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PERSPECTIVE

Accelerating Drug Product Development and Approval: Early Development and Evaluation

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Background and Introduction

A major discovery and early development challenge has been and still is how to develop the best and most impactful medicines for patients as fast as possible, two aims that can appear at face value to be contradicting. This is especially the case in recent times, where the modality landscape has expanded significantly to not only include traditional small molecules and proteins, but also peptides, antibody drug conjugates (ADC), a variety of nucleotide-based therapies such as antisense oligonucleotides (ASO), small interfering ribonucleic acids (siRNA), messenger RNAs (mRNA), and cell and gene therapies [1–3] just to name a few. See Fig. 1 (Source data from [4]) for an overview over BLA (Biologics License Application) and NME (New Molecular Entity) applications approved by CDER. From the figure it can be seen that the number of BLAs trends up, while the number of traditional NMEs trend down. Chen *et al.* [5] have looked at this data in further details and accordingly it can be seen that the number of small molecule filings are going down while the number of protein therapeutics are increasing. All modalities have their own requirements for preclinical and drug product development, which can lead to complexity and attrition [6].

The January 2023 National Institute for Pharmaceutical Technology & Education (NIPTE) pathfinding workshop on accelerating drug product development and approval, the "Early Development and Evaluation" session was focused on development barriers within four aspects – chemistry, manufacturing and controls (CMC), drug delivery, enabling technologies and regulatory barriers; and then providing solutions to the most critical aspects. The barriers identified by participants are summarized in Table I.

As summarized in the table and further outlined in the face-to-face discussions, drug delivery and CMC barriers will slow down late discovery and early development as a result of new science, processes, and downstream capability builds. This is especially true for the new modalities (ADCs, RNA and cell/gene therapies) due to CMC cycles that are very different from more established modalities along with different distribution channels [7, 8]. This also applies for formulation technologies when tailored release profiles and/or sophisticated drug delivery strategies are needed for diseases in hard to access tissues such as the Central Nervous System (CNS) and intracellular targets [9].

In the broader context of preclinical development, the need for simplification and acceleration strategies was identified in two areas: 1) modeling and the use of data/artificial intelligence (AI) and 2) automation. Regarding increased use of computational approaches such as modeling, and AI, the discussion centered around the ability to generate, handle, and make correlations amongst data sets faster, leading to better decisions. An emerging application of using machine learning to detect anomalous particles in liquid formulations

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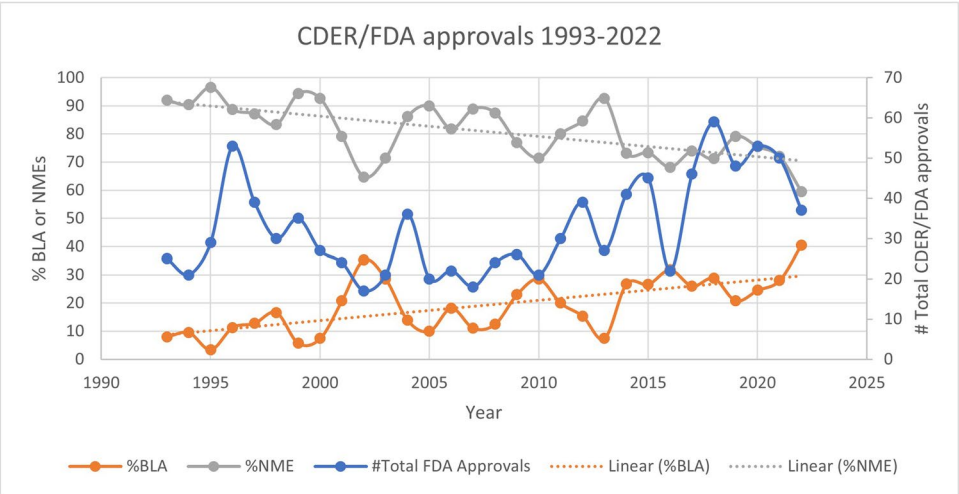

