NAVIGATING THE PHARMA R&D REGULATORY LANDSCAPE

2023

INTRODUCTION

In today's rapidly evolving world, the pharmaceutical industry plays a crucial role in enhancing global health and well-being. The industry though requires a deep understanding of the complex web of regulations & guidelines playing a crucial role in ensuring the safety and efficacy of the approved drugs.

From the moment a pharmaceutical drug is conceptualized to its final journey into the hands of patients, countless regulations shape the processes involved. These regulations are put in place to safeguard public health, ensure product quality, and maintain ethical standards within the industry. However, navigating through the ever-changing landscape of regulations can be daunting.

Our 'Navigating the Regulatory Landscape' eBook has been designed to provide you with invaluable insights into the intricacies of regulations & policies surrounding the challenges and opportunities of Real-World Data, genome editing, biomedical informatics, manufacturing and many more.

We would like to invite you to embark on this educational journey with Oxford Global as we unravel invaluable insights and showcase the latest innovation in this space.

Eszter Sutowski Nagy,
Director of Editorial & Event Content,
Oxford Global

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DAMION NERO, Head of Data Science, Takeda

Damion Nero, the Head of Data Science for U.S Medical at Takeda, shares insights into his role in engaging with regulatory agencies in the field of real world evidence (RWE) generation. With over 14 years of experience in real-world evidence research and health economics and outcomes research, Dr. Nero brings a wealth of expertise in using statistics and machine learning methods to analyse large datasets, including administrative claims and electronic medical records.

One of the primary responsibilities in Dr. Nero's role is data acquisition and assessment, which involves ensuring that the data acquired for research is usable and meets the rigorous standards set by regulatory bodies such as the FDA. Dr. Nero emphasizes the importance of submitting real-world data, in addition to clinical trial data, to support claims about the efficacy of drug therapies or devices.

However, acquiring and assessing real-world data comes with its challenges. The data received by healthcare researchers arrives in a variety forms and structures of inconsistent quality. Often, it is sold by individuals or entities that may not fully understand the industry or its specific requirements for data quality. As a result, Dr. Nero and his team need to devote a significant portion of their time to ensuring the data is fit for regulatory submission.

Two major challenges in the regulation of real-world data are quality control and privacy protection. Vendors who provide the data often lack an understanding of what quality control should entail., creating hurdles in maintaining data standards and ensuring that the data meets the necessary criteria. Privacy protection laws are another obstacle, as the data being generated comes from individuals who have a right to have their information protected. Balancing the need to get treatments to patients faster with privacy concerns can be difficult for industry players, and there can be reluctance to share data in part or at all.

Dr. Nero highlights the need for better clarity and guidance in the area of real-world data regulation. Currently, there is a lack of defined standards for the level of real-world evidence data required to gain regulatory confidence in the effectiveness of a drug. This ambiguity needs to be addressed through a collective effort involving pharmaceutical companies, regulators, and legal bodies. Dr. Nero suggests that this collaboration should take place internationally, given the increasingly global nature of data sourcing.

Looking ahead, Dr. Nero predicts that artificial intelligence (AI) will play a significant role in data regulation in healthcare. Advanced AI algorithms, such as ChatGPT and other sophisticated models, will likely be involved in making assessments, developing guidelines, and automating tasks related to data regulation. AI can offer faster and more resource-efficient solutions, which could potentially replace some of the labour-intensive processes currently in place.

While real-world data and its regulation still face significant challenges in meeting the needs of the industry, there is significant promise in the field at present The evaluation and assessment of data quality remains a key hurdle, as does privacy protection. However, with concerted efforts to establish clear guidelines and international collaboration, the field can progress towards a more standardized and effective approach to real-world data regulation.

*The opinions expressed in this text are solely those of the Dr. Nero and not necessarily those of Takeda. Takeda does not guarantee the accuracy or reliability of the information provided herein.

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JOHN PARRINGTON,

Associate Professor of Cellular & Molecular Pharmacology & Fellow of Worcester College, University of College

John Parrington is an Associate Professor in Cellular and Molecular Pharmacology at the University of Oxford. His research focuses on cell signaling, particularly the role of calcium signals in regulating physiological events and their implications for health and disease. To investigate these questions, he utilises genetically modified cells and organisms, including mouse and human melanoma cell lines, as well as genetically modified pigs.

