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Review Article

REGULATORY CHALLENGES AND LANDSCAPES OF MONOCLONAL ANTIBODY REGISTRATION: GLOBAL OUTLOOK

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ABSTRACT

Objective: This review aims to illuminate the unprecedented growth and versatile therapeutic landscape of monoclonal antibody (mAb) products, highlighting their significant impact on diverse medical fields such as oncology, septicemia treatment, infection management, and substance abuse disorder interventions. This review outlines the challenges associated with the development, manufacturing, and regulatory approval of monoclonal antibodies, emphasizing the need for diligent attention to overcome these complexities. The review comprehensively examines the historical evolution and therapeutic applications of monoclonal antibodies, emphasizing their potent and versatile characteristics that have enabled successful interventions in challenging regulatory approvals. It delves into the critical considerations in manufacturing, regulatory navigation, and the strategic integration of expedited approval pathways, providing a holistic understanding of the intricate terrain of innovation, clinical translation, and impactful patient care in the realm of monoclonal antibody products. Monoclonal antibodies have significantly advanced medical treatment in various domains, revolutionizing cancer therapy, offering new avenues for septicemia management, augmenting the arsenal against infections, and opening novel pathways for addressing substance abuse disorders. Their development and regulatory approval are associated with challenges of scientific innovation, manufacturing, and regulatory compliance. Despite the challenges, monoclonal antibodies have demonstrated remarkable potential in addressing complex medical conditions. The review serves as a compass, guiding researchers, clinicians, and regulatory authorities through the intricate terrain of monoclonal antibody innovation and clinical translation. It emphasizes the need for diligent attention to overcome the complexities associated with their development and regulatory approval while highlighting their significant impact on advancing patient care.

Keywords: Monoclonal antibody, Oncology, Septicemia, Substance abuse, Regulatory approval, Expedited approval

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INTRODUCTION

Monoclonal antibodies (mAbs) are immunoglobulins with a specificity that are generated by using a monoclonal cell line. They represent an enormous category of therapeutic biological products that continue to impact contemporary medical practice, encompassing a wide range of clinical indications. Monoclonal antibodies have taken over the biological therapeutic market in recent years, and there are hundreds of distinctive monoclonal antibodies and mAb-like proteins in research and development. The commercialization of therapeutic mAbs can be mostly due to specificity as well as the advancements in technology that have propelled their growth. Monoclonal antibodies, however, are structurally and functionally complex proteins because they contain numerous functional domains in a single molecule. This has effects on how they are produced, how quality is monitored, and how they are regulated [1].

A successful mAb development program depends on several factors, including high product quality, an adequate preclinical pharmacology and toxicology testing program, and carefully planned clinical trials. However, there are regulatory difficulties with protein products like monoclonal antibodies. Though the accumulated knowledge of these protein products makes it simpler to evaluate their safety, the extraction of biological sources and the development of methods used to develop these products necessitate a constant evaluation of safety concerns [2, 3].

Monoclonal antibodies can recognize and bind a wide variety of molecules, primarily proteins, with high specificity. This ability has been widely used in diagnostics to identify hormones, vitamins, cytokines, allergens, several tumor markers, and various indicators associated with many diseases, including microbial infections [4]. Due to these characteristics, monoclonal antibodies represent the molecules that are most frequently utilized in the fields of clinical evaluation, biomarker identification, and therapeutic target identification.

The market for monoclonal antibodies therapeutics was just $0.3 billion in the world in 1997, but it grew quickly to $186 billion in 2021. The market is anticipated to surpass 445 billion US Dollar (USD) by 2028, exhibiting a compound annual growth rate (CAGR) of 13.2% from 2022 to 2028, despite a multitude of active preclinical and clinical investigations. The therapeutic monoclonal antibody market is expanding quickly and has enormous potential for growth in the United States of America (US), Europe, and Japan's healthcare sector. Due to their sustained investment in research and development, US companies have the majority of authorized antibodies and the highest market share [5].

The focus of this article is to understand the regulatory and approval landscapes by understanding the factors regarding the innovation of monoclonal antibody products as well as challenges regarding Chemistry Manufacture Control (CMC) development, manufacturing, and regulatory compliance. This article also gives insights into the approval pathways of monoclonal antibodies in various countries and their expedited pathway to market these products to the global population.

DISCUSSION

Since the creation of the initial monoclonal antibody in 1975 and the first monoclonal antibody receiving complete regulatory approval in 1986, the realm of monoclonal antibody development has provided a novel method for focusing on specific modifications and defects in the structure of proteins and expression in a variety

of medical conditions and illnesses. Humanized monoclonal antibodies are presently the category of biotechnology-derived entities in clinical investigations that are evolving quickly due to significant recent advances in genetic sequencing and the application of fundamental medical research into clinical practice. The global antibody industry is estimated to be worth USD 20 billion annually [6, 7].

The regulatory landscape of the monoclonal antibodies

The regulatory review procedure has to coordinate the advantages of making newly developed medications available with the costs and advantages of postponing release while possible safety issues are thoroughly assessed. A successful medication development program must include well-planned clinical trials, preclinical research, and careful consideration of product design and production. Title 21 of the Code of Regulations (21 CFR) for the USA, sets forth government rules that must be followed while developing drugs. The US FDA has published a series of guidance documents that reflect the agency's current thinking on a variety of issues, such as the characterization of preclinical and clinical research processes, manufacturing methods, and scientific methods. The "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" guideline is especially relevant to monoclonal antibody development [8].

To promote the global development of medicines, the International Conference on Harmonization (ICH), which is made up of researchers from governmental regulatory agencies in the United States, Europe, and Japan, publishes guidance documents on nonclinical pharmacology/toxicology, manufacturing, and product quality [8] Refer to table 1.

Usually, there are a total of four phases to the clinical investigation process. Initial human trials are represented under Phase 1[9]. These trials' main goal is to pinpoint an effective dose that does not have any obvious major safety concerns. Almost all individuals with cancer participate in phase 1 trials for cancer treatment, which generally involve 10 to 50 people. There are two factors at play here:

1. The concerns of anticancer medication toxicity are so high that it would not be morally acceptable to expose healthy persons to them.

2. Tumor-specific pharmacology is required to assess the pharmacologic effects of anti-cancer medicines which do not exist in healthy patients.

For instance, only people with the tumor can be used to evaluate an oncology drug action by looking at how it affects an enzyme or antigen that is particular to the tumor [10].

