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Review

The Confluence of Innovation in Therapeutics and Regulation: Recent CMC Considerations

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ABSTRACT

The field of human therapeutics has expanded tremendously from small molecules to complex biological modalities, and this trend has accelerated in the last two decades with a greater diversity in the types and applications of novel modalities, accompanied by increasing sophistication in drug delivery technology. These innovations have led to a corresponding increase in the number of therapies seeking regulatory approval, and as the industry continues to evolve regulations will need to adapt to the ever-changing landscape. The growth in this field thus represents a challenge for regulatory authorities as well as for sponsors.

This review provides a brief description of novel biologics, including innovative antibody therapeutics, genetic modification technologies, new developments in vaccines, and multifunctional modalities. It also describes a few pertinent drug delivery mechanisms such as nanoparticles, liposomes, coformulation, recombinant human hyaluronidase for subcutaneous delivery, pulmonary delivery, and 3D printing. In addition, it provides an overview of the current CMC regulatory challenges and discusses potential methods of accelerating regulatory mechanisms for more efficient approvals. Finally, we look at the future of biotherapeutics and emphasize the need to bring these modalities to the forefront of patient care from a global perspective as effectively as possible.

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Abbreviations: ADC, Antibody-Drug Conjugate; ATMP, Advanced Therapy Medicinal Products; BLA, Biologics License Application; BsAb, Bispecific Antibody; CAR, Chimeric Antigen Receptor; Cas, CRISPR-associated nuclease; CAT, Committee of Advanced Therapies; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluations and Research; CDMO, contract development and manufacturing organization; CMC, Chemistry, Manufacturing, and Controls; CMPH, Committee of Medicinal Products for Human Use; CQA, Critical Quality Attributes; CRISPR, clustered regularly interspaced short palindromic repeats; DARPin®, Designed Ankyrin Repeat Proteins; rHuPH20, recombinant human hyaluronidase PH20; GRAS, Generally Regarded As Safe; FDA, Food and Drug Administration; FDC, Fixed Dose Combination; GMP, good manufacturing practice; ICH, International Conference for Harmonization; ICMRA, International Coalition of Medicines Regulatory Authorities; IND, Investigational New Drug; IV, Intravenous; Mab, Monoclonal Antibody; NDA, New Drug Application; OTAT, Office of Tissue and Advanced Therapies; PROTAC, Proteolysis Targeting Chimeras; QbD, Quality by Design; RCR, Replication Competent Retrovirus; TALEN, Transcription activator-like effector nucleases; TME, Tumor Microenvironment; TsAb, Trispecific Antibody; ZFN, Zinc Finger Nucleases.

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Introduction

The field of human therapeutics has drastically expanded from small molecules to complex biological modalities, and this trend has greatly accelerated in the last two decades with significant diversity in the types and applications of novel modalities. Innovations in the development of novel modalities are accompanied by an increase in the sophistication of drug delivery technology that has further enhanced the pharmacological space. Additionally, the pharmaceutical industry is currently adapting to a “data explosion”, but the full and effective utilization of big data is very much in its infancy relative to the technology sector. It is a considerable challenge to manage the inordinate amount of data generated and to integrate the data efficiently across the various disciplines. Innovation in novel modalities has led to a substantial increase in the number of therapies seeking regulatory approval, with more data being generated than ever before. As the industry continues to evolve, regulations will need to adapt accordingly to accommodate

a continuously evolving landscape. The growth in novel modalities represents a challenge for regulatory authorities, as their goal is to provide a timely assessment of the safety, efficacy and quality of these new modalities. The speed of these assessments is a critical factor, as patients are in urgent need of lifesaving treatments.

Historically, for most of the 20th century, small molecules and some biologics, such as insulin and monoclonal antibodies (mAbs), constituted the majority of approved therapeutics. However, as pharmaceutical development continued due to advancements in scientific achievements, more complex biologics have demonstrated clinical efficacy in various therapeutic areas, prompting regulatory authorities to draft additional guidance accordingly. In the current pharmaceutical landscape of accelerated complex protein engineering that allows for the mixing and matching of multiple biologics, an increasing number of novel modalities are being developed which lack any prior regulatory filing experience. The lack of regulatory precedence with new modalities provides an uncertainty for some regulatory requirements which may hinder regulatory approval. An ever-present challenge for innovators is a lack of background knowledge and expectations of reviewers and health authorities, which can vary by jurisdiction and, in some cases, may rely on historical paradigms that may not be relevant for new modalities. This becomes a progressively more complex issue with live modality biologics, such as viral- or cell-based modalities for which quality attributes are poorly defined and current testing technologies are poorly suited. In the age of personalized medicine, this uncertainty will become an increasingly common theme, as technology will be capable of identifying specific biological attributes in patients and tailoring therapies to address heterogeneous diseases. Future product platforms will consist of a high product mix and low volume output production paradigm. Therefore, global regulations must evolve to keep pace with pharmaceutical innovation and even anticipate certain developments ahead of their foreseeable arrival where possible. To this point, this review will address the following:

1. Provide a brief overview of novel modalities and new developments in drug delivery technology. These include technologies such as bispecific and multi-specific antibodies, developments to improve antibodies, gene therapies, vaccines, multifunctional modalities, nanoparticles, liposomes, human hyaluronidase PH20 enzyme, pulmonary delivery, and 3D printing. We will also discuss current clinical applications of these technologies, as well as some of the manufacturing issues associated with them.
2. Provide a brief understanding of the regulatory framework that is currently in place to evaluate these modalities with an emphasis on chemistry, manufacturing and controls. We will also discuss regulatory challenges that manufacturers are currently encountering in the development of these modalities.
3. Discuss specific forward-looking trends in regulatory science that could potentially ameliorate the aforementioned challenges, including the development of accelerated regulatory approvals and the harmonization of guidelines for international regulatory authorities.
4. Provide regulatory recommendations that may address future issues and describe our view of some long-term manufacturing developments that will occur in the future regarding personalized medicine.

Novel Modalities

There is an ever-expanding range of novel modalities of diverse functions, indications and compositions that are in development.