In terms of regulatory considerations, Parrington's work is subject to oversight by the UK's Home Office for animal research and the use of genetically modified organisms (GMOs). The collaboration with his Spanish partner follows the regulations set by the Spanish government and the European Union (EU) regarding GMOs and animal research.

One of the challenges Parrington faces is the changing regulatory landscape due to Brexit. The UK's exit from the EU has brought about changes that may affect the regulations governing his work. Additionally, he highlights the contrasting attitudes towards gene editing and GMOs across different countries, with the EU having more restrictive regulations compared to countries like the USA and China. This discrepancy can pose challenges when it comes to commercialising technologies developed in the EU, such as gene-edited pigs for agricultural purposes.

In terms of future trends, Parrington emphasizes the importance of clear and adaptable regulations in fields like agriculture and medicine. He notes that the UK has a relatively liberal approach to gene editing research, with regulatory bodies like the Human Fertilisation and Embryology Authority (HFEA) being open to approving research on human embryos for scientific purposes. However, he recognizes the need for regulations that prioritize safety and ethical considerations, especially in areas such as clinical gene editing and human reproduction.

Parrington believes that scientific advancements will continue to emerge, and legislation must keep pace with these developments. He mentions ongoing research in human embryology, such as the generation of artificial eggs and sperm from stem cells, which could have profound implications for human reproduction. Balancing the prevention of abuse with the exploration of exciting scientific possibilities is crucial, and collaborative efforts between scientists and policymakers are necessary to develop effective and globally applicable legislation.

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REVISION OF THE EU PHARMA LEGISLATION: A FRAMEWORK FOR INNOVATION

Virginia Acha,
Associate Vice President -
Global Regulatory Policy, MSD

The revision of the EU Pharma Legislation has been a highly anticipated development in the life sciences industry. After 20 years, the European pharmaceutical legislation is undergoing significant changes that will shape the future of the industry. In this article, we will explore the key proposals and their implications for regulatory opportunities and innovation.

Background of the EU Pharma Legislation Revision

The European pharmaceutical legislation comprises a directive from 2001 and a regulation from 2004, collectively known as the general pharmaceutical legislation. These regulations establish the rules and procedures for the use of medicines and research within the European Union. The revision aims to combine these regulations with the orphan regulation and pediatric regulation, streamlining the legislative framework.

Objectives of the Revision

The proposals for the revision of the EU Pharma Legislation aim to address several key objectives:

- Timely and Equitable Access: The revision seeks to ensure that patients have timely access to innovative medicines across all member states of the European Union. Efforts are being made to enhance the security of supply and promote competition in research and development (R&D) and production.
- Environmental Sustainability: The proposed changes aim to make medicines more environmentally sustainable, considering the impact of the pharmaceutical industry on the environment.
- Antimicrobial Resistance: Efforts to combat antimicrobial resistance are being prioritized, with the revision proposing measures to encourage and support initiatives in this area.

Key Changes in the EU Pharma Legislation Revision

Regulatory Data Protection (RDP) Modulation

One of the significant changes proposed in the revision is related to regulatory data protection. The revision suggests introducing new incentives and requirements to improve access to medicines for all parties involved. However, this change poses challenges for the industry, as it may favor the manufacturers of generic and biosimilar drugs.

Enhancing Early Competition

The revision also aims to enhance early competition in the pharmaceutical industry. This includes extending the Bolar provision to pricing and reimbursement in health technology assessment (HTA). These measures aim to promote a competitive environment for R&D and production, encouraging innovation and faster drug approval times.

Improving Transparency and Collaboration

Transparency and collaboration are key aspects of the proposed revision. The changes aim to improve the overall approach to public funding and collaborations within the pharmaceutical industry. Efforts are being made to broaden transparency and ensure effective use of public resources.

Implications and Expectations

The proposals for the revision of the EU Pharma Legislation have raised various expectations and concerns within the industry. While there is a focus on improving access to medicines and addressing regulatory challenges, there are debates about the balance between innovation and access.

Some experts argue that the proposed changes may favor generic and biosimilar manufacturers, potentially impacting innovation in the industry. Others believe that the revision provides an opportunity for regulatory modernization and improved access to medicines for patients across Europe.