Table 1: List of guidance documents published by ICH for monoclonal antibody development

S. No.	Guideline	References
1	Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) Q11, 2012.	[9]
2	Pharmacovigilance planning E2E, 2004.	[9]
3	Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E, 2004.	[9]
4	Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A. 1999.	[9]
5	Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B, 1999.	[9]

Phase 2 trials involve around 200 to 300 patients who are exposed to experimental treatments, aiming to gather initial insights into important effects against tumors and treatment-related impacts. These effects might include measurable outcomes like objective response rates. On the other hand, Phase 3 trials focus on establishing the clinical benefits of anti-cancer therapies. This is usually achieved by demonstrating their impact on patient survival and disease progression, such as progression-free or disease-free survival. The studies were carefully designed to separate the effects of the treatment from other treatments and the natural progression of the cancer. Rigorous controls are implemented, often through randomization and comparison with a designated control group. These Phase 3 trials are essential for proving the treatment's efficacy and are executed with high standards [8–10].

Moving to Phase 4 studies are conducted after a product has gained marketing authorization. The nature of these studies, whether randomized or controlled, depends on the specific question to be answered. For example, they may include establishing safety and efficacy in patient populations not included in the original application, in children or the elderly, in people with new medical problems, or in people at different stages of the disease [8–10]. These studies could also aim to optimize dosing or scheduling and gather extra safety data, like information about the immune response.

Approval landscape of the monoclonal antibodies

There were about 162 antibody treatments authorized by a minimum of one drug regulatory agency as of 30 June 2022, nine of which were subsequently discontinued. According to the number of worldwide authorizations, just three pharmaceutical regulatory organizations, which are the Food and Drug Administration (FDA) in the USA, the European Medicines Agency in Europe, and the Pharmaceuticals and Medical Devices Agency in Japan, were responsible for the first approval of 93% of antibody treatments. The remaining 7% of antibody therapies were initially approved by Canada, Brazil, Cuba, India, and Russia [11].

In comparison to other nations and areas, the US has the most approvals. It took the FDA 8 additional years before it approved the second antibody therapy in 1994 after the first antibody therapy (OKT3) was authorized in 1986. This was Abciximab, an anti-clotting medication used to treat cardiovascular disease that works by attaching to the αIIbβ3 integrin. Every year since 2000, the FDA has authorized a minimum of one antibody treatment. Due to this, the US has been the country with the most antibody treatment approvals for over twenty years [11].

The first antibody therapy approved in Europe is nebacumab, an anti-endotoxin antibody for the treatment of sepsis. The only human IgM antibody ever produced, nebacumab, was discontinued in 1993 because subsequent clinical trials showed that it did not lower mortality. Between 1995 and 2014, European Medicine Agency (EMA) approved just over 5 antibodies per year, but as of 2015, the total number of approved antibodies has increased to more than 10 [11].

In terms of clinical trials and approvals, Japan trails behind the USA and Europe by around ten years. However, during the past ten years, Japan has seen a remarkable advancement in mAb therapy. The first antibody approved in Japan is anti-CD52 alemtuzumab, a humanized antibody developed by Sanofi Genzyme for the treatment of cancers of the myeloid and lymphatic systems. The first domestically produced antibody to be approved in Japan was tocilizumab, a humanized antibody that attacks the interleukin 6 receptor (IL-6R), used to treat rheumatoid arthritis in 2005. Since then, especially after 2014, the number of approvals in Japan has gradually increased [11]

Factors for increased mAb innovation

Multiple driving forces have contributed to the successful development of mAb innovation. These include advances in molecular biology technology, a better understanding of therapeutic targets as a result of scientific research, an enhanced level of familiarity with this class of drugs among developers and regulators, and regulatory actions that promote accelerated drug development.

As a result of knowledge gained from the human genome project, genomics, and proteomics, there is an impending increase in new targets for cancer treatment. The proper techniques and data must be supplied to guarantee that the clinical trials and regulatory requirements for the authorization of mAbs targeted for desired conditions are met. However, a flexible, case-specific approach to biologics evaluation is required due to the uniqueness of each product and the rapidly advancing technology for antibody production. A solid scientific understanding of relative benefits and dangers should serve as the foundation for this strategy [10, 12].

Therapeutic areas

Monoclonal antibodies have the highest and fastest-growing market share in the biological pharmaceutical business and are now used to treat infections, cancer, and chronic inflammatory diseases. In addition to paving the way for customized medicine and making it possible to track a patient's reaction to therapy, monoclonal antibodies have also produced a wide range of innovative medications for the treatment of disease. Monoclonal antibodies are being used to treat several conditions, including cancer, immune-mediated disorders, multiple sclerosis, age-related macular degeneration, osteoporosis, and asthma. Additionally, they are being studied for the treatment of migraines, the prevention of central nervous system diseases like Alzheimer's disease, and metabolic diseases like diabetes. Therapeutic monoclonal antibodies have the potential to attach to a variety of antigens on the surface of cancer and tumor cells. They can also be used to deliver a variety of payloads to the target cells, including specific killer cell types, radioactive ligands, cytokines, poisons, drug-loaded liposomes, and radioactive ligands [14]. These antibodies, often referred to as immunoconjugates, can destroy cells directly or internalize cells and release payloads there. They are explained as antibodies that have been joined to another molecule, such as a radioisotope, toxin, or label [13-15]. Refer to fig. 1 for the mAb mechanism of action.

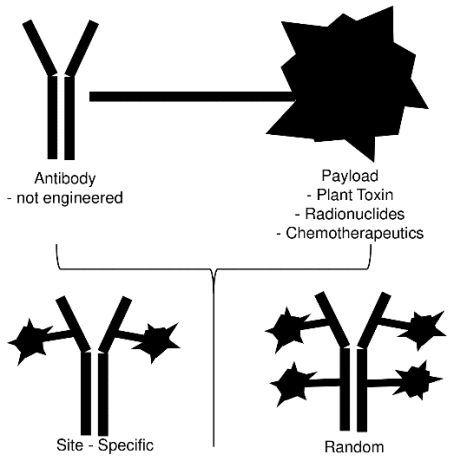

Fig. 1: Schematic representation of different types of antibody-drug conjugates (ADCs) and their components [13]

Monoclonal antibodies find predominant medical applications in oncology, immunology, and hematology, extending to diverse targets. These antibodies exhibit a range of disease indications, with a cancer-related aspect, covering conditions like lymphoma, myeloma, melanoma, glioblastoma, neuroblastoma, sarcoma, colorectal, lung, breast, ovarian, and head and neck cancers. Oncology remains the prime domain for monoclonal antibody therapy, often targeting immune checkpoint proteins like PD-1 (nivolumab, pembrolizumab), CTLA-4 (ipilimumab), and PD-L1 (durvalumab, atezolizumab). Additionally, the biological disease modifier Adalimumab effectively treats TNF-mediated chronic diseases, including rheumatoid arthritis and psoriatic arthritis, with FDA approval granted in 2002 by Abbvie. Adalimumab's versatility extends to ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, and juvenile idiopathic arthritis, proven to alleviate moderate to severe rheumatoid arthritis symptoms either independently or in combination therapy [13, 15, 16].