Some of these new modalities are under clinical investigation in late-phase trials with the number of approvals expected to increase exponentially. This section provides a brief overview of some of the most promising novel biologic modalities including novel antibodies, gene therapy, vaccines and multifunctional modalities.

Antibodies

Bispecific and Multi-Specific Antibodies

Bispecific antibodies (BsAbs) and their derivatives represent an extension of monoclonal antibody biotechnology that can specifically target multiple antigens to elicit a range of biological effects. The first BsAb that was approved by the European Medicines Agency for human use was the trifunctional antibody catumaxomab, for the treatment of malignant ascites. Catumaxomab promotes tumor cell killing by facilitating an interaction between a T cell and an EpCAM-expressing tumor cell by forming a cytolytic synapse, thereby stimulating the T cell to release cytotoxic granules to kill the malignant cell. Additionally, catumaxomab can function via an ADCC mechanism via Fc effector function. The clinical and regulatory success of this molecule has fueled optimism to leverage BsAb technologies to target other tumor types and even other non-neoplastic indications such as bleeding disorders and even the diagnosis of infections.^{1,2} Protein engineering efforts have extended BsAbs further to generate multi-specific protein-based molecules, such as trispecific antibodies (TsAbs). A recent example of this modality is a product candidate in Harpoon Therapeutic's TriTAC® platform called HPN424, which is a phase I TsAb candidate with 3 separate binding domains joined by linker peptides that target PSMA on prostate cancer cells, CD3 on T cells, and serum albumin to extend the half-life.³ Thus, BsAbs and TsAbs have demonstrated great promise in the treatment of various diseases.

Although BsAbs and TsAbs present promising technologies and viable therapeutic options, several issues need to be addressed to manufacture these modalities for patient treatment. For example, for hetero-IgG-based BsAb constructs formed from 2 distinctive heavy chain subunits and 2 distinctive light chain subunits, random assembly during synthesis can result in 16 unique combinations, in which only two represent the desired product.^{4,5} Additionally, purification, analytics, and characterization of BsAb molecules presents additional challenges.⁶ Therefore, manufacturing of bispecific antibodies requires both sophisticated protein engineering and formulation for the creation of high quality and consistent products. Still, BsAbs and TsAbs offer the potential to expand available targets for therapeutic intervention and improved risk-benefit profiles in historically difficult to treat indications and are becoming a major interest of pharmaceutical companies, as there are an increasing number of products and accompanying clinical trials for these modalities.

Nanobodies

Nanobodies® are functional heavy-chain-only variable domain antibodies that are structurally very similar to single-chain variable fragments that lack light chains and the first constant CH1 domain within the heavy chain. The variable domain of these heavy-chain-only antibodies are capable of full antigen-binding potential and have a strong affinity to their cognate antigen. One of the advantages of using nanobodies over mAbs is their small size, which allows for increased vascular permeability and retention effect as well as poor lymphatic drainage, which aids in achieving drug accumulation into the tumor microenvironment (TME).^{7,8} In 2019, Sanofi's caplacizumab was the first nanobody to receive FDA approval for the treatment of acquired thrombotic thrombocytopenia purpura.⁹ Researchers have also shown that nanobodies can be conjugated with various components such as drugs or

radionuclides for targeted therapy. For example, one group created nanobody-liposomes that recognize the ectodomain of EGFR and tested it *in vivo* to find that this modality resulted in a significant inhibition of tumor cell proliferation.¹⁰ Therefore, in the future, it is possible that we may see additional novel therapeutic nanobodies used in the clinic and potentially patient care.

Masking Antibodies

Antibodies are one of the largest classes of therapeutic proteins in the biopharmaceutical industry, but their intended action can be limited in solid tumors due to on-target off-tumor effects caused by binding to the target molecule on non-malignant cells.^{11,12} Masking antibodies are antibody prodrugs that take advantage of tumor-specific protease activity for activation, thereby limiting drug activity in healthy tissues.^{13,14} They are comprised of a monoclonal IgG antibody or fragment that targets the tumor-associated antigen and a masking peptide linked by a protease-cleavable substrate linker peptide. The tumor-specific proteases will cleave the peptide linker, thus relieving the masking activity and allow the antibody to bind to the target cancer cells. CytomX Therapeutics has developed masking antibodies that are undergoing various stages of clinical trials targeting diseases such as breast cancer.¹⁵

DARPs

Designed ankyrin repeat proteins (DARPs®) have a hyper-variable loop to engineer specific protein-protein interactions selected by phage display, are genetically engineered proteins that are smaller than antibodies, and recognize targets with improved affinity, resulting in superior tissue penetration.¹⁶ The developmental and manufacturing-related advantages of DARPs include resistance to aggregation, high expression in *E. coli* vectors, and adaptable protein engineering allowing the capability to target 3 proteins simultaneously.^{17,18} Companies such as AbbVie, Amgen and Molecular Partners have DARPs that are undergoing various stages of clinical development.¹⁹

Cell and Gene Therapies

CAR T Cell Therapies

While innovation of antibody modalities represents critical and clinically important developments in biologic therapeutics, cell-based therapies, such as CAR T cells, have also made notable advances throughout the recent past. A chimeric antigen receptor (CAR) is an engineered receptor comprised of an extracellular antigen-recognition domain targeting a specific antigen, an intracellular CD3-zeta T cell receptor signaling domain that activates T cells upon antigen binding, and typically a co-stimulatory domain (often CD28 or 4-1BB) to enhance T cell function, leading to target cell lysis as well as T cell proliferation and cytokine secretion. Clinical success of this technology has led to the approvals of Novartis' Kymriah®, Gilead's Yescarta®, and more recently Gilead's Tecartus®.^{20,21} Current innovation in this field seeks to improve the functionality of CAR T cells in light of issues such as the often-immunosuppressive TME, an obstacle in the treatment of solid tumors because of the many mechanisms that cancer cells can utilize to prevent the CAR T cells from functioning appropriately.^{22,23} New engineering designs that incorporate additional immunomodulatory payloads into the engineered cell product are entering clinical trials, such as a Phase I CAR design in which the extracellular portion consists of the IL-4 alpha subunit combined with an intracellular IL-2/IL-15 beta subunit, thereby utilizing IL-4 in the TME to activate T cells.²⁴ Another change being explored clinically is the switch from engineering T cells to natural killer cells, as they do not exhibit the same safety complications, such as

off-target effects or cytokine release syndrome, do not undergo cell exhaustion, and could potentially be used in an allogeneic setting.²⁵

