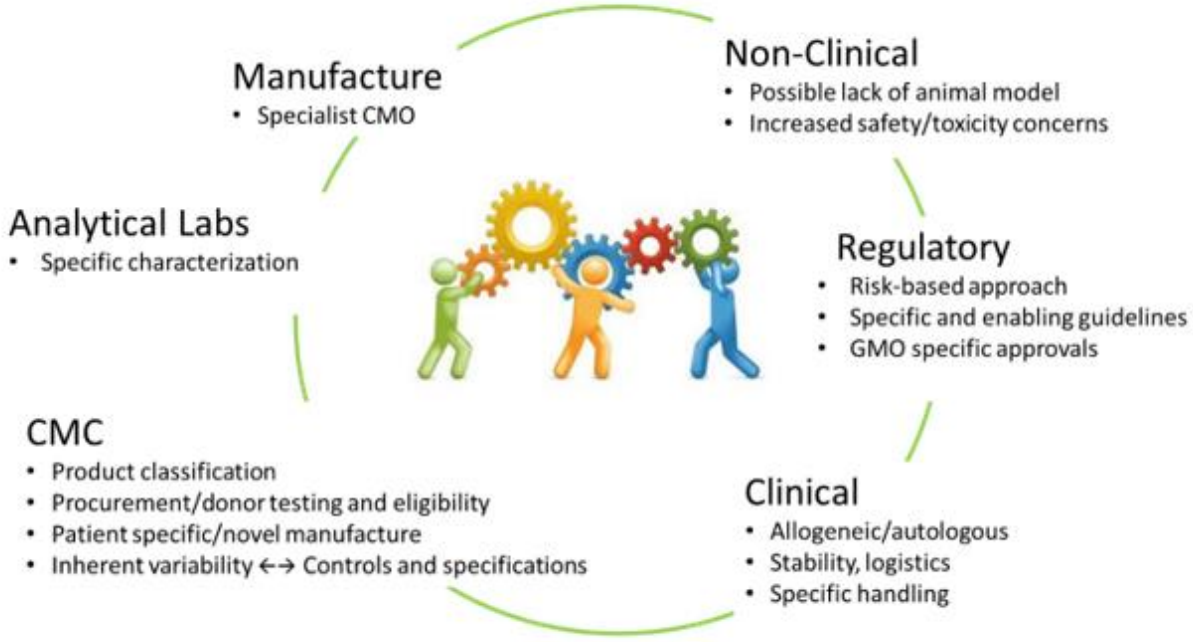

FIGURE 1 Advanced therapies require a multidisciplinary development approach: 'Beginning with the end in mind'

Development of advanced therapies needs to address all the 'cogs' in the development wheel early on to ensure proper alignment of the development machinery and avoid potential trip hazards at any stage of product development.

CMC considerations

Product diversity is a key point for understanding advanced therapies in that there is greater multiplicity of cellular/gene/tissue products. Therefore, a one-size-fits-all approach does not work precisely, with there often being specific and novel nuances across products.

The goal of any drug product development is to manufacture a product to a predefined quality and to realize a process that is robust and reproducible. The objective is to deliver a product that meets quality, safety, and efficacy requirements.

For any drug product development program, CMC is directly on the critical path. Although it may be possible to compact some time and cost aspects through strategic consideration, the wake-up call is that there are no shortcuts for the attributes of quality and safety. The CMC is the clinical product, so it must be pitch perfect. Advanced therapies have more complex parts, with which developers must deal in terms of their characterization, manufacture, controls, and applied specifications. All these factors need adequate development time to apply the appropriate measures, or else the entire development program runs the risk of stumbling and falling at some point thereafter.

Some exemplary common CMC consideration points (not exhaustive) where cell therapy (CT) and gene therapy (GT) programs can be tripped are:

Manufacturing process

- [CT] Front-end consideration needs to be made of initial donor testing and eligibility, and procurement and testing of the source material (e.g., cell/tissue biopsy, bone marrow apheresis, etc.). Controlled transit (specialist bio-courier) of the source material to the site of manufacture is essential. Establishments that manufacture somatic cells and tissue-based products are required to have a registered Tissue Establishment License in place at the point of procurement onward.
  Trip Action Point: Map out the requirements, certifications, and logistics upfront and establish a chain of custody.
- [CT, GT] Cell and gene therapies have different production rationales, with gene therapy and allogeneic cell therapy production generally supporting larger scale up, and autologous cell therapy and cell-based gene therapies generally having smaller scale footprints because of patient specific batches. It is important to be able to clearly define the drug substance and drug product demarcation. This often can be confused for cell and gene therapies and needs to be correctly marked up from the outset to make sure any holding and testing points are correctly applied.
  Trip Action Point: Mark-up of process flow diagram and operational application.
- Viral safety/aseptic control/sterility testing: Cell and gene therapy products are not able to undergo conventional viral inactivation/clearance steps or terminal sterilization because the product is a living cell or a viral vector. Considered aseptic operation