Antibody function in immunotherapy

Apoptosis induction, growth inhibition, ligand mimicry, and immunomodulation are just a few of the diverse ways that antibodies work. Bispecific antibodies help to kill tumor cells by combining mAb specificity with effector cell cytotoxicity. At particular sites, enzyme-linked antibodies can convert prodrugs. Although they have a shorter half-life, antibody fragments have better tissue penetration [15].

Unconjugated MAbs in cancer

Monoclonal antibodies were initially seen as a promising cancer treatment, but early studies have been disappointing. Production involves identifying tumor-specific proteins, immunizing mice, and fusing immune cells to generate antigen-directed hybrid cells. Second-generation tests focus on specific tumor antigens. Monoclonal antibody 17-1A reduces colorectal cancer and rituximab treats non-Hodgkin's lymphoma. In breast cancer, trastuzumab targets HER2. Monoclonal antibodies destroy cancer cells using the complement. Anti-idiotypic monoclonal antibodies mimic tumor antigens and induce an immune response; challenges remain around mAb therapy, including tumor sensitivity and drug resistance. Monoclonal antibodies can reduce tumor size but rarely achieve complete remission. Specificity and cross-reactivity issues need to be addressed. Humanized antibodies and new technologies offer potential breakthroughs to make mAb therapies more effective [14, 15].

Recombinant immunotoxins in cancer therapy

Production involves identifying tumor-specific proteins, immunizing mice, and fusing immune cells to generate antigen-directed hybrid cells. Second-generation tests focus on specific tumor antigens. Recombinant immunotoxins are fusion proteins that combine fragments of mAbs with bacterial toxins and hold promise for cancer treatment. The choice between intact antibodies and fragments depends on binding specificity and affinity. Some animal studies suggest that intact antibodies may be more effective due to a longer half-life and bivalent conjugation. The development of bispecific antibodies and single-chain variable fragments may improve efficacy due to faster clearance from non-tumor tissues and deeper tumor penetration. These innovations can target tumor vascular cells, restrict blood supply, and potentially prevent metastasis [15].

Use of MAbs in therapy of asthma

The pathophysiology of allergic asthma involves IgE-mediated immunological responses. A recombinant humanized anti-IgE antibody (rhuMAB-E25), which bonds with free IgE and inhibits its interaction with mast cells and basophils, was found to be effective in reducing allergic asthma with low IgE reduction in serum levels and reduced asthma symptoms when compared to placebo in a recent study in patients with moderate to severe allergic asthma. Even if the study needs to be interpreted carefully, it still represents a positive step toward more successful asthma treatments [15].

Use of MAbs in therapy of septicemia

Sepsis affects around 400,000 cases in the US and 25,000 in the UK annually, with a mortality rate of 40-70%. Monoclonal antibodies targeting TNFα and receptors can hinder cytokines, potentially leading to secondary sepsis. It is promising to focus on the essential elements of the outer membrane of Gram-negative bacteria, such as bacterial endotoxin or lipid A. Lipid A triggers a harmful inflammatory response. Antibodies directed at the core region or lipid A, more conserved elements, could effectively combat a range of Gram-negative bacteria [15].

Use of MAbs in therapy against complications of viral infections

In patients with compromised immunity, the cytomegalovirus (CMV) can cause serious sickness with possibly fatal consequences. Respiratory Syncytial Virus (RSV) and Herpes Simplex Virus (HSV) Infections have also been addressed with monoclonal antibodies. An FDA-approved humanized monoclonal antibody palivizumab, has shown effectiveness against RSV in infants. For HSV, monoclonal antibodies have been explored, targeting glycoproteins and

potentially aiding in various herpetic conditions. Monoclonal antibodies against Ebola virus glycoprotein have been identified, showing protection in mice, but further research is needed [15].

Use of MAbs in therapy of substance abuse

Immunotherapy shows promise in addressing drug addiction, particularly for substances affecting the central nervous system like phencyclidine (PCP) and cocaine. PCP addiction's complexity arises from its pharmacokinetics and potential for violent psychotic episodes. Monoclonal antibodies offer a novel approach by acting as "sponges" in the bloodstream, binding to PCP molecules and halting their entry into the brain [17]. This innovative approach has demonstrated impressive potential, with studies revealing a single antibody dose's prolonged effectiveness against PCP. Antibody fragments have gained favor due to improved pharmacokinetics and reduced immunogenicity, enhancing their suitability for combatting PCP addiction. Immunotherapy's scope extends beyond PCP, as active research explores its application for other CNS-affecting drugs. Methamphetamine addiction is being considered a potential target, where antibody-based interventions akin to the PCP approach could prove effective. Similarly, innovative strategies are being explored for cocaine addiction, including catalytic antibodies mimicking natural esterases to counteract cocaine's effects. While catalytic antibodies may not match high-affinity anti-cocaine antibodies, they hold the potential for medical crises and withdrawal therapy. These advancements highlight immunotherapy's capacity to reshape drug addiction treatment, providing newfound hope for individuals grappling with substance abuse disorders [15, 18].

Regulatory breakthrough for cancer therapy

The immune system employs a complex network to identify and remove pathogens like viruses and bacteria, as well as damaged or cancerous cells. Antibodies, a key component, recognize and bind to specific molecules (antigens) on cell surfaces, like those of cancer cells. This binding flags the cells for immune responses, either attracting disease-fighting molecules or triggering processes leading to cell destruction [21] Monoclonal antibodies are designed to function diversely, some with multifaceted actions. Certain types can simultaneously lag cancer cell growth, induce cell-membrane destruction, inhibit cell growth, hinder blood vessel formation, block immune suppressors, directly attack cancer cells, deliver radiation or chemotherapy, and connect cancer and immune cells in various ways. Refer to Fig. 2 [19].

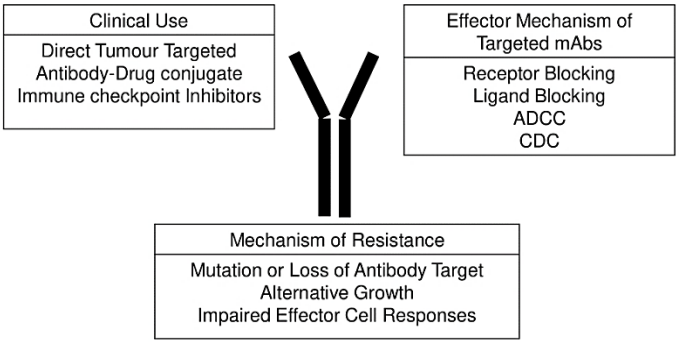

Fig. 2: Monoclonal antibodies in cancer therapy [19]

Challenges in the development of monoclonal antibodies

The research and development of monoclonal antibodies hold great promise for revolutionizing medical treatments, but they are not without significant challenges that must be addressed. challenges that span various stages of design, production, and clinical application. Below are a few of the challenges.