One of the manufacturing challenges associated with CAR T cells is the highly variable patient-specific apheresis material coupled with poor understanding of material attributes. In addition to highly variable starting material, the cells can also show reduced function as a result of multiple rounds of prior chemotherapy, which poses additional risk for manufacturing failure and can also increase upstream complexity and introduce variability in the manufacturing process. Sponsors must define specifications and characterize a final product despite the interpatient variability. Sponsors must also execute the manufacturing process fast as possible, as they are in a race against time to provide therapy to a patient that no longer has other treatment options. It is possible that material quality attributes and process controls may improve cell product manufacturing, as the relationship of these attributes and process parameters on final product quality become more apparent.

Gene Editing

Genetic engineering is the modification of DNA through insertion, deletion or the replacement of DNA or RNA in living organisms. The major technologies in use for genetic modification include zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), and clustered regularly interspaced short palindromic repeat (CRISPR)-associated (Cas) (CRISPR-Cas) nucleases. Genetic modifications can be applied in two different settings: a) *ex vivo* whereby somatic cells are taken out of an organism to be transduced in a laboratory setting with a viral vector, or b) *in vivo*, whereby changes are made directly inside an organism using a viral vector or lipid nanoparticle formulation. Currently, companies such as Sangamo are investigating ZFNs in clinical trials to treat β -thalassemia and sickle cell disease, while TALENs and CRISPR are also undergoing clinical trials by companies like Cellectis and CRISPR Therapeutics respectively for the manufacture of CAR T cells.^{26,27}

Specific manufacturing issues that may arise during production and implementation of genetic editing technology include the targeted delivery of the genes to the intended tissues to reduce the risk of deleterious off-target effects. To limit the development of off-target effects, manufacturers will need to employ methods to mitigate the reduced fidelity of the CRISPR system to improve the safety profile of the therapy.^{28,29} In addition to off-target effects, many manufacturers make use of viral vectors as a means of transferring the genetic material necessary for gene editing; however, they can present with unwanted effects in patients, such as immunogenicity.

Vaccines

Vaccines have been widely successful in improving human health, and although the field of research is too large for the scope of this review, recent improvements in vaccine technology should be highlighted. For example, certain nanoparticle formulations have been demonstrated to protect vaccine components from premature degradation, improve stability, and have enhanced adjuvant properties.³⁰ Moderna's mRNA-based SARS-CoV-2 vaccine, which uses a lipid-nanoparticle formulated vaccine, is currently undergoing Phase 3 trials for the treatment of COVID-19.³¹ In addition, researchers are making efforts towards the development of cancer vaccines, however, these can be difficult to design because the immune system is generally adapted to target non-eukaryotic pathogens. Despite this, cellular vaccines that utilize an individual patient's tumor lysate loaded onto antigen-presenting dendritic cells to elicit a strong T cell response from

patients are also currently being investigated in clinical trials.^{32,33} Vaccine manufacturing can be a challenging endeavor, as the final product can suffer from inherent variability in both starting material and assays used to demonstrate quality.

Multifunctional Modalities

Multifunctional modalities combine different modality types through either fusion or conjugation, thereby modulating potency and cellular uptake as well as improving the accuracy of cell delivery. Of these two methods to generate a multifunctional modality, conjugate modalities seem to be utilized more frequently, and function by either synergizing the pharmacological activity of both components or improving the function of one modality via the function of another.³⁴ One of the more successful multifunctional modalities that exist are antibody-drug conjugates (ADCs), which are composed of a highly specific targeting antibody, a cytotoxic agent, and a linker to combine the two elements.³⁵ Many ADCs have already been approved, with a recent example being McKesson's sacituzumab govitecan, which was approved by the FDA in 2020 for the treatment of triple negative breast cancer.³⁶

Another type of multifunctional matchmaker modality that employs the induced proximity principle is the proteolysis targeting chimera (PROTAC), which is a hetero bifunctional molecule that downregulates target intracellular protein levels by utilizing the ubiquitin degradation pathway.³⁷ Arvinas is currently conducting clinical trials for PROTACs against various cancer targets.³⁸ Other potential future multifunctional modalities include a hormone that contains a combination of glucagon and thyroid hormone (Glucagon/T3) to treat various indications such as high LDL-cholesterol levels or improve glucose tolerance in rodent models of obesity.³⁹ Although these multifunctional modalities have not yet begun clinical trials, they are a good example of future fusion proteins that are on the horizon. Manufacturing challenges associated with some of these multifunctional modalities will likely revolve around the lack of historical precedence. Because there is often no predicate molecule type that manufacturers will be able to emulate, critical quality attributes as well as the process controls necessary to produce a consistent product will need to be defined. In addition, novel assays will need to be developed that confirm the safety and efficacy of these products prior to regulatory approval.

Delivery Considerations

The drug delivery system is critical to providing a safe and efficacious product to the patient. This section provides a brief overview of some promising drug delivery approaches which comprise liposome and nanoparticle technology for a targeted delivery, a coformulation approach for delivering more than one biologic in a single dose, non-invasive organ-targeted pulmonary drug delivery for biologics and 3D printing for solid dosage forms for a personalized medicine.