Next Steps for the New EU Regulatory Framework

The publication of the proposals for the EU Pharma Legislation revision marks an important milestone. The next steps involve a thorough review of the proposals by relevant stakeholders and regulatory authorities. This review process will help shape the final version of the revised legislation.

After the revision is finalized, it will be essential for industry players, regulatory bodies, and healthcare professionals to adapt to the new framework. Compliance with the revised regulations will be crucial for ensuring timely access to innovative medicines and promoting a competitive and sustainable pharmaceutical industry.

Looking to the Future of Pharma Legislation

The revision of the EU Pharma Legislation is a significant development that will shape the future of the life sciences industry in Europe. The proposals aim to improve access to medicines, enhance competition, and address regulatory challenges. While there are debates about the impact on innovation, the revision provides an opportunity for regulatory modernization and improved patient care. The next steps involve a thorough review process, leading to the finalization of the revised legislation. Industry players must adapt to the new framework to ensure compliance and promote a thriving pharmaceutical industry in Europe.

ARVIND RAO,
Associate Professor of Biostatistics, University of Michigan

In his work, Rao faces challenges at the data, model, and output levels. Data quality and curation are crucial, as good-quality data is essential for accurate results. Complex deep learning models with millions of parameters require careful calibration and verification. Federated learning, which operates within the constraints of decentralised medical data, poses challenges in terms of model drift and calibration. On the output side, quantifying model prediction uncertainty and understanding error propagation are important considerations. Additionally, interpreting AI predictions and integrating AI outputs into human decision-making processes requires attention.

Rao seeks clarity in several areas of regulation. Safety considerations for AI systems in healthcare, data reliability in evolving and learning systems, human-AI hybridization and teaming dynamics, and regulation for combining multiple AI systems from different vendors are among his concerns.

Looking ahead, Rao predicts increased interconnectedness between government, academia, and industry communities in addressing the complexities of AI regulation. He expects a focus on understanding the human-AI ecosystem and trust, including the ethical implications of explainability in a medical-legal context. The issue of misinformation generated by AI models and its impact on the reliability of information will also be a key topic for regulators.

Overall, Rao's insights provide a comprehensive overview of the current challenges, desired clarifications, and future predictions in the regulatory landscape of biomedical informatics and AI in medicine.

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SRIDEVI NAGARAJAN,
Head Digital Regulatory Strategy, AstraZeneca

Sridevi Nagarajan, Head of Digital Strategy at AstraZeneca, was interviewed regarding her job role and thoughts on the regulatory landscape. She described her job as balancing technology and the business of science, using her background in health science research and technology to conceptualise business problems and deliver valuable outcomes in line with the organisational vision. She emphasised the importance of collaborative innovation and the opportunity to interact with both internal and external stakeholders.

Regarding the biggest challenges in regulation at present, Nagarajan highlighted the need for change and the natural human instincts to push back against that change, whether good or bad. She discussed the role of digital technologies in addressing these challenges, with approaches including knowledge sharing and using technology as a tool to understand and solve business problems.

In terms of digital trends influencing regulatory, Nagarajan emphasized the significance of generative AI and its role in presenting facts and convincing with data and information. She also mentioned the importance of natural language processing (NLP) and other AI trends that can be leveraged to meet the growing needs of regulators.

Some of the biggest rising trends in healthcare for Nagarajan included cell and gene therapy, RNA therapy, decentralized and virtual trials, digital therapeutics, and the use of real-world data. From a technology perspective, she highlighted the potential impact of generative AI, NLP, blockchain, and quantum computing on healthcare. She explained how these technologies can improve transparency, collaboration, communication, and the development of new drugs and treatments.

Nagarajan concluded the interview by emphasizing the importance of realising the dream of delivering medicines to patients. She expressed gratitude for the opportunity to discuss digital and the future of healthcare.

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ANDREW ROBERTSON,

Vice President, Head of Global Regulatory Policy and Innovation, Takeda

In the interview, Dr. Andrew Robertson, Head of Global Regulatory Policy and Innovation at Takeda, provides insights into the relationship between the pharmaceutical industry and regulatory agencies.