Cost

One of the most pervasive concerns about mAb is the substantial cost associated with their development and production. The intricate processes involved in creating these specialized molecules necessitate cutting-edge technologies, skilled personnel, and rigorous quality control measures. These factors contribute to the high price tag, limiting patient access to these potentially life-saving treatments and underscoring the importance of finding cost-effective solutions [20].

Manufacturing

Manufacturing therapeutic antibodies presents a formidable challenge in its own right. The production process of monoclonal antibodies and therapeutic antibodies is intricate, involving living cells and intricate biochemical processes. Scaling up the production while maintaining consistency and quality adds another layer of complexity. Ensuring uniformity and stability in large-scale production can be challenging, and even minor deviations can have profound implications for safety and efficacy. Stringent quality control measures must be established to guarantee that the final product meets the necessary safety and efficacy standards [21].

Immunological engagement

Immunological engagement introduces an intricate balance between the desired therapeutic effects and potential immune responses. While therapeutic antibodies are designed to engage with specific targets, their interaction can inadvertently trigger the production of anti-drug antibodies (ADAs) in some patients. These ADAs can neutralize the therapeutic antibodies or induce adverse immune reactions, compromising the treatment's efficacy and safety. The challenge lies in devising strategies to minimize the generation of ADAs while preserving the therapeutic benefits [20, 21].

Target identification

Identifying suitable targets for monoclonal antibody and therapeutic antibody therapy is a fundamental challenge, especially in cases where diseases lack well-defined antigens or receptors that can be targeted. This challenge requires a deep understanding of disease biology, advanced molecular biology techniques, and thorough validation to ensure that the selected targets are pivotal in the disease process [20]

Identifying suitable targets for therapeutic antibodies adds yet another layer of complexity. Not all diseases offer well-defined antigens or receptors that can be effectively targeted by antibodies. This challenge requires an in-depth understanding of disease biology, advanced screening techniques, and validation to ensure that the selected targets play a vital role in the pathophysiology of targeted disease. Success in target identification hinges on deciphering the intricate molecular landscapes underlying various diseases.

Optimizing efficacy

Optimizing the efficacy of these antibodies is paramount. Challenges such as poor tissue penetration, short half-life, and low binding affinity can limit their effectiveness. Advanced engineering techniques are necessary to enhance their properties and interactions with target cells or molecules, improving their therapeutic potential [20].

Bioavailability

Bioavailability, another formidable challenge, dictates the ability of therapeutic antibodies to reach their intended targets within the body. Hindrances such as poor tissue penetration, rapid clearance from circulation, and potential immunogenicity can collectively impede the optimal delivery of these molecules to the desired sites of action. Achieving optimal bioavailability requires innovative engineering strategies to enhance tissue permeation and circumvent immune-related obstacles, thereby maximizing the therapeutic impact [23].

Formulation

Formulation emerges as a decisive factor in the journey of therapeutic antibodies from laboratory design to clinical application. The specific formulation of antibodies can significantly influence their stability, bioavailability, and immunological interactions. Striking the delicate balance between maintaining structural integrity and optimizing pharmacokinetics is essential. Developing formulation strategies that mitigate potential challenges, such as aggregation or instability, is paramount to ensure the therapeutic efficacy and safety of the final product [20, 21].

Addressing these multifaceted challenges necessitates a concerted effort from the scientific community, industry partners, and regulatory bodies. Continued investment in research and development is imperative to unravel the complexities of therapeutic antibody design and optimization. Collaboration between academia and industry can harness diverse expertise and resources to drive innovation. Advancements in technology and manufacturing processes will underpin breakthroughs in antibody engineering and production. By surmounting these challenges, the development of therapeutic antibodies holds the potential to revolutionize medical treatments, offering more effective and precisely targeted therapies across a spectrum of diseases.

Mitigating these challenges demands a multifaceted approach. Continued investment in research and development, collaboration between academic institutions and industry partners, and advancements in technology and manufacturing processes are essential. By addressing these hurdles, the field of monoclonal antibodies can unlock its full potential, offering targeted and effective treatments for a wide array of diseases.

Recommendation to improve research and development of monoclonal antibodies

To advance the research and development of monoclonal antibodies, a multifaceted approach encompassing innovative strategies and collaborative efforts is imperative. To improve research and development of monoclonal antibodies, the following recommendations can be considered.

Invest in antibody engineering

Channeling resources into antibody engineering research can catalyze the discovery of superior therapeutic candidates. Cutting-edge techniques like phage display, yeast surface display, and transgenic animal models allow for the creation of mAbs with heightened specificity, reduced immunogenicity, and improved tissue penetration. Investment in this field could yield monoclonal antibodies that precisely target disease-causing molecules while minimizing off-target effects, bolstering the therapeutic potential of these molecules [22].

Optimize antibody efficacy

Focused efforts on enhancing MAb efficacy can revolutionize their clinical impact. Strategies to control antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) can make use of the immune system's built-in mechanisms to destroy target cells, and strategies to increase antibody binding affinity can enable them to more effectively neutralize disease-causing substances. Extending antibody stability and half-life can prolong their therapeutic presence, reducing dosing frequency and improving patient compliance [23].

Explore novel targets

Pioneering research into new targets is pivotal for expanding the scope of monoclonal antibody therapies. By delving deep into disease biology and uncovering previously overlooked antigens or receptors, researchers can uncover promising avenues for treatment. This exploration could potentially unveil monoclonal antibody therapies for diseases that were previously deemed challenging or untreatable.

Collaborate with academic institutions and industry

Collaboration between academic institutions and pharmaceutical companies can accelerate the research and development of monoclonal antibodies. Academic institutions can provide expertise in antibody discovery and characterization, while pharmaceutical companies can contribute resources for clinical trials and commercialization [24].

Invest in advanced technologies

Advancements in technologies such as high-throughput screening, next-generation sequencing, and computational modeling can greatly enhance the efficiency and effectiveness of monoclonal antibody research and development. Investing in these technologies can lead to faster identification and optimization of therapeutic antibodies [25].

Promote regulatory support

National regulatory agencies assume a vital role in the approval and commercialization of monoclonal antibodies. These agencies should provide updated guidance documents for the marketing approval requirements of monoclonal antibodies. Collaboration and continuous interaction between the manufacturer or sponsor with the national regulatory authorities will significantly help the industry streamline the regulatory approval process and ensure timely approval for safe and efficacious medication to the global population.

Regulatory considerations on the CMC development of monoclonal antibodies

Innovative development of monoclonal antibodies presents various hurdles for sponsors to meet regulatory requirements during product development. Guidance documents prepared by national regulatory authorities attempt to address the challenge of demonstrating the safety, quality, and efficacy of monoclonal antibodies when they work within certain constraints. Traditional assessment methods require additional manufacturing considerations that can lead to patient degradation. Various pharmacopeias, such as the USP, have published proposals to change the current evaluation paradigm to increase the ability to deliver drugs to patients without compromising patient safety.