and sterility-release testing needs to be properly factored in. In the case of gene therapies, it can be a challenge if a filtration stage is used because typically, the viral product may be the same approaching size as the filter pore size, leading to significant product loss.
Trip Action Point: Plan aseptic and adventitious agent control strategy well in advance as these take time. Can the process produce enough material to include testing and retain samples?

- [CT] Patient specific batches (e.g., autologous cell or cell-based gene therapies) may involve bespoke designs and disposable process flow paths/systems. These processes may not be robust in their infancy.
Trip Action Point: Make sure there is enough time for development as it can lead to costly batch failure.

In addition, all product contact parts need International Organization for Standardization and CE (conformité Européene) certification according to the territory.

Characterization

- Identity/purity: Clear and comprehensive identity markers and key sequence mapping should be respectively identified for CT and GT products. Certain process impurities often not considered.
Trip Action Point: Take note.
- [CT] All cells that do not contribute to the mode of action are viewed as being impurities. It is important to be able to measure and express the ratio of each individual impurity.
[CT] Cell selection "beads" need to be demonstrated to be cleared by the process. Likewise, any antibiotics used (e.g., at the point of cell procurement or primary cell establishment) will also need to be shown to be cleared by the process.
Trip Action Point: Clearance may, in principle, be mathematically demonstrated on pape,r but further supporting test analysis may be necessary.
- Biological action/potency assay challenges.
Trip Action Point: Often not properly addressed; having an acceptable assay needs early stage focus.

Controls

- Cell therapies and cell-based gene therapies have inherent variation because they are natural biologic products. In addition, the quality of the human source material can vary substantially, leading to the need to establish "wider birth" ranges for certain controls and specifications. Although this may be accepted by the health authorities, enough product batches and supporting development information must be generated to properly support the value ranges of the controls and specifications.
Trip Action Point: This can sometimes be too rushed, and one should plan for having enough batch and supporting data for meaningful interpretation.

- Process validation: Cell and gene therapy processes are natural biological systems with a degree of variability compared with more exacting small molecules. Process validation for advanced therapy products needs to be designed around the actual product type and the available supporting development data. Meanwhile, owing to the wider variability, more than the standard notion of three batches should be evaluated.
  Trip Action Point: Process validation appears to catch most people out. Address this early and seek external advice if necessary.
- Stability: Cell-based products typically have short shelf lives because of their susceptibility to environmental factors, particularly if cryopreservation is not possible.
  Trip Action Point: Plan-controlled logistics.

Medical device/combination products

- Some cell and gene therapy products will necessitate the use of a co-medical device – especially if the product needs to be administered to a certain site in the body, for example.
  Point of awareness: Full medical device evaluation, testing and compliance therefore needs to be fully accounted for (not in the scope of this paper) and in line with the clinical product development.

The preceding points are far from an exhaustive list. The important message is that, although these items seem to be common sense, they are, in reality, being observed as recurrent errors by advanced therapy developers. All the aforementioned elements are required to fulfil regulatory expectation. If any of these parts are not properly addressed, it can easily take several weeks to rectify omissions that could have a significant impact on the start of the clinical trial and hence be a critical factor in the time and cost continuum. Although it is easy to list these pertinent factors on paper, they also need to be properly put into practice.

Nonclinical investigations

Nonclinical development of cell and gene therapies requires careful forethought. Owing to the specific and varied nature of these therapies, standard pharmacology and toxicity testing may not always be suitable to properly determine safety and biologic activity that is predictive of the human response.

Nonclinical design is complex, and especially in the case of cell and gene therapy products; therefore, that aspect will not be expanded upon in this article. Some examples (though not exhaustive) in consideration of nonclinical development studies, and which are sometimes not adequately addressed, include:

- Animal models: [CT/GT] The relevance of animal models for nonclinical proof of concept studies and safety testing should be rationally evaluated and justified. The chosen animal model should simulate the human disease condition as closely as possible. In certain instances, there may not be a suitable animal model, particularly in the case of cell

and gene therapy products, and ex vivo or in vitro data may need to be otherwise generated.