He emphasizes the crucial role that regulatory agencies play in ensuring the safety and efficacy of drugs for patients. These agencies provide a level of review and assurance that patients are receiving safe and effective treatments for their diseases, while also holding the industry accountable for meeting high standards.

Robertson explains that interactions with regulatory agencies begin early in the drug development process to ensure that the development strategies and clinical trial designs align with regulatory requirements. This partnership continues throughout the entire lifecycle of the drug, including post-approval, to ensure that marketed drugs continue to meet their intended outcomes. Collaboration with regulatory agencies is essential to maintain a strong level of innovation while prioritising patient safety.

The balance between innovation and safety is a key consideration for regulatory policy. Robertson emphasizes that safety is always a priority and that decisions regarding drug development take into account the disease context, existing treatments, and the impact on patients' lives. The benefit-risk profile of a drug is evaluated, and a holistic approach is taken to determine the best options and opportunities for patients. Innovation is pursued in the interest of patients, rather than for its own sake.

Regarding the regulatory paradigm, Robertson believes that it is currently fit-for-purpose but acknowledges the need for ongoing evaluation and adaptation. He points to the example of the COVID-19 pandemic, where the collaboration between regulatory agencies and pharmaceutical companies led to the rapid development of vaccines, diagnostics and treatements. The regulatory processes need to support high levels of innovation and expedite the development of treatments for various diseases. For instance, in the case of gene therapies for rare paediatric diseases, Robertson highlights the importance of finding solutions that allow for feasible and meaningful studies without compromising safety and efficacy. Creating a sustained and efficient approach to partnership with regulators begins with a foundation of science. Robertson emphasizes the importance of presenting data to regulatory agencies to demonstrate the possibilities and anticipated outcomes. Flexibility is necessary to accommodate different contexts, while predictability in decision-making allows companies to take risks in a proactive and informed manner. Open lines of communication and ongoing dialogue are essential for a successful partnership.

The reauthorization of the Prescription Drug User Fee Act (PDUFA) every five years is a significant factor in the US regulatory outlook. It establishes the relationship between the industry and the FDA, ensuring that drug applications are reviewed within specific timelines. The reauthorization process provides an opportunity to evaluate existing tools and seek guidance on emerging issues, such as the use of digital endpoints and real-world evidence. The goal is to expedite and improve the efficiency of drug development.

Working globally requires considering the regulatory requirements of multiple countries. Robertson mentions the influence of the FDA and the need to collaborate with regulatory agencies in Europe, Japan, Australia, China, and Latin America. Patient demographics, standards of care, and the ability to conduct clinical trials efficiently in each country must be taken into account. Harmonization of regulatory approaches across countries can simplify the drug development process and reduce the burden of navigating different regulatory systems.

Looking ahead, Robertson highlights key issues in working with regulators, such as integrating innovative technologies like wearables and cloud-based data exchanges. However, he emphasizes that predictability, transparency, and mutual understanding of industry and regulatory priorities are fundamental. The ultimate goal is to benefit patients while maintaining effective regulation.

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GOOD MANUFACTURING PRACTICES: OVERCOMING REGULATORY APPROVAL HURDLES

Securing regulatory approval is often the end goal in the development of a new therapeutic product. But what steps can be taken to avoid some of the common curveballs encountered in the industry?

Good manufacturing practices – known in the industry as GMPs – exist to ensure the therapeutic supply chain is responsibly run and well-regulated. GMPs require that manufacturers and packagers of therapeutics take proactive steps to ensure product safety, purity, and efficacy. However, there is no unified agent responsible for enforcing GMPs and pharmaceutical regulatory affairs. These are upheld by national or international regulatory bodies such as the FDA, the European Medicines Agency (EMA), and the UK's Medicines and Healthcare Products Regulatory Agency (MHRA).

As a consequence, developing or trialling a new product across regulatory jurisdictions can pose headaches for the companies behind these experimental treatments. Other challenges can arise in the process of assay development, particularly concerning the use of materials. Securing regulatory approval is often the end goal in the development of a new therapeutic product. But what steps can be taken to avoid some of the common industry curveballs?