Since a few years ago, other conventional medical product developers have used Quality by Design (QbD) as a benchmark in the creation of medical products to construct risk-based methods about quality, safety, and efficacy. Improved product and process expertise aids the sponsor in delivering high quality along with consistency in therapeutic product production.

In monoclonal antibody therapy, critical quality characteristics (CQA) are frequently not adequately characterized, and sponsors typically have barely any patient-level relevant data to meet these CQA requirements. Sponsors may start clinical trials with less precise potency parameters, but they will be required to tighten them as more clinical information is gathered to guide subsequent specifications and lot releases. The CQAs must be firmly established by the time product development reaches the manufacturing approval stage to minimize problems with changing specifications after approval. The national regulatory bodies additionally stated their recommendations on clinically pertinent CQAs may be incorporated into advice, which would be advantageous in establishing expectations and product quality standards. The manufacturing phases of monoclonal antibody products should be supported by reports of adequate quality data, as poor CMC documentation is a major reason why regulatory applications are rejected. The use of Contract Development and Manufacturing Organizations (CDMO) for the commercialization of materials and the ensuing requirement for technology transfers across various sites for various manufacturers further intensify this. Additionally, manufacturing by CDMOs may make use of confidential technology with little disclosure to the sponsor.

Any modification in production should be thoroughly risk-assessed to determine its potential effects. These challenges will probably be

inevitable throughout the lifecycles of monoclonal antibody medicines as sponsors either develop their manufacturing facilities, adopt new technologies, or rely on CDMOs. For monoclonal antibody therapeutics, the inherent unpredictability in raw materials and complicated production processes add extra levels of risk. The effective development of advanced medicines will depend on a thorough understanding of the causes of variation, their effects on final product quality, essential process parameters, and pertinent control measures [21, 26].

Regulatory challenges in approval of monoclonal antibodies

The most significant challenge in monoclonal antibody production lies in the manufacturing process. Monoclonal antibodies are large and complex molecules that necessitate innovative and special manufacturing processes. Establishing and ensuring the consistency of quality, purity, and potency throughout the manufacturing process is of utmost importance and requires extensive do [27]. The national regulatory authorities require a sponsor to submit an extensive blueprint of processes involved in the manufacturing of monoclonal antibody products [28].

Immunogenicity poses another challenge as it induces an immune response in patients, thus leading to a compromise in efficacy and adverse events. As advised by the national regulatory bodies, the safety concern regarding the patient's health remains paramount, which leads to exhaustive evaluation of the potential immunogenicity risks.

Differences in regulatory requirements for each country can be regarded as a regulatory challenge for the sponsor or manufacturer of the monoclonal antibody. This difference can lead to fragmented approval processes, hindering timely patient access to critical therapies. Collaborative efforts between regulatory agencies, industry stakeholders, and international organizations are necessary to align standards and expedite the development and approval of monoclonal antibodies on a global scale [28, 29].

Mitigating these challenges mandates collaborative engagement between regulatory authorities, pharmaceutical manufacturers, healthcare providers, and patient advocacy groups. By fostering transparent communication, leveraging real-world evidence, investing in robust clinical trials, determination of manufacturing processes, regulatory approval for mAbs can be navigated more effectively. Addressing these challenges not only facilitates the regulatory clearance of promising therapies but also ensures that the benefits of mAb innovations are accessible and impactful across diverse patient populations.

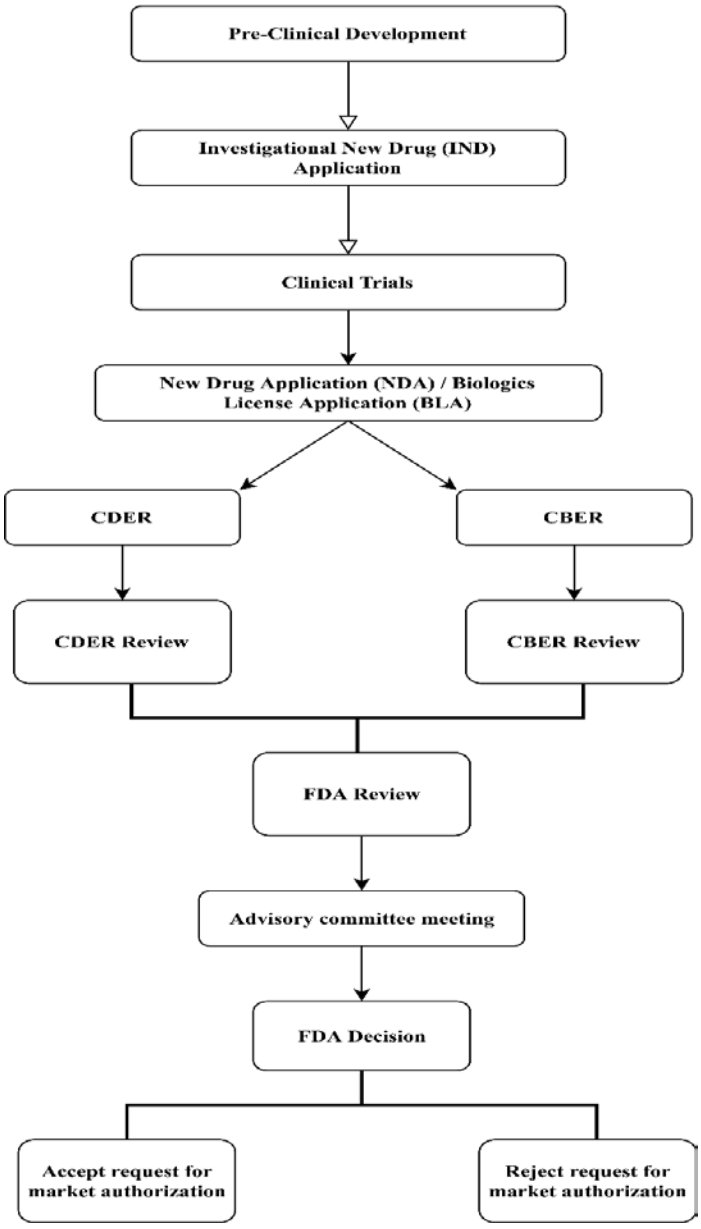

Fig. 3: Approval procedure for monoclonal antibody products in the USA [32]