- Safety/toxicity: [GT] Expression of the therapeutic gene product in specific or nonspecific tissues may give rise to unforeseen toxicity, including the possibility of adverse inflammatory, immune, or autoimmune responses. Additional diligence is required in this regard.
- Manufacture: The manufacture of the nonclinical product is sometimes seen to be little more than at bench scale in this stage. It is easy to overlook at the nonclinical stage that the process needs to be suitably representative of the planned clinical product and to ensure equivalent comparability between the nonclinical and clinical product.

Comprehensive, risk-based evaluation is essential in addressing the above potential "trip" points in advance and to allow for the nonclinical studies to be properly translated to the clinical design. Scientific advice can be of value. For example, the FDA's Center for Biologics Evaluation and Research recommends that, for cell and gene therapy, product plans for preclinical studies should be discussed before they are initiated.

Clinical investigations

Approval and conduct of clinical studies pose additional special considerations in the development program to ensure a time- and cost-efficient development program. Cell and gene therapies undergo the same essential clinical testing program from phase 1 through phase 3 before approval as traditional treatments. However, additional review and approvals for clinical trials using genetically modified organisms (GMOs), requirements for site staff training, factoring in specialized equipment and safety considerations, as well as additional concerns with genetic testing, can readily consume appreciable time before a clinical study can begin.

Clinical trials involving GMOs may require additional approvals from statutory bodies, in addition to approval from the local regulatory agency and appropriate ethics committee. A GMO is defined as "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."[5] GMOs include viral vectors, as often used in gene therapies or genetically modified human cells, with the inclusion of CAR-T cells. Historically, any clinical research in the US involving recombinant nucleic acids and receiving funding from the National Institutes of Health (NIH) had to register and potentially be presented at a Recombinant DNA Advisory Committee (RAC) meeting to obtain approval for the clinical study. However, this process has been streamlined, and RAC meetings were eliminated in April 2019, except for very specific cases. The RAC name was also officially changed to Novel and Exceptional Technology and Research Advisory Committee to better reflect the aim of addressing various issues associated with emerging biotechnologies. However, the NIH guidelines and registration requirement still apply, but clinical studies are primarily under the oversight of the FDA.[6] Institutional Biosafety Committee approvals at the clinical trial site may be required.

Outside of the US, the approval timeline for clinical trials can be influenced by two factors nationally: first, whether there is a distinction between "contained use" or "deliberate release," and second, whether additional approvals from other agencies are required.

Each country in the EU decides on "deliberate release" and "contained use," although the definitions are provided in two European Commission directives. Deliberate release "means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general public and the environment."[5] Contained use means "any operation in which micro-organisms are genetically modified" or manipulated "for which physical barriers, or a combination of physical barriers together with chemical and/or biological barriers, are used to limit their contact with the general population and the environment."[7] Australia makes a similar distinction, with either "Dealings Involving Deliberate Release" or "Dealings Not Involving Deliberate Release."

While it is beyond the scope of this article to provide in-depth information on the national approval requirements, the table below provides four diverse global assessment procedures at a very high level. The reader is advised to obtain further information from the national regulatory body websites.

TABLE Clinical trial approval considerations for GMO-based advanced therapies

Consideration	Australia	Japan	Spain	United Kingdom
RA/EC timelines extended?	No	Yes, depending on PMDA meeting	Potentially Yes (+50 days)	Potentially Yes (+30 days)
GMO considerations				
DR/CU distinction	Yes, DR and CU	No, Cartagena protocol	Always DR	Yes, DR and CU
Approval body (MoE)	IBC, followed by OGTR	PMDA or MHLW	Ministry of Agriculture, Food and Environment	DR: DEFRA CU: HSE, LBC
MoE approval timeline	DR: 150 days CU: 90 days	Up to 1 year	About 3 months	DR: 90 days CU: Varies

Clinical trials using GMOs undergo additional scrutiny and require approvals by environmental risk assessment bodies in addition to regulatory agency and ethics committee approvals. This table summarizes the potential for extended statutory assessment timelines for the regulatory agency and ethics committees. It also shows the additional approval requirements for four representative countries, highlighting the diversity of assessment mechanisms in place globally.