Liposomes and Nanoparticles

Liposomes are spherical, self-closed structures formed by a bilayer of amphipathic phospholipids with an internal aqueous cavity. The properties of liposomes can be characterized by size, number of lamellae, composition, ligand addition, and charge which all contribute to determine their stability *in vivo* and *in vitro*. Liposomal drug delivery systems are unique because they can be used for both lipophilic and lipophobic drugs. Liposomes display certain advantages such as biocompatibility and ability to carry large drug payloads such as DNA and RNA, and can be modified to better suit their pharmacological purposes.^{40–42} An interesting

example of a sterically stabilized liposome is ThermoDox®, a heat-sensitive liposome which is currently approved for the treatment of hepatocellular carcinoma.^{43,44}

Liposomes can further be modified by combining them with nanoparticles, which are a wide class of materials that include particulate substances.⁴⁵ Nanoscale-sized particles exhibit unique structural, chemical, mechanical, magnetic, electrical, and biological properties which can be utilized as delivery agents by encapsulating or attaching therapeutic drugs and delivering them to target tissues more precisely with a controlled release. VYXEOS®, developed by Jazz Pharmaceuticals, represents a recent approval for a product utilizing liposomal nanoparticle drug delivery. It is a combination chemotherapy nanoparticle that encapsulates both cytarabine and daunorubicin to treat acute myeloid leukemia. It demonstrated improved efficacy at a lower dosage compared to free drug treatment, and also displayed an increased overall survival time in comparison to the control group.⁴⁶

Although the manufacturing of liposomal drug formulations has advanced significantly, there are considerable challenges that remain. Such challenges occur when nanoparticles and other ligands are used to alter molecular targeting, as these require the addition of more synthesis steps. Product quality is another important consideration as the manufacturing of liposomes can require multiple lipids, nanoparticles, and active pharmaceutical ingredients that may not be uniformly distributed. In addition, the manufacturing of nanoparticles typically requires the use of organic solvents, which can be difficult to completely remove from the final formulation.⁴⁷

Subcutaneous Delivery and Coformulation

Biotherapeutics are parenterally administered typically either by intravenous (IV) or subcutaneous routes. An IV administered dose is injected directly into the systemic circulation and can be adjusted according to patient weight, though it typically requires dose preparation and administration in a clinic and can be inconvenient from a patient-centric perspective. Subcutaneous administration has the flexibility of being delivered either in a clinic or self-administered. mAb therapies often require anywhere between 80 mg and 1000 mg per patient which translates to a concentration range of 150–200 mg/mL for the biologic.⁴⁸ High concentration mAbs injected subcutaneously must be transported to the lymphatic system before reaching systemic circulation. Dose retention in the subcutaneous space can be a limiting factor for bioavailability. Various factors including but not limited to the molecular weight, concentration of the biologic, viscosity, injection volume and the rate of clearance of the drug from the subcutaneous space govern the bioavailability of the drug product.⁴⁹ The maximum volume injection limit for a subcutaneous administration is much lower than other routes of administration and multiple doses may be required for solubility limited biologics.⁵⁰

Subcutaneous administration is often associated with pain due to drug product formulation properties (pH, buffer, viscosity and osmolality), administration technique (needle gauge, angle of injection), injection site and injection site reactions.⁵¹ The ideal method of parenteral administration to maximize patient comfort would be a single-dose of an optimal formulation administered at the least painful site with the correct technique. ENHANZE® is a novel drug delivery technology for subcutaneous administration using recombinant human hyaluronidase PH20 (rHuPH20).⁵² Based on multiple clinical trials, rHuPH20 has shown promise in increasing injection volumes and increased bioavailability when compared to subcutaneous injections without rHuPH20.⁵³ Traditional biotherapeutics can now be coformulated with rHuPH20 for a subcutaneous administration. For example, Rituxan Hycela®, a

combination of rituximab and human hyaluronidase, is used for the treatment of follicular lymphoma, diffuse large B- cell lymphoma and chronic lymphocytic leukemia.⁵⁴

A combination of one or more molecules preferably in a complementary formulation design space has led to the development of co-formulated or fixed-dose combination (FDC) products, with or without the use of rHuPH20. Examples of recently approved coformulations include Roche's Phesgo®, Rituxan Hycela®, Herceptin Hylecta®, Novo Nordisk's Xultophy®, and Sanofi's Soliqua®.⁵⁵ Coformulated drugs represent a patient centric approach which increases patient comfort and compliance, reduces the cost of goods in manufacturing, and increases therapeutic yield.^{56,57} Coformulation is a fast-evolving space, but it poses significant biophysical and biochemical challenges for drug development when the formulation design space and administration regimes are different.

Pulmonary Drug Delivery

Pulmonary delivery is an organ-targeted delivery which may improve the risk-benefit profile of certain therapeutics by delivering directly to the lungs. In fact, there are certain instances in which the therapeutic dose response is greater when compared to systemic delivery. A recent study has explored the potential of delivering a full-length mAb for lung cancer in an animal model where a biologic was delivered using a digital inhaler.⁵⁸ The size of the biologic is an important factor, as full-length antibodies have low bioavailability and the smaller sizes of new modalities have the potential for better tissue penetration. A prerequisite for pulmonary drug delivery development is a generally recognized as safe (GRAS) formulation with optimal particle size for maximum deposition of the particles in the desired section of the lung.⁵⁹ Biologics are susceptible to various stresses and it is important to establish a stable formulation and in-process parameters that can ensure drug product as well as combination product stability for pulmonary delivery. The most common method of pulmonary drug delivery is with a nebulizer. Jet, ultrasonic and mesh nebulizers are the three types of nebulizers currently available on the market. To achieve the optimal particle size and particle deposition in the desired area of the lung, it is critical to understand the aerodynamic properties of the nebulizer with the chosen modality. Factors such as viscosity, formulation, concentration of the biologic, excipients and concentration of excipients play an integral role in developing a stable pulmonary drug product.⁶⁰ Despite its challenges, pulmonary delivery has the potential to deliver biologics locally with minimal or no side effects as compared to systemic delivery for respiratory and oncology diseases.

3D Printing

Conventionally pharmaceuticals are manufactured in large quantities, however manufacturers have recently explored options to reduce the manufacturing footprint of medicines. One emerging technology is 3D printing, which is currently limited to 3D printed devices, tablets, transdermal patches and vaginal delivery systems.⁶¹ To date one 3D printed tablet, SPRITAM®, has been approved by the FDA for the treatment of epilepsy.⁶² 3D printing has great potential to advance personalized medicine for patient-centric healthcare that enables customized doses for a specific patient population. In addition, 3D printing has a smaller manufacturing footprint which may enable access to patient populations currently unreachable by conventional supply chains. However, 3D printing of drug products is still an emerging field and many questions remain to be answered regarding product quality attributes for a stable drug product. 3D printing may be the next big

thing in personalized medicine, however a risk-based strategy based on prior knowledge and an understanding of the differences in manufacturing systems is still required before a safe and efficacious product can be made.⁶³ This technology has future potential applicability in the field of biologics.