Good Manufacturing Practices: Navigating the Regulatory Obstacle Course

Marta Freitas, Principal Scientist at Quell Therapeutics, works on quality control for the validation of new treatments. In her experience, a complication of certain requirements for manufacture such as GMPs is that different regulators may pursue different criteria. "That can be challenging when you're trying to submit your documentation in an early stage," she said. Since the UK is no longer part of the EMA, the legislative process for licencing medicines and approving new treatments across regulatory zones has become more complicated.

> **"Have all your ducks in a row... make sure you've got every aspect of your process and your risk assessment ready to go."**

Subsequently, a key advantage in the pursuit of approval is to nail down a workable approach right at the start of the development cycle. "Trying to get that early-stage understanding and agreement between the regulators at the beginning is crucial", agreed Amina Al-Mossawi, Regulatory Manager of Pharmaceuticals at UCL. "Understanding what the regulatory requirements are right from the start and having that understanding and that communication will hopefully save a lot of time."

Another aspect highlighted by Al-Mossawi is ensuring the actual process of validation and approval is as simple as possible. "Have all your ducks in a row," she advised: "make sure you've got every aspect of your process and your risk assessment of your scientific justification all aligned and ready to go." In addition, avoid posing open-ended questions. "At the end of it they're going to question you as to whether you know your process better or not." This is particularly relevant in the case of potency assays and pharmaceutical regulatory affairs.

Quality Control in Assay Development

In Freitas' experience, one of the bigger challenges associated with quality control is developing a good potency assay which shows the product is working as intended. "It's really important to understand the list of assays that you need to fully characterise your product and make sure that whenever it's released for the patient it's safe and efficient," she explained.

Often, regulators are looking for alignment between a potency assay and associated method of action (MOA). Successful potency assays should demonstrate usable biomarkers or representative assays. However, shifting timeframes can pose another hurdle to defining potency and manufacturing assays. In non-oncology settings, researchers may find that primary endpoints for the phase II study align poorly with the associated potency assay.

Subsequently, a key consideration for securing regulatory approval is ensuring every assay is aligned. Rather than constantly submitting different applications and having regulators repeatedly chasing them back with questions, a better approach is to be proactive in predicting what will be asked for. "If you make all of your anticipated changes that you're going to have with your phase I and phase II assays, you'll make a lot more headway," said Al-Mossawi.

Supply and Demand for Larger Patient Groups

Another focus with production and supply is being able to develop the required therapeutic at the right quantities. Jenny Prange is Head of GMP Production, Chief Scientific Officer and Co-Founder at Muvon Therapeutics. A biotechnologist by training, her company offers muscle regeneration therapy to patients suffering from stress urinary incontinence.

The product being developed by Prange and her team is autologous, so batches are produced at a rate of one per patient. "It's not really that we have to target a lot of patients with one clinical production, it's rather having the capacity to run several productions in parallel," she explained. This can be a limiting factor in the move to upscale in accordance with pharmaceutical regulatory affairs.

"It's about having a good strategy to scale up your entire process," agreed Freitas. "It's thinking in advance about how you can meet that demand so you don't face a hard stop when you actually get to that point." Adequate strategic provision is a key tenet to success, as is working with the regulators to ensure the approval process is as smooth as possible.

Good Manufacturing Practices and Patient Proximity: Therapeutics Across Regulatory Borders

Being as close as possible to the patient during manufacture is another important challenge. Freitas spoke of her experience in a previous company with patients in the US, but the product was manufactured in the UK. "That's adding pressure to the process to try and have the product out as soon as possible," she explained. In the case of autologous therapies, this can mean a long and costly journey for the product.

Many companies and suppliers are now moving towards decentralised procedures where a product is part-manufactured, then finished and released at the bedside. "That way the patient can receive it as fresh as possible without too much time elapsing between the actual manufacture and the patient receiving it," said Al-Mossawi. "I think we're still working towards decentralised, point of care manufacturing – we'll have to see where we're heading towards and what that leads to."

However, aligning approaches with GMP guidelines can pose individual complications as well. "Specifically when it comes to your GMP manufacture and you're undergoing part manufacture within the GMP facility, that has its own challenges within the training and the regulatory requirements," continued Al-Mossawi. "Going on to the bedside of the patient, you lose control of the environmental factors and how they're going to finish off the manufacture of that product remotely."