Regulatory approval procedure for monoclonal antibodies

United States of America

To approve a monoclonal antibody according to the US FDA, the following steps are generally followed. Refer to fig. 3 [30, 32, 34]. The monoclonal antibodies are marketed only after getting market authorization from the Food and Drug Administration. The product approval can vary as drugs or biologics, For example: If the monoclonal antibody product is for oncology purposes it is regulated as a drug product which is reviewed by the Center for Drug Evaluation and Research (CDER). The applicant should submit a pre-clinical development report along with an IND application to CDER. The CDER reviews the application and approves to conduct of clinical trials in humans for safety and efficacy reports. After the successful completion of a clinical trial, the applicant can submit an NDA application to CDER for review. The FDA reviews and an advisory committee meeting is set up for the final decision. If the drug meets all the predetermined requirements, then it is approved for market authorization but if it does not meet the requirements, then a rejection letter is given to the applicant [30]. Otherwise, if the monoclonal antibody product is regulated as a biological product, it will be reviewed by the Center for Biologics Evaluation and Research (CBER) [34]. The applicant should submit preclinical data along with an Investigational New Drug (IND) application to CBER. The CBER reviews the application and approves to conduct of clinical trials in humans for safety and efficacy reports. After the successful completion of a clinical trial, the applicant can submit a Biological Licensing Application (BLA) to CBER for review. The FDA reviews and an advisory committee meeting is set up for the final decision. If the biological product meets all the predetermined requirements, then it is approved for market authorization, but if it does not meet the requirements, then a rejection letter is given to the applicant [32].

Europe

Monoclonal antibodies are regulated as biological products in the European Union. The EMA conducts centralized evaluations of monoclonal antibody drugs in the European Union. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency can evaluate a marketing authorization application (MAA) in a mere 210 d, not counting the time during which applicants are required to provide more data. To speed up the development and approval of medications with promising effectiveness and the potential to meet patients' unfulfilled medical requirements, the EMA has launched regulatory initiatives as below [33, 34]:

Centralized procedure

Up to 210 "active" days may pass before a new drug application is evaluated. Refer to fig. 4. At least one "clock stop" during this active review period is used by the applicant to prepare their responses to the CHMP's queries. beyond day 120 and maybe beyond day 180, when the CHMP decides on a list of queries or unresolved concerns that the applicant corporation must answer, the clock stops. By day 210, the CHMP had an opinion based on the evaluation. After 67 d have passed since the CHMP's verdict, the European Commission typically renders a binding authorization [33, 34]. The EMA put conditional marketing authorization (CMA) into effect in 2006. A CMA may be issued if the CHMP finds that there is a favorable benefit-risk balance, the need for the medication will be met, the applicant may be able to provide comprehensive data, and the risks associated with the need for additional data outweigh the benefits to public health from the medicinal product's immediate accessibility. The establishment of accelerated assessment (AA) for pharmaceuticals of significant public health interests, particularly therapeutic innovations, is another move to speed up the authorization of drugs. AA cuts the CHMP's evaluation period from 210 to 150 d. At any stage of drug development, manufacturers can request EMA's Scientific Advice on the best approach and study design to obtain reliable data on the quality, safety, and efficacy of the drug and to avoid significant objections regarding the development of the study. This is particularly useful for small and medium-sized enterprises with limited knowledge of drug regulation. Refer to Fig. 4 [34, 35].

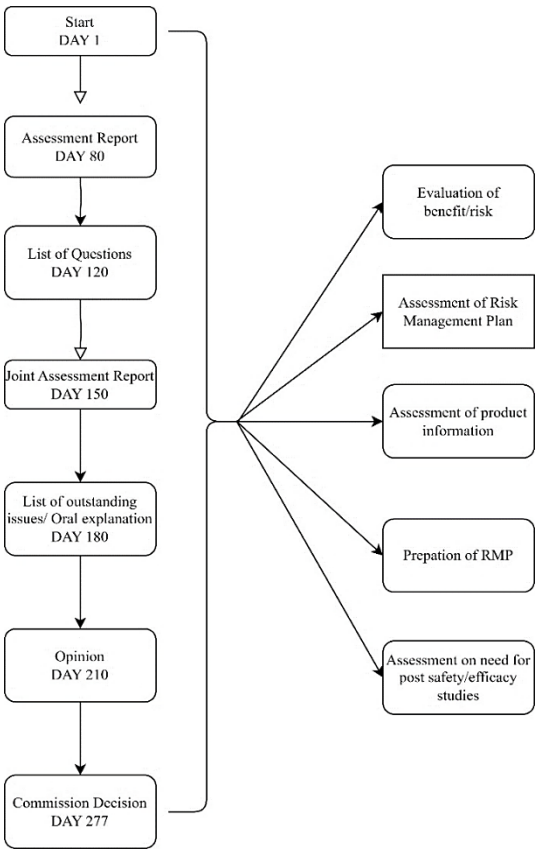

Fig. 4: Centralised procedure for monoclonal antibody products by EMA [34]

Japan

In Japan, monoclonal antibodies are regarded as bio-pharmaceutical goods and are subject to the same regulations as pharmaceuticals. The primary goal of the pharmaceutical affairs legislation is to establish an approval system that guarantees the high quality, effectiveness, and safety of the medications to be marketed and utilized in the healthcare sector of Japan [35, 36].

Applicant must submit data for product designation evaluation to determine the biological product's categorization as stated above when submitting a Japanese New Drug Application (J-NDA) for a biological product. For each part used in the manufacturing process that is derived from an animal or a human, a specific form must be completed. The classification of the human-or animal-derived material, the method of screening/controlling the humans or animals as the source of raw material, and the purpose of use. Standards for biological components have been developed to ensure the high quality, potency, and safety of pharmaceutical products. The following steps make up the approval review process. Refer to Fig. 5 [35].

1. J-NDA assessment procedure
2. Compliance Review (inspections of GCPs included)
3. GMP audit (which can also be done as a paper audit)

The New Drug Application forms for obtaining marketing authorization are submitted by the applicant to the Pharmaceuticals and Medical Devices Agency (PMDA). After reviewing the submitted application, the PMDA may decide that face-to-face contact with the applicant is essential. Applicant must interact and respond to PMDA's questions during the meeting, and the PMDA reviewer will then write a review report following the in-person consultation. The PMDA arranges an Expert Discussion if any significant problems are discovered during the evaluation. It includes interaction on the suggested important problem between the PMDA reviewer and an outside expert. After evaluation, the experts provide the results and the GMP conformity investigation reports to the Ministry of Health and Labor Welfare (MHLW). NDA may be approved by MHLW, in coordination with the Pharmaceutical Affairs and Food Sanitation Council (PAFSC). Upon approval, MHLW's Evaluation and Licensing Division issues the approval certificate. The pharmaceuticals assessed by the agency get a certification of approval from the PMDA [36].

The MHLW typically needs roughly a year to complete a processing request. A maximum time frame of roughly 18 to 24 mo from the application to the approval is possible if the applicant takes an additional 6 to 12 mo to reply to the questions (QandA session). Without accreditation clearance and a Good Manufacturing Practice (GMP) inspection report, marketing authorization cannot be acquired [35, 36].