Regulatory CMC Considerations

This section primarily focuses on current regulatory CMC considerations from the US perspective.

Current Regulatory Framework

For a new therapy to be approved by the FDA in the United States, manufacturers must first submit an investigational new drug (IND) application for approval to conduct clinical trials, followed by either a biologics license application (BLA) or new drug application (NDA) to acquire market authorization. In the US, expedited regulatory pathways are granted for a broad range of therapeutic modalities that address critical patient needs (break-through designation, fast track, accelerated approval, or priority review).²⁰ In general, the Center for Biologics Evaluation and Research (CBER) is responsible for overseeing biologics, with the Office of Tissue and Advanced Therapies (OTAT) responsible for cell and gene therapies. Cellular therapies include cellular immunotherapies, cancer vaccines, or other types of autologous and allogeneic cells for therapeutic indications including hematopoietic and embryonic stem cells, while gene therapy is used to modify or manipulate the expression of a gene to alter the biological properties of living tissues for therapeutic use.^{64,65} However, it should be noted that certain well-characterized biologics such as mAbs, cytokines, growth factors, and enzymes are regulated by the Center for Drug Evaluation and Research (CDER). Recently, a multitude of resources for complex biologics and live modalities including cellular and gene therapy guidance documents as well as a framework for the regulation of regenerative medicine products have been developed by CBER. This includes the Regenerative Medicine Advanced Therapy (RMAT) Designation for the acceleration of approvals.⁶⁶

Outside the United States, the European Medicines Agency (EMA) evaluates advanced therapy medicinal products (ATMPs) for marketing approval through a centralized approval procedure. There are detailed marketing authorization procedures described on the EMA website, with the Committee for Advanced Therapies (CAT) providing specific expertise to aid in the assessment. Accelerated regulatory pathways of the EMA include the PRIME (PRiority MEDicines) scheme, conditional marketing authorization, accelerated assessment, or exceptional circumstances. It should be noted that most of the products that have obtained PRIME designation are ATMPs.⁶⁷ Once marketing approval has been obtained through the centralized procedure, it is valid in all European Union member states as well as Iceland, Norway and Liechtenstein. Typical ATMPs include gene therapies, cell-based therapies, tissue-engineered products, and combined ATMPs. Numerous guidance documents that are specific to each of these types of advanced modalities are available.^{68–70}

As evidenced by the previously described US and EU regulatory frameworks, novel biologics are supported by varying levels of published guidance or regulations, and sponsors are expected to meet all CMC requirements prior to regulatory approval. In general, manufacturers must provide enough data to demonstrate that their manufacturing process is adequately controlled to consistently ensure identity, purity, and potency of the final drug product. Determination of clinically relevant potency or a suitable surrogate can be a considerable issue for these novel modalities because

traditional methods are typically not a reliable indication of clinical activity in a patient for the intended indication. Therefore, in lieu of a true potency assay, a more complicated functional assay that is more reflective of the mechanism of action may be required. However, the complexity of *in vitro* cell-based assays, which often use cell lines, can pose challenges in extrapolating relevant information for the *in vivo* clinical environment. In some cases, sponsors may explore validation of other endpoints that are indirect but relevant for potency, such as using vector copy number for a gene therapy. In these situations, sponsors should ensure sufficient data and documentation to support the alternative method in order to reduce the risk of rejection by regulatory agencies. Other important regulatory hurdles include the extensive characterization of the manufacturing process for these biologics, and both process parameter controls and critical quality attributes must be identified with strict statistical boundaries. Sponsors must also provide data demonstrating comparability of their products as the manufacturing process changes throughout the product lifecycle from clinical trial application to marketing application. Comparability determination can pose a considerable challenge during technology transfers, especially when the product is tailored to an individual as is the case with several of the newer novel modalities. Considering regulatory uncertainties for these novel modalities, health authorities often provide channels for early communication to facilitate industry/agency engagement. In the US, these can be both product-specific, with Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT), or non-specific, through the CDER Emerging Technology Team and the CBER Advanced Technologies Team.⁷¹⁻⁷³

In general, biologics must be characterized more extensively than small molecules for marketing approval to ensure safety and efficacy. For example, for a protein based therapeutic manufacturers must provide information such as the amino acid sequence, post-translational modifications e.g. glycosylation, disulfide bond configuration, and biological activity along with the appropriate documentation for cell growth and harvesting, details regarding the batch records, in-process controls, and process validation.⁷⁴ The FDA has recently issued draft guidance regarding the development of BsAbs.⁷⁵ In addition, the above-mentioned modalities such as CAR T cells or CRISPR fall under the category of gene therapy products, and there is currently drafted CMC guidance that contains applicable principles. However, one aspect that is reiterated in the information regarding the viral vectors to deliver the gene of interest is that the sponsor must provide detailed information regarding the components and process that were used to manufacture the vector.⁶⁶ Finally, there are a number of FDA guidance documents that have been created regarding the manufacturing of vaccines over the decades, however, it should be noted that recently the FDA drafted new guidance regarding vaccines for COVID-19.^{76,77}

The FDA has developed guidance documents for specific drug delivery considerations discussed in this paper such as liposomes, nanoparticles and coformulation. These documents typically contain information regarding the Agency's current thinking on the design for the finished product. For example, guidances for liposomes and nanoparticles are similar, and require the manufacturer to provide a detailed description of the components, physico-chemical properties, surface characteristics, particle size, stability, viscosity, critical quality attributes (CQAs) and characterization of the drug product. Since both liposome and nanoparticle drug products are sensitive to process control and manufacturing scale changes, manufacturers should leverage prior knowledge and assess a risk-based strategy to control process parameters that impact product quality. In addition, manufacturers should provide detailed descriptions of the manufacturing processes for lipid and

nanoparticle components and the types used in the liposome formulation, due to the complex drug release profiles of these delivery systems. Appropriate agency review discussions are recommended to establish human pharmacokinetic bioavailability and bioequivalence behavior of liposomes.^{78,79} The FDA guidance for coformulation addresses the development of two or more new investigational drugs for use in combination. The manufacturer must have a compelling rationale as to why the drugs cannot be developed individually. It is advised that the sponsor conduct clinical trials of the individual drugs along with the combined formulation in Phase I, and provide a characterization data package demonstrating that the combination is superior to monotherapy with individual drugs.⁸⁰