While it can be difficult to know in advance the best materials to use for production, this is a crucial decision that can affect cost and material usage further down the line. Manufacture in accordance with correct development protocol represents a complicated challenge, but with adequate investment of both time and money at an early stage, clinical trials developed at the bedside could be achievable. The key for success in pharmaceutical regulatory affairs is to work proactively with GMP guidelines and the necessary regulators from the outset.

APPROACHES TO COMBINATIONAL IMMUNOTHERAPIES: FROM CLINIC TO APPROVAL

Our panel discussing combination therapeutics addresses challenges, modelling, and the importance of biomarkers.

Biomarkers & Immuno US 2022 featured a wide range of fascinating panel discussions prospecting the present and future of combination immunotherapy. The workshop Advances in Combination Therapeutics included a compelling panel discussion section on the Approach from Clinic to Approval.

Moderating the panel was Russell LaMontagne, President and Chief Executive Officer of Boston Immune Technologies and Therapeutics. Joining him on the panel was Pravin Kaumaya, Professor of Medicine at Ohio State University Medical School.

Kaumaya kicked off the discussion by outlining that combinational immunotherapy has focused on the use of immune checkpoint inhibitors (ICIs) in tandem with various other strategies. Radiation, chemotherapy, and targeted therapies have all taken combinational approaches to treatment with ICIs.

The ICIs that are so far approved by the FDA target PD-1 (nivolumab and pembrolizumab), CTLA4 (ipilimumab), and PDL-1 (atezolizumab, avelumab, and durvalumab). Kaumaya noted that there has since been a large volume of ongoing research in combining those immune checkpoint inhibitors together — "as well as the new and emerging ones like LAG3, TIGIT, et cetera," he said.

Evidence from the clinic when comparing the outcomes of monotherapies and combinatorial approaches highlights prolonged benefit for some patients, while others can experience toxicity. Because of this, Kaumaya stressed the need for researchers to focus on dosing type and volume when working with monoclonal antibodies.

Challenges with the Development of Combination Immunotherapy

LaMontange pointed out that one goal of using ICIs was to improve the efficacy of other immunotherapeutic modalities. However, he said that "the challenges that you deal with in the immune system are complex. For example, the fact that these antibodies are expressed on many cell types that respond and interact with each other."

There are further issues that emerge from designing trials for combination therapies. One problem in doing so is the fact that it is uncommon to have naïve patients: "The patients in those trials have distorted immune systems — so, who knows if your marker is expressed or not?"

Until more recent data, the first generation of combination products had low efficacy, but LaMontagne wondered whether this was due to inadequately designed trials. He explained: "we need to work out how to design trials to understand what is effective or not." One important question is what sort of toxicity can be expected: "these are pretty aggressive diseases by the time you get to these investigational therapies, but the toxicities are high too."

A key objective concerns patient population and investigating which patients that are going to respond to antibody treatment. LaMontagne exemplified this:

> **"We found that in mouse studies, it wasn't as simple as just combining two therapies. In our studies, the sequence of administration impacted the efficacy of the combination with PD-1."**

LaMontagne's team had thought to swap the order of the drugs administered due to similar scenarios emerging from earlier studies. Therefore, better modelling and novel trial designs were recommended by LaMontagne to tackle the specific challenges of combination approaches. Translating

Animal Models to In-Human Studies

One audience member asked how confident the panel were that animal data will be informative for human trials. For instance, if the preclinical animal data shows that a therapy needs to be administered first and checkpoint inhibitors after, will this need to be addressed using separate human cohorts? Doing so may run the risk of complicating clinical development and increasing cost significantly.

Kaumaya weighed in on this question, answering, "Of course the mouse immune system is not a one-to-one recapitulation, but it does provide a good indication as to where to go and how to refine things." Furthermore, he noted that preclinical testing "has to start somewhere," and that animal modelling was an important part of guiding researchers on how to move forward.

He mentioned that there are a number of different potential models for preclinical testing, including humanised mice for monotherapies and dual therapies. Comprehensive models for immunotherapies include dogs and non-human primates. "However, non-human primates are not looked on very favourably upon by National Institutes of Health because of the number of the animals available," Kaumaya added.