Fig. 1 CDER approvals (NME and BLA) 1993–2022 (adapted from [4]). CBER approvals not included.

through training of a convolutional neural network encoder highlights the potential of using AI/ML technologies to accelerate formulation decisions (see Salami *et al.* [10]). Similarly, deep learning convolutional neural networks have also been explored to detect internal tablet defects (see Ma *et al.* [11]). The need to minimize animal use for ethical reasons [12] and increasing animal access as a barrier was also identified. The context of the automation barriers is related and prevalent in discovery to generate more data faster. The output from automated data generation may coincidentally be an important feed for computational approaches leading to selection of better preclinical candidates. However, an additional important point was identified - that automation could be used more in traditional manual areas of early development such as drug substance and drug product production methods and associated related analytical development needs.

Finally, regulatory considerations, policies and the global landscape in early medicines development were reviewed. The challenges identified were mostly focused around modalities, formulations, processes and other concepts that are new in drug development. Following the introduction of such concepts, there will be a time period where the medicines development community (e.g., pharmaceutical companies, academic partners, contract research/manufacturing organizations, distribution channels, regulatory agencies) coalesces on a process for drug development (see Bak *et al.* [8] for a detailed overview of cell and gene therapy barriers). Reducing this lag time could greatly accelerate time from bench to patient.

Based on the barriers identified in this part of the workshop, three areas were selected for solution development via panel discussions with the participants: 1) New modalities CMC challenges, 2) Accelerating safety/toxicology studies,

Table I Early Development Barriers Related to Drug Product Development and Approval (as Identified by Participants in the Workshop)

Drug Delivery/CMC	Discovery/Preclinical	Enabling Technologies	Regulatory/Global
CMC and drug delivery for new modalities –ADCs, RNA, cell and gene therapies	Poorly soluble small molecules vs getting fast into Phase 1	Handing big data	Barriers originating from operating in a global environment
Formulation and drug delivery technologies with tailored release profiles	Accelerating preclinical toxicology studies	Data readiness for AI/ML	Policies/guidance impacting medicines development (e.g., inflation reduction act)
Automation of DS/DP manufacturing, CMC analytics	Agents to enhance/modify the repose of the active	Personalized/patient centric delivery options	Filing burden in multiple jurisdictions
Synthesis process development such as rewiring for continuous processing	*In vitro* models to predict human performance	Automation implementation and use in pipeline	Guidance for complex formulations
Variability in excipients			Import/export – operating in a global environment

DS: Drug substance; DP: drug product; AI: artificial intelligence; ML: machine learning

and 3) CMC Regulatory Barriers for Novel Technologies and Modalities.

Suggested Acceleration Strategies toward the Selected Barriers

Accelerate Chemistry Manufacturing and Controls of New Modalities

This panel discussed two primary factors impeding acceleration of new modalities' CMC development to help identify solutions. First, it was acknowledged that the speed of development associated with traditional modalities is often aided by leveraging platform bioprocesses and analytical methods built upon the foundation of prior experience and correlation between critical quality attributes and clinical efficacy or safety. These critical quality attributes are interrogated using well-defined methods which enable the development of risk-informed control strategies to ensure adherence to clinically-relevant specifications. Novel modality development often consumes significant time and resources optimizing off-platform technologies that can result in low-yielding processes. Low-yielding processes are not cost effective and hence require iterative design to develop a scalable and robust, commercially viable manufacturing process, thereby slowing development. Commensurately, new product-related impurities with unknown clinical impact can result from the utilization of novel cell lines and purification technologies, which further slow introduction into clinical studies. The new process and product-related impurities subsequently require the development of off-platform analytical methods, thus relinquishing efficiency gains typically associated with established high-throughput analytical tools. Further, the limited ability to extrapolate knowledge from "similar molecules" impedes rapid risk assessments and requires arduous interrogation of impurity profiles including the conduct of additional preclinical studies.