CU, contained use (Australia: Dealings Not Involving Deliberate Release); DR, deliberate release (Australia: Dealings Involving Deliberate Release); HSE, [UK] Health and Safety Executive; IBC, Institutional Biosafety Committee; LBC, Local Biosafety Committee; MHLW, [Japanese] Ministry of Health, Labour and Welfare; MoE, Ministry of Environment [as overarching term for additional GMO approval bodies]; OGTR, [Australian] Office of Gene Therapy Regulation; PMDA, [Japanese] Pharmaceutical and Medical Device Agency; RA/EC, regulatory agency/ethics committee.

Logistics

While additional approval requirements on the critical path might directly affect the clinical trial start-up time, various other logistical considerations at site level can also influence the timeline and/or overall feasibility of the trial. The logistical challenges will depend on the type of product. For example, products based on living cells, such as cell therapies and cell-based gene therapies, have an inherently short shelf life at ambient temperatures so careful consideration should be given to transportation logistics from the site of the source biopsy to the manufacturing facility, and to the return to the clinical site for autologous/allogeneic patient administration. Handling of the starting material (such as the patient's own cells for an autologous cell-based therapy) and the final drug product may require use of specialized equipment, such as laminar flow hoods, cryogenic storage, special centrifuges. Staff must be appropriately trained to use the equipment and handle the products. Moreover, certain advanced therapy products require the co-use of specific medical devices.

The preceding considerations are a small fraction of the overall logistical requirements for conducting a global advanced therapy clinical study. Contract research organizations, or CROs, have a key role in providing training for nurses, physicians, pharmacists, and other site staff, as well as providing clinical logistics coordination to oversee patient and sample transportation and tracking in close collaboration with sites and sponsors.

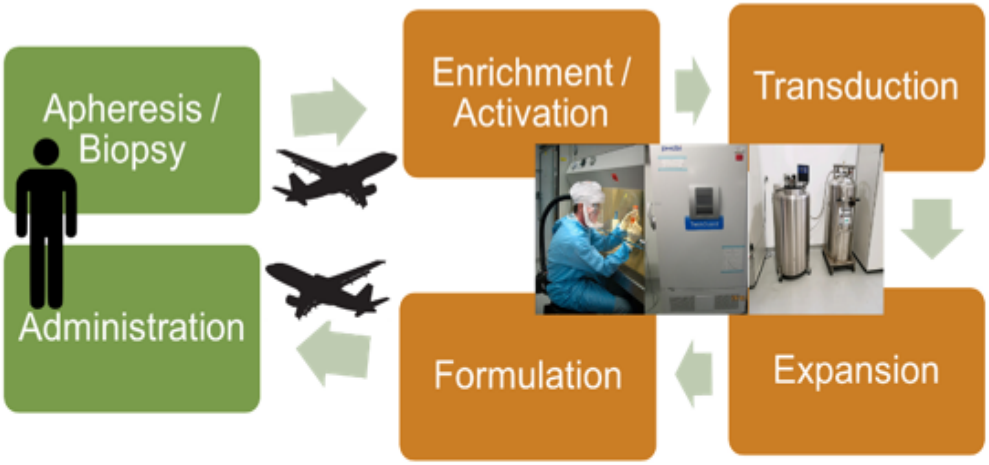

FIGURE 2 Logistic considerations for autologous cell-based therapies
Human cells are inherently vulnerable to environmental factors and need well-designed logistics to ensure controlled temperature maintenance. Geographic considerations regarding the location of clinical sites (extract source material and administer drug product) in relation to the manufacturing site (producing drug product) can be an important factor in clinical trial planning.

Patient counseling and eligibility

Genetic counseling as a prerequisite to genetic testing to evaluate patient eligibility for a clinical trial is an additional steppingstone in numerous countries. Some countries may require the general availability of counseling, whereas others mandate genetic counseling before genetic testing can be done. Also, specially trained personnel might be necessary to conduct the genetic testing. The specific national requirements should be factored in during clinical trial planning to ensure availability of qualified personnel as required and possibly included in the informed consent forms.

Regulatory authority guidance

Advanced therapy product development must follow all good practice requirements for small-molecule and biologic products. However, owing to the complexity of the products and added risks to clinical trial subjects, there are further specific requirements for advanced therapies. In addition, clinical trial design may need to encompass specifically tailored trial designs including single-arm studies and/or study designs using a synthetic control arm. In many cases, it is not feasible and/or ethical to conduct standard double-blind studies for advanced therapies because of the invasive methods used to extract human source material or administer the advanced therapy product, and ease of distinction between placebo and investigational product.

Furthermore, all advanced therapies require extended, long-term follow-up periods and/or the establishment of registries. The use of tailored trial designs is critical to ensure a time and cost-effective development program leading to patient and payer acceptance.