Biomarkers, Dosing, and Future Outlook

According to Kaumaya, biomarkers are vital for picking the right combination for the right population. Preclinical studies in mice can guide researchers in combinations of checkpoint inhibitors with other modalities like oncoviruses, chemotherapy, and radiotherapy. However, Kaumaya predicted that targeted therapies and finding their right doses will unveil the prodigy for immunotherapy.

LaMontagne noted that the very concept of immuno-oncology was still young, "so there is still a lot to be learned." Significantly, his team believe that they have identified a potential biomarker which they are finding new and challenging.

> **"You really have to invent your biomarker for your drug if you are going to try and move it forward, I don't think there's a way to do it otherwise,"**

Furthermore on the subject of dosing, it is notable that ICIs for PD-1 and PDL1, as well as targeted therapies, are administered in combination with chemotherapy. Kaumaya said that "everything is given with chemotherapy; the question revolves around dosing and the regimen that you use."

At its current stage, the field of immuno-oncology and combinatorial approaches therein is vast and open: "hopefully we'll learn more as various labs continue to work on it," added Kaumaya. "The number of combination immunotherapies being tested in clinical and preclinical studies is mind-boggling. So, we will likely learn much more as we move forward."

SELECTION BIOMARKERS: SHAPING THE FUTURE OF DRUG DEVELOPMENT AND REGULATORY APPROVAL

While constraints on the integration of NGS approaches in selection biomarker validation for new treatments still need ironing out, their benefits in assisting clinical trial progress are undeniable.

When it comes to validating the efficacy of new drugs and therapeutics for future use, biomarkers are a surefire means of assessing a treatment's method of action (MOA). Functionally speaking, selection biomarkers as validation methods ensure therapeutics are, like a good darts player, precise and accurate. This is increasingly key for securing regulatory approval, as Elizabeth Sheppard, Global Pricing & Market Access Director for Oncology Diagnostics at AstraZeneca, explained at Biomarkers 2023.

An Overview of Selection Biomarkers

In oncology, selection biomarkers are characteristics of certain conditions that may be measured in a patient's tumour or bodily fluids. They can be used to identify patients who are most likely to benefit from a specific treatment while avoiding exposure to ineffective treatments. Selection biomarkers can be crucial to securing regulatory approval for a therapeutic in development by signposting its efficacy, or by pointing researchers towards alternative treatment approaches.

Implementing patient advocacy groups is one way to increase access to and improve communication between clinicians and patients.

> **"Almost eight in ten women diagnosed with breast cancer today are predicted to survive their disease for at least ten years... when you think about biomarker-targeted therapy, that's huge."**

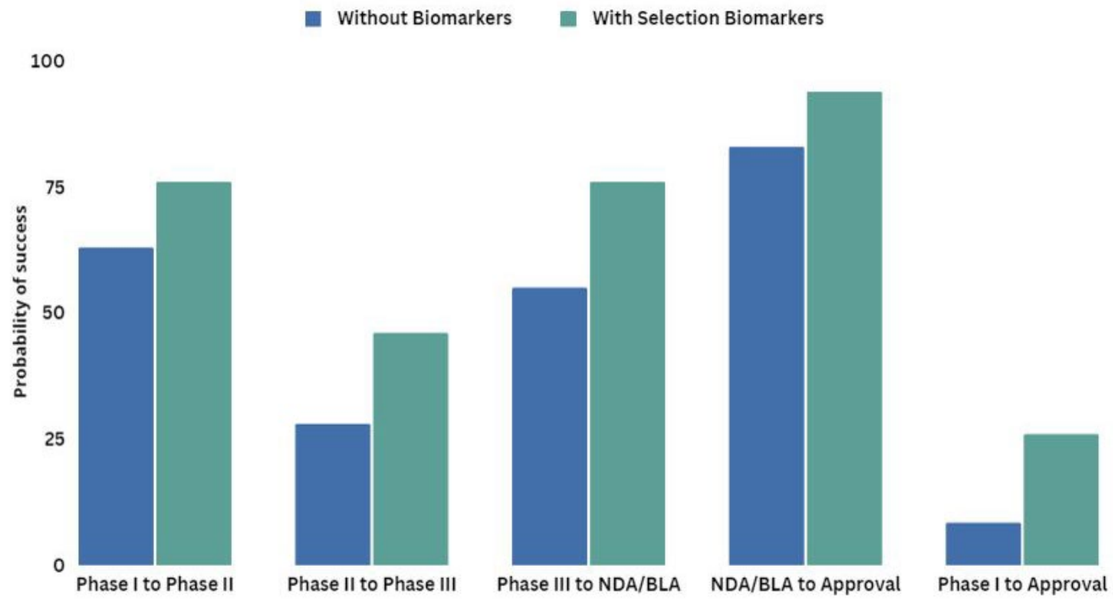
Several kinds of selection biomarkers are used in oncology, including genetic biomarkers, protein biomarkers, and imaging biomarkers — biomarkers based on imaging techniques, such as MRI scans. Some examples of selection biomarkers in oncology include the HER2 protein in breast cancer, which is used to determine if a patient is a candidate for targeted therapy with drugs such as trastuzumab, and the EGFR mutation in lung cancer, which is used to predict responses to EGFR inhibitors.