Second, the bio performance of novel modalities can rely on functional excipients such as specialized delivery vehicles or permeation enhancers to deliver the active moiety to the biological site of action. These functional excipients can be novel in and of themselves and have confounding immunogenicity profiles relative to the active of interest, complicating decipherment of critical quality attributes associated with the active versus the excipient. Further, the lack of preclinical models available in early development result in insufficient data to inform linkage of quality attributes to long-term efficacy or safety. Consequently, the CMC control strategies can be ambiguous leading to modifications in process and specifications late in development, potentially delaying product launch.

The panel discussed accelerating CMC understanding of novel modalities between academia, industry, and agencies in 3 categories.

Better Elucidation of the Mechanism of Action With several novel modalities reaching the stages of clinical development and regulatory approval, there is an opportunity to better elucidate the mechanism of action of these novel modalities through academic-industry-agency collaboration. A deeper understanding of the mechanism of action of novel modalities and building preclinical models will help shed light on critical quality attributes necessary for a safe and efficacious product. Clarity on clinically-relevant critical quality attributes can streamline process and analytical development and thereby accelerate the development and launch of such modalities.

Platforms This panel discussed the value of building a pre-competitive knowledge base around common platforms being used for the development of novel modalities. Democratizing foundational scientific data on characteristics and performance of such platforms can accelerate the adoption of the technology across multiple therapeutic targets, consequently setting precedence for future molecules.

Analytical Tool Kit Finally, the panel discussed accelerating the build of a comprehensive analytical toolkit leveraging the expertise from traditional modalities and applying them to novel modalities. As an example, techniques like nuclear magnetic resonance (NMR) are typically associated with small molecule characterization. The panel discussed the untapped potential with cross-modality application of established and novel techniques, further contributing to the democratization of knowledge pre-competitively.

Accelerating Preclinical Toxicology Studies

With the increasing shift from conventional small molecule drugs to as mRNA vaccines, anti-sense oligonucleotides and other biologic-based modalities, there is increasing demand to assess the safety of these drugs in a human-relevant preclinical species. This has increased pressure on the availability of non-human primates resulting in delays and increased costs for the regulatory-required studies. The panel discussion on accelerating preclinical toxicology studies focused on two main points. The adoption of new approach methodologies (NAMs) such as organ-on-a-chip or micro-physiological systems (MPS) and organoids and the adoption of machine learning or other *in silico* approaches. The need for such approaches has also recently been reflected in an article by several Food and Drug Administration (FDA)authors [13].

New Approach Methodologies

There has been a significant investment in the development and use of MPS and organoid systems in the early stages of drug discovery to identify key safety issues early in the discovery process but to date, their use as an alternative to the standard preclinical animal studies has not been widely accepted [14]. Some of this lack of acceptance stems from experimental complexity which leads to some variability in the data being generated making validation challenging. In addition, there remain some engineering challenges with reproducing the complex biology of a human organ.

Use of Machine Learning (ML) and Other *In Silico* Approaches

Machine learning and artificial intelligence has been applied in toxicology for over 30 years and has become increasingly mainstream in the assessment of environmental hazards and bulk chemicals. In pharmaceutical discovery, ML approaches have been widely used early in the discovery phases and have also been incorporated into ICH M7 regulatory guidelines for the Assessment and Control of DNA reactive (mutagenic) impurities [15]. However, historically animal study data has not been captured in a standardized way that would be amenable to machine learning. With the adoption of the CDISC SEND (Standard for Exchange of Nonclinical Data) format for all preclinical study submissions to the US FDA, there is now an opportunity to use preclinical data in machine learning applications. However, the complexity of the data in terms of different study designs, study measurements and other confounding factors such as study location means that the size of data needed may exceed that available within one organization. Data sharing initiatives such as the European Union funded eTRANSAFE [16] project have made some progress in pooling SEND data from multiple pharmaceutical companies with the intent of employing this approach to advance the prediction of the safety profiles of new medicines but perhaps this could be expanded even further. One research topic that has emerged from looking at preclinical data is the opportunity to use a virtual control group in a preclinical study as opposed to the standard concurrent controls used today. Although this would not replace the need for animal testing, it would reduce the numbers of animals required by 25% or more depending on the study design.