These descriptive FDA guidance documents on new modalities and drug delivery systems are very useful in navigating the complex approval process. However, while extensive guidance has been available for conventional small molecules and well-characterized biologics from global regulatory agencies, the trend towards having modality-specific guidance for each new type of therapeutic on a regional basis will be difficult to sustain as the pace of guidance development inevitably will lag behind the inventive science and newer discoveries may be harder to classify under the existing knowledge base. The resulting divergence in regulations will also add to the challenges in managing the drug development process. Individual regulator-sponsor discussions are resource-intensive and are not necessarily conducive to the overall goal of global harmonization and streamlined approvals.

Regulatory CMC Challenges

These advanced modalities discussed previously present sponsors with unique challenges in meeting regulatory expectations during product development and lifecycle management. As an example, regulatory guidance has been provided by the FDA for some aspects of cell and gene therapy, however at the time of initial publication this guidance is often in draft status. Guidance documents such as these attempt to address aspects distinct from more traditional modalities, and to facilitate the demonstration of safety, quality and efficacy of advanced therapies while operating under specific constraints. For example, the guidance on cell and gene therapy allows some potential latitude in sterility testing for therapies where time may be a constraint for patient treatment, as in the production of autologous cell therapies. Traditional testing methods would necessitate additional manufacturing time that risks patient disease progression and thus patient ineligibility and exclusion from treatment. The US Pharmacopeia has itself published proposals for the modification of current sterility testing paradigms to maximize opportunities for delivery of treatments to patients while not compromising patient safety.⁸¹ This is consistent with the broad recognition of the promise that cell and gene therapies represent, where existing paradigms may not be appropriate.

Quality by Design (QbD) has been an aspiration in medicinal product development for over a decade for other conventional modalities, with the goal of establishing risk-based methods relating to quality, safety and efficacy to deliver greater quality and consistency in therapeutic manufacturing through enhanced product and process understanding. However, the relative lack of historical experience with cell and gene therapies presents many challenges for sponsors in defining a QbD framework. In addition, CQAs are often poorly defined for these advanced therapies and sponsors often have little or no patient-level clinical data to inform CQA definitions or thresholds. For example, in some gene therapies the definition of potency as a CQA can be proximal to the mechanism of action, such as enumeration of cell differentiation. In other

cases, potency is defined using a proximal measure of function, such as in the case of CAR-T therapies, where potency is often defined by production of inflammatory cytokines. These measures indicate target-specific activation of T cells but are poor predictors of clinically relevant features that drive long-term disease. Sponsors can initiate clinical studies with less well-defined potency criteria but will be expected to refine those definitions as clinical data are acquired, to inform future specifications and lot release. As programs advance to licensure, the CQAs should be well defined to avoid the challenges of altering specifications post-market authorization. The health authorities have also indicated that guidance may be updated to incorporate recommendations on clinically relevant CQAs, which would be beneficial in setting expectations and product quality standards.

The generation of the appropriate quality data supporting the phased development of these modalities requires careful planning because insufficient CMC documentation represents one of the greatest sources for non-approval of regulatory submissions. Part of this issue can be attributed to difficulty in selecting relevant reference standards for new modalities, especially for technologies that are evolving rapidly. This is further compounded by the frequent utilization of contract development and manufacturing organizations (CDMOs) for the production of material, and the subsequent necessity of technology transfers between different sites for different manufacturers. Manufacturing by CDMOs may also utilize proprietary technologies with limited transparency for the sponsor. In addition, the maintenance of adequate sample retention may also be challenging, as drug product may be limited in the case of patient-specific modalities. Comparability also poses unique challenges compared to other biological modalities. The application of ICH Q5E for comparability studies may not be the most appropriate approach for some advanced therapies such as autologous cell therapies where the lot is defined by the patient.⁸² This is compounded by the fact that process development and comparability studies necessitate the use of healthy donor surrogate material. Furthermore, in cases where CQAs and critical process parameters (CPPs) are not well defined, Q5E guidance may not apply, leaving sponsors to find other routes to provide evidence of comparability. While any change in manufacturing should be evaluated with a thorough risk assessment of the impact of the change, the relatively limited experience with advanced therapies makes that assessment a challenging endeavor. These challenges will likely be inevitable during the lifecycles of these therapies, as sponsors either develop their own manufacturing capabilities, adopt new technologies, or rely on CDMOs. The inherent variability in starting materials and complex manufacturing methods adds additional layers of risk for cell-based therapies. Understanding the sources of variance and their impact on final product quality as well as an understanding of CPPs and relevant control strategies will be crucial in the successful development of advanced therapies.

Guidance documents have also been provided in the field of drug delivery, where the innovation is focused on the delivery of patient-centric solutions to increase both patient comfort and compliance. The birthplaces of many of these innovations are academic labs or start-up entities that may not be well equipped to deal with either the commercialization of the technology or the associated regulatory hurdles when compared to established institutions or biopharmaceutical manufacturers. For innovative solutions, specific regulatory drug delivery guidance is often lacking and therefore there is an additional burden on the manufacturers to educate the agencies during this process. This lack of a clear regulatory pathway hinders the transition of a product utilizing a novel drug delivery mechanism to the clinical and commercial phases of development. There may be little clarity on how to assess the

product's feasibility and manufacturability, and there often are additional quality requirements compared to conventional technologies such as those related to materials of construction as well as usability.