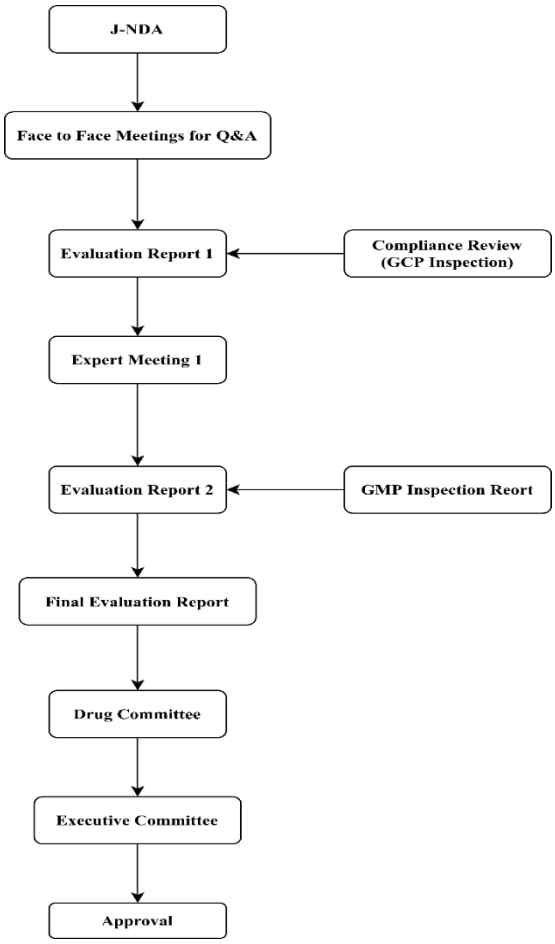

Fig. 5: J-NDA procedure in Japan [35]

Expedited approval procedure

United States of America

The FDA has created four techniques to speed up the research and development and assessment procedure for new pharmaceuticals seeking full marketing clearance in the area of increased drug approvals.

Priority review

The FDA designates initial BLAs, NDAs as well as efficacy supplements for priority review or standard review across its two-step priority review regardless of whether the sponsors have requested a special designation. Priority review is only available for new products that treat serious or life-threatening conditions and "provide a significant

improvement in safety or efficacy in the treatment, diagnosis, or prevention of a serious disease over existing treatments"[37]. The FDA evaluates the significance of new products individually, considering factors such as higher efficacy, improved adverse response profile, enhanced patient compliance impacting critical outcomes, and data demonstrating safety/efficacy in new subpopulations. Although randomized superiority trials against current therapy are expected, the FDA maintains flexibility in acceptable evidence. Priority Review offers a significant advantage, reducing review time by four months. Products designated for priority review undergo FDA assessment within six months of NDA submission [38, 39].

Accelerated approval

The most notable expedited program for pharmaceuticals intended to treat critical disorders is known as "accelerated approval". Accelerated approval has the advantage of speeding up the approval process (for priority review designations) or granting tax incentives as well as exclusivity (for orphan drug designations).

The provision for accelerated approval allows the use of surrogate endpoints, such as radiographic images or analytical evaluations that are likely to indicate clinical benefit, as well as intermediate clinical objectives, like effects on morbidity or mortality, to anticipate a drug's therapeutic advantage. This approach expedites approval, but Sponsors must provide sufficient scientific data supporting the chosen surrogate or intermediate objective. Drugs approved through this process must generally offer significant benefits over alternatives. Following approval, Sponsors are required to conduct additional studies to confirm clinical benefit, initially entailing a substantial commitment. Special labeling emphasizes the need for further confirmation post-market. If a drug fails to demonstrate efficacy after approval, it may be withdrawn from the market[38,39].

Fast track (designation)

This designation expedites and simplifies the FDA approval procedure for medications that would address severe illnesses and unmet medical needs [38, 39].

The demand for monoclonal antibody medication to address untreated diseases is evident. Even in cases where therapies are available, a fast-tracked medicine can prove its worth by outperforming existing treatments. This entails surpassing current medications, averting severe side effects, improving outcomes for life-threatening conditions through early detection, reducing treatment-disruptive toxicity, and meeting emergent healthcare needs. The FDA assesses requests within 60 d, requiring preliminary nonclinical, mechanistic, or clinical data for evaluation.

The following aspects may apply to a drug with a Fast Track designation:

1. The FDA should be consulted more often to discuss the medicine's development strategy and to make sure the required information is gathered to support drug approval.

2. The FDA has to communicate in writing more frequently about issues, including the design of proposed clinical studies that include the use of biomarkers.

3. When the relevant requirements are satisfied, admissibility for Accelerated Approval and Priority Review are considered.

4. Instead of waiting until every part of the NDA is finished, rolling review enables pharmaceutical companies to submit portions of their BLA or NDA for FDA consideration.

Breakthrough therapy designation

An expedited approval procedure known as "Breakthrough Therapy" is offered for novel medicinal products meant to treat critical or life-threatening illnesses. Preliminary clinical proof, often from Phase 1 or Phase 2 studies with a substantial patient count, is essential, along with comparative research against existing treatments focusing on clinical benefits, yielding robust data. Non-clinical evidence can also support applicability. Sponsors begin with an IND application, meeting criteria leading to automatic breakthrough therapy designation, granting benefits like accelerated FDA actions, transparent communication, and optimized trial design. FDA's guidance highlights rolling review and potential priority review based on clinical submission data. This process speeds up the creation and evaluation of ground-breaking medicines, encouraging rapid and significant improvements in medical care [38, 39].

Europe

Accelerated review

EMA and its CHMP offer accelerated review for marketing approval requests, expediting the process when a product holds significant therapeutic innovation and public health value. Applications under centralized review may take up to 210 d for assessment, excluding information wait times, but this can be reduced to 150 d upon CHMP's approval if compelling reasons are presented. EMA recommends a pre-submission meeting with CHMP and related committees 6-7 mo before a marketing application and requests for accelerated review should be made 2-3 mo before application submission. For successful accelerated assessment appeals, consultation with the EMA Program Manager is advised, with pre-submission session requests and relevant materials submitted online to EMA [40].

Conditional marketing authorization

EMA encourages the creation of drugs that meet unfulfilled medical requirements. In cases where the immediate availability of the medicine is greater than the risk associated with the need for additional data, applicants may be given conditional marketing authorization for such medicines based on less extensive clinical data than is typically required. Human-use medications are qualified if they are used to treat, prevent, or diagnose gravely disabling or life-threatening illnesses. Its application is also designed for a pandemic or other public health catastrophe [41].