Overcoming CMC Regulatory Barriers

While advances in the discovery and development of new modality drugs is very encouraging, the reality of taking the drug through clinical development to achieve successful regulatory approval can be very challenging. Some of the contributing factors are listed below:

1. Complexities of the new drug modalities
2. Limited and/or poor understanding of the mechanism of action of the new drugs
3. Fragility and vulnerability of the patient population
4. Lack of adequate regulatory precedence and regulatory guidance
5. Novelty of the new excipients, formulations, complex manufacturing processes and analytical testing methods
6. Lack of harmonized global regulatory processes to support global clinical trials
7. Changing regulatory environment and government policies

Regulatory bodies are fully supportive of the accelerated development of novel modality drugs and have implemented several initiatives to enable the process. The panel discussions mainly focused on the regulatory initiatives embraced by the US FDA, one of the global health authorities leading and enabling the development of innovative therapies. For example, the FDA has implemented distinct approaches to accelerate the availability of drugs that treat serious diseases that include Priority Review, Breakthrough Therapy, Accelerated Approval and Fast Track. Other FDA initiatives and programs include Critical Path Initiative [17] and Emerging Technology Program (ETP) [18]. In 2016, the US government unveiled the twenty-first Century Cures Act (Cures Act) to further help accelerate medical product development and bring new innovations to patients faster, which allowed the FDA to establish new expedited product development programs, including the Regenerative Medicine Advanced Therapy (RMAT) program [19]. Similarly, several innovation initiatives [20] are adopted by the European Medicines Agency (EMA) to make safe and effective innovative medicines available to patients in a timely manner, which include Accelerating Clinical Trials in the EU (ACT EU) initiative [21] and establishment of Quality Innovation Group [22]. EMA has also been promoting the development of Advanced Therapy Medicinal Products (ATMPs) such as cell/tissue and gene therapies [23].

While there are ample initiatives to support the accelerated development of innovative medicines, the novelty, complexity and the unknowns due to lack of adequate scientific information, understanding of the mechanism of action and precedence hamper the ability of the regulators to assess the safety of these new drugs. These issues are further compounded by the complexity and novelty of the excipients, formulations, manufacturing process and analytical tests, which add to the Chemistry, Manufacturing and Controls (CMC) regulatory challenges.