Emerging Trends in Regulation

While accelerated regulatory pathways do exist, the clinical criteria and timing for these approvals tend to differ widely between countries. Work continues on other mechanisms to gain rapid approvals for novel therapies now being developed and utilized by many individual regulatory agencies in order to bring critical medicines to patients. The clinical phases of development are often condensed and thus at the time when evidence of clinical efficacy is seen the final commercial process may not have been fully developed and characterized.⁸³ If only a few clinical batches have been made, there is less experience and information on the proposed commercial specifications, and less stability data. In addition, transfer to the final commercial manufacturing site might be rate-limiting. These CMC challenges thus need to be discussed with individual regulatory agencies, often at different times, while simultaneously filing marketing applications and continuing global clinical trials as well as negotiating post-approval commitments. The ideal public health goal of reaching as many patients as possible worldwide could therefore take years even in cases of unmet medical need. Most recently, the pharmaceutical industry is experiencing even more pressure to accelerate drug development due to the COVID-19 pandemic. While pressures mount to develop therapies such as a vaccine, anti-viral, cell or gene therapy, immunomodulator, neutralizing antibody or a combination of agents that is an effective COVID-19 treatment, industry as well as health authority regulators are exploring all possibilities to accelerate a viable candidate. These acceleration efforts should be further evaluated and if possible, applied to the development of many of these novel modalities as they too often serve to treat an unmet medical need.

The global ramifications of the current ongoing pandemic on the speed of drug development are already demonstrated by the highly accelerated research efforts for preventative, interventional, and even curative therapeutics which would have been unthinkable even a few months ago. An important example of this is the Moderna mRNA COVID-19 vaccine, which started Phase 1 trials in March 2020 only a few weeks after the initial viral sequence was identified, and at the time of writing has just entered Phase 3 clinical trials in thousands of patients.⁸⁴ Regulators have worked around the clock to assess safety and efficacy of ongoing trials. Repurposing existing drugs is also a challenge as demand fluctuates making supply chain predictions difficult. During this public health emergency, quick actions are necessary and lessons learned from the strategies employed should be utilized and adapted in order to maximize efficiency in the future. Creating and maintaining appropriate manufacturing capacity including regulatory considerations remains a high priority. For example, the harmonization of post-approval change management will help streamline supply chains even with an increase in the number and positioning of various manufacturing sites.

International consensus on quality, safety and efficacy standards for pharmaceuticals facilitates patient access to new therapies. Global harmonization efforts have been ongoing for many decades, exemplified by the collaboration now known as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which was established in 1990. As of May 2020 ICH has 17 Members and 32 Observers including regulators, research-based industry organizations, and non-profit organizations.⁸⁵ Global harmonization on national, regional,

interregional, and international levels is supported by the World Health Organization (WHO), founded in 1948, which is a specialized agency of the United Nations concerned with international public health and is responsible for providing leadership on global health matters including setting standards and providing technical support to countries.⁸⁶ Individual regional harmonization efforts are also ongoing, for example, in Latin America, Africa, the Middle East, and Southeast Asia.

Consultations and coordination among regulators on different continents have of necessity been proactive and very productive during the pandemic. This trend towards better and more productive dialogues with international regulators is very promising and needs to continue to evolve in the direction of performing simultaneous submissions and potentially reliance on scientific reviews by other agencies to facilitate highly accelerated approvals. It provides a framework for potential solutions to some of today's challenges as outlined in the April 2020 statement⁸⁷ from the International Coalition of Medicines Regulatory Authorities (ICMRA), in which all of the members committed to "*working together to ensure the regulatory processes related to COVID-19 are as efficient as possible to support the development and delivery of effective and safe medical products to populations in need worldwide*"; and to "*aligning on regulatory requirements and collaborating on accelerated procedures from the development to the approval, including rolling reviews and approval of trials, drugs, biologics and vaccines*". A recent publication from the Bill and Melinda Gates Foundation calls for national regulatory authorities to facilitate and drive reliance practices through sharing scientific assessment reports for use in others' decision-making processes, and stresses that the ability to accept decisions made by trusted reference countries will support accelerated global rollout of approved critical products to achieve equitable access.⁸⁸ In addition, WHO recently released their "Good Reliance Practice" document in June 2020 focused on the use of work sharing, joint activities and recognition in order to avoid duplication of efforts.⁸⁹

Other lessons learned from the ongoing pandemic include the unprecedented speed of communication among the various groups collaborating across the globe in the race to develop therapies. Guidance documents are also being published with greater rapidity than ever before, and these documents are valuable to understand the inherent flexibility that will be critical to regulatory assessment and approval. Communication with sponsors and ongoing dialogue will also look very different in the future, with more real-time information-sharing, involving perhaps even collaboration and not competition among different companies, regulators, medical professionals, and academic institutions. Not only have the industry and regulators partnered in the rapid development of suitable therapies, for example through the Emergency Use Authorization and Coronavirus Treatment Acceleration Pathway (CTAP) in the US, but through this partnership flexibility within the post-approval life-cycle management space is being leveraged to ensure manufacturing capacity for a potential COVID-19 therapy, once a treatment is available.⁹⁰

Undoubtedly, during the pandemic the workload throughout the industry is immense, both from the viewpoint of regulators and sponsors. With the dramatic advancements in science being envisioned, there is a high probability that even after the pandemic subsides, the number of novel personalized therapies seeking approval will grow at a faster rate as sponsors look to restart development programs that were delayed by the coronavirus outbreak.⁹¹ Thus, there is more acceptance now of innovative ideas including new applications of artificial intelligence and machine learning that have the potential to make disruptive progress in the efficiency and speed of drug development and totally change the paradigm for the future.