Elizabeth Sheppard has worked in the oncological field of precision medicine for a significant portion of her career, and has seen improvements in treatment options for patients with breast cancer as they can be increasingly tailored to their specific needs without risking side effects. "Overall, almost eight in ten women diagnosed with breast cancer today are predicted to survive their disease for at least ten years or longer," she said. "When you think about biomarker-targeted therapy and biomarker-targeted production, that's huge."

Targeted Therapies and Selection Biomarkers in Regulatory Approval

In the context of oncology agents, selection biomarkers have proven to be instrumental in increasing the likelihood of clinical trial success. As Sheppard explains, 75% of all new drugs for solid cancer approved by the FDA in 2021 were targeted therapies. Across the Atlantic, 86% of all new drugs for solid cancer approved by the EMA in 2020 were targeted therapies. While biomarker testing rates vary by region and type — uptake is highest for established biomarkers such as HER2 for breast cancer and BRAF for melanoma — the probability of trial success with selection biomarkers is much higher.

"If anyone knows how expensive clinical trials are, what does 17.5% actually mean?", asked Sheppard. This is the difference in the likelihood of a new therapeutic progressing from Phase I to approval with a selection biomarker (25.9%) versus without a selection



biomarker (8.4%). While the argument for including selection biomarkers in the validation methods for the development of a new therapeutic is concrete, integrating biomarker testing approaches can require some planning and consideration. "Getting the actual technology is key, because comprehensive next-gen sequencing is really expensive," explained Sheppard. "Centralised laboratories are becoming more apparent because it's a little easier to get all the rests to go to one place and it's a little more economical."

Current Barriers to the Broader Update of NGS in Oncology Clinical Practice

While the significance of selection biomarkers in achieving regulatory approval for cancer treatments is clear, there are a range of barriers that impede the broader uptake of next-gen sequencing (NGS) approaches in clinical practice to facilitate this. One of the biggest obstacles is the existing policy environment and infrastructure, concerning the implementation of NGS healthcare strategies: at present, there is a shortage of dedicated personnel and funding for NGS. Other issues include a lack of synchronisation between regulatory processes for treatment and diagnostics, as well as a limited awareness of the opportunities presented by NGS for healthcare policymakers.

Additionally, there are significant variations across Europe in terms of test access, multi-biomarker access and test quality, and at present there is a lack of standards to evaluate novel biomarkers and technologies. "Regulatory framework also plays an important part," added Sheppard. These frameworks for biomarkers and precision medicine can vary by country, and are evolving significantly in both the EU and China. Greater consistency across national borders will help selection biomarkers to become more widespread as validation methods for precision medicine treatments.

Tomorrow's Forecast for Selection Biomarkers in Precision Medicine

While constraints for the integration of NGS approaches in selection biomarker validation for new treatments will likely continue to be an issue in the coming years, the benefits are undeniable. "Prior to the advent of precision medicine, the treatment options for breast cancer were not tailored to the conditions of patients and had significant side effects," said Sheppard. "It's really helped us in finding the genetic information in the specific understanding of responses."

Conventional approaches to cancer treatment have been superseded by more nuanced approaches, with a greater degree of variability for an individual patient's condition enabled by selection biomarkers as validation methods. Testing for biomarkers can guide the use of precision medicines by selecting treatments that are most likely to work for a specific patient, rather than taking a more generalised approach to treatment provision and therapy.