Global regulators recognize the value of advanced therapies, particularly given their potentially curative effect, and they have provided ample guidance for all stages of product development. Recent guidance on clinical study design also addresses the need for deviation from traditional study designs to those involving more real-world data. Available key guidance documents in the European Union and the US will be the subject of an upcoming publication.

Early interactions with regulatory and health authorities is encouraged to obtain supportive direction and acknowledgment of the approaches to be taken in the development program. Key regulators have pointed out it is pertinent to understand the product and its aims as early as possible to provide proactive advice with this further alluding to the avoidance of common trip hazards. This also further opens the door to priority advanced therapy support vehicles, such as EMA and FDA early scientific advice (e.g. INTERACT, pre-investigational new drug meetings), participation in the regenerative medicine advanced therapy and the EMA's priority medicines schemes, where possible, and other more widely available mechanisms supporting efficient product development.

Conclusion

Advanced therapies are a dynamic and fast-growing sector of the pharmaceutical industry. Due to their additional complexity over traditional biologics, they require added ingenuity in line with the particular nature of the

cell or gene therapy product type, demanding a carefully considered technical and regulatory development approach to anticipate and mitigate potential risks upfront.

Regulatory agencies have implemented additional requirements for overall product development, the conduct of clinical trials and/or data needed for product approval. It is therefore imperative to conduct an in-depth regulatory intelligence collection with national requirements for countries intended to be included in the clinical trial. The investigation of associated timelines, particularly for GMO-based products, will also ensure a country selection that supports an achievable timeline for study start-up in a global environment.

Developers of advanced therapies also need to include strategies beyond the clinical development to ensure patient access with a sound understanding of not only regulatory expectations but also the health technology assessment/payer evidence requirements to ascertain approval and reimbursement. The important take-home messages are to "begin with the end in mind" and to develop sound technical and regulatory strategies, to better anticipate and avoid many of the trip hazards that could prove costly, both in time and money, all of which could critically affect the overall clinical study program.

Abbreviations

CMC, chemistry, manufacturing, and controls; **CT,** cell therapy; **EMA,** European Medicines Agency; **EU,** European Union; **FDA,** [US]Food and Drug Administration; **GT,** gene therapy; **GMO,** genetically modified organisms; **NIH,** National Institutes of Health; **RAC,** Recombinant DNA Advisory Committee

References

All websites were accessed on 31 July 2020.

1. Alliance for Regenerative Medicine. Advancing gene, cell, & tissue-based therapies. ARM Annual Report and Sector Year in Review: 2019. https://alliancermstg.wpengine.com/sector-report/2019-annual-report.
2. CISION PR Newswire. Global cell and gene therapy market to reach $11.96 billion by 2025. https://www.prnewswire.com/news-releases/global-cell-and-gene-therapy-market-to-reach-11-96-billion-by-2025--300896848.html. Released 6 August 2019.
3. European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Annex Part IV. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20121116&from=EN. Last amended 27 October 2012.
4. Food and Drug Administration. Cellular & gene therapy products. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products. Last updated 20 June 2019.
5. European Commission. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0018:20080321:EN:PDF.
6. National Institutes of Health. Office of Science Policy. NIH guidelines – April 2019. https://osp.od.nih.gov/biotechnology/nih-guidelines/.
7. European Commission. Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:125:0075:0097:EN:PDF.

8. European Commission. Proposal for a regulation of the European Parliament and of the Council on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=COM:2020:261:FIN&from=EN. Dated 17 June 2020.

About the authors

Kirsten Messmer, PhD, RAC, is a principal regulatory affairs specialist in regulatory intelligence solutions at PPD. She received a doctorate in neuroscience from the University of Sheffield, UK. She can be contacted at Kirsten.Messmer@ppdi.com.

Richard Dennett, PhD, is a senior director of regulatory affairs CMC, global development solutions at PPD. He obtained his doctorate and BSc (Hons) degrees in applied biochemistry at Liverpool John Moores University, UK. He can be contacted at Richard.Dennett@ppdi.com.

Both authors are members of PPD's Advanced Therapy Forum, a group of dedicated professionals with global expertise and hands-on experience in nonclinical, clinical, CMC, and regulatory aspects of gene- and cell-based therapies, as well as tissue-engineered products.

Citation Messmer K, Dennett R. Advanced therapies: 'Trip hazards' along the development pathway Regulatory Focus. July 2020. Regulatory Affairs Professional Society.