A Look into the Future - Recommendations from an Industry Perspective

Though the challenges that lie ahead may appear daunting for the biotherapeutics industry and regulators, the opportunities for advancement are foreseeable and attainable. In the future, the manufacturing paradigm will change along with the regulatory landscape, as companies must now manage the expansion of therapeutic modalities from synthetics, therapeutic proteins and mAbs to include ever more complicated therapies, including live modalities. With this transition, product portfolios now often consist of over a dozen different modalities that require diverse manufacturing platforms. Large batch fed production is likely no longer the optimal production model, specifically with low volume output, high diversity product portfolios. For these products, modular manufacturing models are more suitable as several products can be produced within a single facility at smaller scales providing the enhanced capability of switching manufacture more easily from one product to another in response to supply needs. For example, MIT researchers have already developed a benchtop system to rapidly manufacture biopharmaceuticals on demand which can be easily reconfigured to produce different drugs, enabling flexible switching between products.⁹² The RNA "printers" being developed by CureVac and its collaborators would be able to make thousands of vaccine candidate doses at the point of use, for example in hospital pharmacies in individual countries around the globe.⁹³

As industry progresses towards personalized/precision therapies for smaller patient populations, we will likely see more and more utilization of modular facilities with turnkey construction/fabrication. Additionally, due to varying regional regulatory requirements and the potential regulatory relief provided to in-country manufacturing, there may be more movement towards in-country, regional modular production. Ultimately, companies will probably want to leverage a mix of manufacturing facilities from large fed-batch production to continuous modular production in order to optimize their manufacturing networks. Manufacturers of the future will increasingly make use of automated networks and hardware that will improve the modular production process. This is because the automated networks will combine their collective computing power to monitor manufacturing and take the appropriate corrective and preventative actions to maintain the proper supply chains. These automated systems will also be capable of analyzing the quality of the drug product during manufacture to make sure that it remains within the appropriate statistical controls. By better harnessing the data available to us in an efficient and automated manner, and by leveraging modular manufacturing technologies we have an opportunity to deliver therapies to patients in an accelerated manner.

In addition to harmonization trends and acceleration options for products with great unmet medical need, the conventional regulatory assessment paradigm will also need to change drastically. In addition to understanding the intricacies of novel modalities and manufacturing technologies upon approval, there has to be a fundamental ability to adapt to the rapid improvement cycles for these new technologies and provide regulatory flexibility in order to keep up to date.⁹⁴ The regulatory paradigms could evolve to a real-time "learning" mode that utilizes the vast amount of data generated by the aforementioned automated systems instead of assessing every post-approval CMC change individually based on outdated platforms or data. Furthermore, regional post-approval lifecycle management activities must be harmonized and based upon science- and risk-based principles as outlined in ICH Q12.⁹⁵ Essentially, a global convergence of regulation provides an optimal setting for accelerated drug development, product lifecycle

management, and the advancement and acceptance of innovative technologies.

At the present time, there is acknowledgement that the pharmaceutical industry is not as “digitally mature” as many other industries; it is one of the least prepared and one of the most inefficient in leveraging the vast amounts of data available in an automated fashion.⁹⁶ In consideration of the fact that the volume of data generated in the biopharmaceutical industry will grow even faster in the future than it does today, innovative solutions for assembling, distributing and reviewing regulatory information are being considered. Structured content and data management (SCDM) solutions, in which data are collated into centrally organized content blocks for use across different documents, may aid in the efficient processing of data, creating opportunities for automation and machine learning in its interpretation. This technology will enable the industry to automate CMC content and data, drive changes in the agency review paradigms, improve filing preparation and review timelines, and enable real-time updates and data tracking. Thus, there is potential to truly drive harmonization of global regulatory filings and agency review processes including fostering connections with other sectors of the healthcare industry.⁹⁷ For instance, increasing this type of interconnectivity could allow for earlier detection of adverse events for marketed and experimental therapeutics or enhance biomarker and target discovery, but most importantly deliver life-altering therapeutics to patients at a faster pace and lower cost.

Applying CMC data and regulatory authoring automation concepts opens the possibilities to perform cloud based regulatory reviews, whereby a sponsor could upload structured Common Technical Document Module 3 content to a web-based cloud. The information uploaded to this cloud could be readily available to health authorities around the world in real time, thus essentially eliminating the common practice currently employed by biopharmaceutical regulatory departments of submitting filings to different regions in “waves”. Thus, in a cloud-based system, an application would be submitted once, concurrently to all health authorities where a product registration is desired or, if already commercially marketed, where a registration exists. Health authorities could benefit from a cloud-based application through real-time, parallel reviews, and potentially an opportunity to leverage harmonized or mutually recognized assessments. The benefits of SCDM and cloud-based regulatory reviews might include decreased filing and review costs, a substantial decrease in review time, concurrent, consistent, and simultaneous global filings, real-time data analysis and assessments, and seamless data updates when required in the post-approval stages. Cloud-based reviews could provide a data exchange ecosystem that transforms and revolutionizes the current country-specific submission and review paradigm. Thus, regulatory innovation for the future can build upon the principles inherent in existing harmonization frameworks such as ICH and WHO. It is acknowledged that a truly global dossier has existing hurdles currently with country-specific laws and regulations because final decisions on regulatory submissions still need to maintain the individual authority mandates, however sharing of scientific content could be envisioned with the adoption of suitable confidentiality agreements. In the US, the FDA has mentioned the idea of having a single worldwide dossier for quality in the cloud. In this future state, textual communication would ideally be limited to approval and rejection letters and applicant responses.⁹⁸ The goal is for industry and health authorities to collaborate in the development of SCDM for CMC applications, to potentially streamline compilation of quality data in regulatory submissions with a coordinated effort for the efficient use of a regulator's review time to make more informed decisions. As an industry we must leverage technology to progress regulatory mechanics to manage the “data

explosion” and to optimize innovative drug development to deliver products faster to patients around the world.

Conclusions

These innovative modalities and the advanced technologies involved in their manufacture are playing an increasingly important and prominent role in addressing major health challenges as well as aspire to bring increasingly significant benefit to patients with traditional incurable indications. However, while the recent COVID-19 pandemic has inspired an unprecedented level of international collaboration, it has also highlighted the shortcomings of the established phased-development of therapeutics to rapidly and effectively respond to an acute health crisis. With the current COVID-19 situation, the health care sector struggles to develop suitable, effective treatments to meet the emergent medical need, as well as to secure manufacturing capacity to successfully supply a potential therapy internationally. The required urgency risks reaching an impasse where progress is limited because innovation and regulation are out of sync. Therefore, it is critical for industry and health authorities to work together towards a confluence of innovation and regulation and accelerate access to life-saving therapeutics to millions around the globe.

Conflicts of Interest

All authors are employees of Amgen Inc (except LG who is a summer intern). All authors contributed to the writing of the report and approved the final version of the manuscript and the decision to submit the manuscript for publication.

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