Conditional marketing authorization from the EMA's CHMP may be granted if certain criteria are met: the medication demonstrates a favorable benefit-risk ratio, the applicant can provide comprehensive post-authorization information, the drug addresses an unmet medical need, and the benefits of immediate patient access outweigh potential risks despite incomplete data. This authorization is valid for a year, and renewable annually. Once granted, the MAH must fulfill specified conditions within designated timeframes. These requirements can include completing existing or new research or gathering further information to verify the benefit-risk balance of the treatment is still favorable [41].

Japan

Priority review designation

Priority review can be provided for pharmaceutical products deemed particularly significant from a medical perspective, such as novel medications treating severe illnesses and satisfying very high medical needs.

Criteria for priority review

1. Target indication severity

2. Disease progression and irreversibility

3. Excellence compared to presently accessible treatments

At every level of the review process, products of priority review are prioritized to the greatest extent feasible. As a result, the MHLW procedure might be cut from 12 mo to 6 mo, resulting in an overall approval duration of 12 to 18 mo. It is made known when a medicine product under priority review is accepted [42].

Sakigake designation system

The Sakigake Designation System helps to support the research and development of novel pharmaceuticals for the safe and effective management of severe diseases in Japan [43].

For sponsors, the Sakigake designations have multiple benefits such as priority consultations are permitted for Sakigake products at any phase of research, pre-application documentation assessments, and

assessment of a data-protection term, known as a re-examination period, lasting up to ten years following regulatory authorization. Additionally, for treatments that are granted marketing authorization, a possible 10-20% premium in prescription cost is provided. Considering these benefits in Sakigake, the criteria for scientific evidence for authorization in products bearing the designation is often the same as in those without designation [44, 45].

Criteria for designation

Medicinal products for illnesses in desperate need of novel treatment that meet the subsequent criteria:

1. Initially or concurrently applied for authorization in Japan along with other nations.

2. Significant effectiveness of current medicines can be anticipated based on findings from non-clinical research and early phases of clinical trials (Phase I and II)

3. Treatment for which commercialization is necessary as soon as possible (Orphan Disease)

4. Highly effective treatment against the targeted orphan disease

The conditional early approval system

Conditional Early Approval System for pharmaceutical products was created to allow patients earlier access to medications with high therapeutic usefulness for serious conditions. Qualified medications are those suggested for serious illnesses with few efficient treatments, and conducting a confirmatory clinical study is challenging or impractical due to factors including a limited subject population. This technique allows for faster approvals of goods exhibiting the appropriate levels of safety and effectiveness based on nonconfirmatory clinical research results by mandating applicants to complete post-marketing studies as a condition for approval. Refer to Fig. 6 [46, 47].

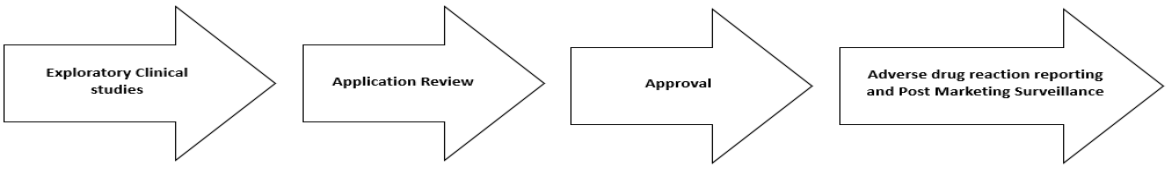

Fig. 6: Conditional early approval for orphan drug [46]

Conditional early approval can be given if all of the prerequisites listed below are satisfied [47]:

1. There is no traditional therapy or greater therapeutic value that can be established compared to current therapies.

2. Conducting a confirmatory study can be challenging or would require an excessive amount of time.

3. Post-marketing requirements, surveillance, or clinical investigations must be carried out.

Future perspective

When we compare chemical pharmaceutical drugs to therapeutic antibodies we observe an exponential difference in target specificity, lower systemic toxicity, and a longer life which needs to be improved. The future growth of the market involved in monoclonal antibodies shows a strong compound annual growth rate (CAGR) of 13.2% for the next five years. Among all available biological or bioderived products, monoclonal antibodies are being studied for clinical trials to the maximum extent. Moreover, monoclonal antibodies represent more than one-third of all new entities under both clinical and preclinical development in various parts of the globe. The estimated evaluation of the monoclonal antibody sector is 445 billion dollars by 2028.

Challenges are bound to be prevalent in the continual research and development of monoclonal antibody therapeutic products, even though the human genome project ended over two decades ago, identification of a new therapeutic target and validation of the same remains elusive and challenging. Novel monoclonal antibodies for enhanced therapeutic use and efficacy may open a new target playground for new therapeutic monoclonal antibody products. As we see above only 162 monoclonal antibodies have been approved till 2021 this suggests that the competitive market of monoclonal antibodies offers a plethora of challenges.

Furthermore, individual target pathways may not provide sufficient therapeutic benefits when being modified alone, but if combined with other target pathways these monoclonal antibodies can exhibit a synergistic activity.

Keeping in mind all these points, the future of monoclonal antibodies lies in the hands of national regulatory authorities. they should promote more regulatory-compliant documents for manufacturers and sponsors so that they can provide a safer, more efficacious, and regulatory-compliant product that will benefit the global population and help them get faster marketing approval for their products.

CONCLUSION

The intricate web of regulations, therapeutic applications, approval processes, and pathways for monoclonal antibodies has been discussed and highlighted. Upon a closer examination of the increased demand for monoclonal antibodies within the pharmaceutical market, a variety of factors driving innovation in monoclonal antibody therapy has surfaced since the inaugural discovery of monoclonal antibody products in 1975. Navigating the intricate challenges posed by CMC development, manufacturing, production, and regulatory compliance stands as an imperative, albeit formidable, stride toward establishing safe and efficacious pharmaceutical products.

In the United States, monoclonal antibodies find themselves positioned under both drug and biological regulations for attaining marketing authorization. Conversely, within the domains of Europe and Japan, monoclonal antibody products are regulated as biological and biopharmaceutical regulatory approval pathways.

The expedited approval procedures serve as a pivotal instrument in propelling these products into the marketplace, endowing them with fierce competition over existing therapies. This strategic maneuver addresses unmet medical demands on a global scale, bridging critical gaps in patient care and enhancing therapeutic outcomes.

The current landscape, while promising, is merely an introduction to the boundless potential harbored within the future of the monoclonal antibody market. With the continual unveiling of novel therapeutic monoclonal antibody products, a plethora of unprecedented opportunities take shape, promising to reshape and redefine the boundaries of mAb therapy.

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AUTHORS CONTRIBUTIONS

SM played a comprehensive role by conceptualizing and designing the study and was involved in literature search, data acquisition and analysis, statistical analysis, manuscript preparation, editing, and review. SM supported in study design and was actively involved in content preparation, data synthesis, manuscript preparation, editing, and review of the same. AM contributed to manuscript preparation, editing, and review. MP helped in the study conceptualization and review of the manuscript.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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