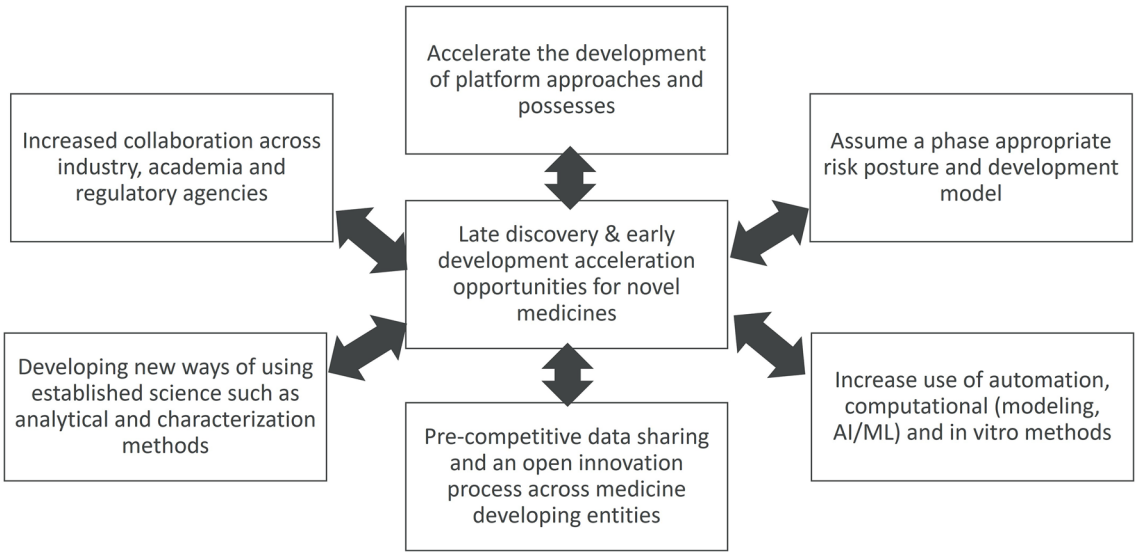

Fig. 2 Key learning/recommendations from the January 2023 NIPTE pathfinding workshop, "Early Development and Evaluation" session.

During the panel discussion, the regulatory team discussed several possible approaches to reduce the regulatory burden and accelerating the advancement of the novel drugs in the clinic. A "phase appropriate" model utilizing risk- and science-based approaches is a viable option for CMC development. Considering the potential involvement of novel technologies, excipients/materials, processes, and testing procedures associated with the new modality drugs, it is prudent to communicate such plans with the Agency before the filing of an Investigational New Drug (IND) to avoid delays during regulatory review. Potential current Good Manufacturing Practices (cGMP) compliance barriers for the manufacture of Phase 1 drug supplies could be handled following the FDA Phase 1 cGMP guidance [24].

Knowledge sharing among the companies was discussed to distribute lessons learned via precompetitive routes. The team discussed operational impediments such as drug importation challenges leading to slow start of clinical trials and cost of supplies impacted by nonrefundable value added tax, contributing to the high cost of clinical trials.

The team emphasized the need for a deeper collaboration between the health authorities and industry to identify practical solutions to overcome the CMC regulatory barriers for speedy development of novel modality drugs. This will require an "outside the box" thinking from the regulators and embracing a firmer reward/risk approach. Recent use of the Emergency Use Authorization (EUA) paradigm to bring novel mRNA vaccines to manage the Covid-19 SARS virus pandemic provides a good example of creative ways to bring lifesaving medicines to the deserving patients in a timely manner.

Conclusion and Perspective

Key learnings from the Early Development and Evaluation session of the NIPTE pathfinding workshop are summarized in Fig. 2. Many of the take-home messages may appear intuitive but researchers involved in medicines development will conclude that these all involve significant new ways of working, redefinition of processes within and in between institutions, and a different relationship to the data that is generated to support new medicines. It will also involve alternate requirements to skills/talents for the people working with the inspiring tasks of bringing new medicines to patients. For example, we focused in on drug delivery and CMC at the workshop and in the article. CMC (as inherent in the acronym: chemistry, manufacturing and controls) used to be a pure chemistry discipline, but today with medicines produced by biological methods and to impact processes in cells, significant biology knowledge is also required.

Lastly, due to the more collaborative environment and with science disciplines mixing (including the influx of data science) there is also a need for a much broader skillset, which includes significant soft skills and business acumen. Therefore, the overarching take home message from the workshop is one of collaboration between key players - science, drug discovery and development wise but also in terms of broadening the scope of current talent and to develop the scientists of the future.

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Author Contributions *Annette Bak:* Organized and introduced session 1 of the NIPTE workshop; used feedback from participants to

frame breakouts; participated in breakouts; drafted introduction, tables and figures, and conclusion of paper; reviewed and commented on all sections.

Rubi Burlage: Hosted one workshop breakout; drafted breakout session of paper; reviewed and commented on all sections.

Nigel Greene: Hosted one workshop breakout; drafted breakout session of paper; reviewed and commented on all sections.

Prabu Nambiar: Hosted one workshop breakout; drafted breakout session of paper; reviewed and commented on all sections.

Xiuling Lu: Workshop organizing committee, Notes from breakout sessions, reviewed and commented on all sections.

Allen Templeton: Organized and introduced session 1 of the workshop; used feedback from participants to frame breakouts; participated in breakouts; edited, reviewed and commented on all sections.

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Declarations

Conflict of Interest The authors of this article have no conflicts of interest to declare.

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