Part A: General Overview of Regulatory Affairs

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Contents Page

Abstract

A general overview of regulatory affairs in the biopharmaceutical industry is given. Naturally derived or chemically synthesised small molecules that contain an active pharmaceutical ingredient (API) in addition to biologics are developed by the industry for treatment of diseases. Biologics are complex macromolecules derived from cells and biological processes, and there has been a significant increase in the variety of biologics available on the pharmaceutical market over the years. The clinical filings in each region differ as separate regulatory authorities are responsible for the evaluation of applications. An investigational new drug application (IND) in USA, a clinical trial application (CTA) in Europe, a clinical trial notification (CTN) in Japan and a CTA in China must be submitted to proceed with clinical trials.

After the success with clinical trials, a new drug application (NDA) must be submitted to the FDA for the sale and marketing of new drugs. A Biologics Licence Application (BLA) must be submitted to the FDA for the market approval of biologics. The EMA evaluates marketing authorisation applications (MAAs) in Europe, and the European Committee (EC) takes decisions upon these recommendations. For the market approval of a new drug product in China and Japan, an NDA must be submitted to NMPA and PDMA respectively. Since China only joined ICH in June 2017, there are ongoing regulatory changes. ICH was formed to implement harmonised guidelines regarding quality, safety and efficacy of drugs, and the common technical document (CTD) is the required format for new drug applications in the previously mentioned regions. EC, PDMA/Japan and FDA/USA are founding regulatory members of ICH.

There are various programmes to expedite the review times of these applications in respective regions, and a brief overlook of these systems was investigated. A case study regarding the approval of COVID-19 drugs and therapeutics in these regions was also examined: emergency use authorisation (EUA) in USA, conditional marketing authorisation in Europe, special approval for emergency (SAFE) system in Japan, and conditional approval in China.

Drug approval trends were studied, and the importance of small molecules, monoclonal antibodies (mAbs) and glycoconjugate vaccines in the current pharmaceutical market and for the treatments of diseases in the future were considered.

1. Introduction

The Organisation for Professionals in Regulatory Affairs (TOPRA, n.d.) describes regulatory affairs as a profession that was 'developed by governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals.' Pharmaceutical and biotechnology companies dedicate a large amount of money and time in manufacturing a drug product, therefore regulatory affairs is as essential part of the process to ensure all the guidelines set by regulatory authorities are met during drug development.

Historical calamities such as sulphanilamide in 1937 and thalidomide in 1950s have led to an increase in legislations and laws associated with safety, efficacy and quality of drugs. In the interests of public safety and also to minimise losses to biopharmaceutical companies, several regulatory agencies have been established in different regions to assess the market authorisation of a new drug product. Examples of these authorities include the US Food and Drug Administration (FDA) in USA, European Medicines Agency (EMA) in Europe, Pharmaceutical and Medical Device Agency (PDMA) in Japan and National Medical Products Administration (NMPA) in China. Typically, clinical trial applications and marketing authorisation applications must be submitted to these agencies, and post-marketing surveillance is carried out once a drug is approved. There have been continuous efforts to harmonise the guidelines for safety, efficacy and quality of medicinal products in each region in the recent years.

The purpose of this review- Part A in a series of two reviews, is to highlight the importance of regulatory affairs in drug development and to examine different classes of drug that have been approved by regulatory authorities in the recent years. Therapeutic areas will be studied to recognise the leading medicinal products being developed by the industry. Small molecules and biologics are leading classes of medicinal products approved by regulatory authorities, and they will be considered in this review. The pharmaceutical market will be explored in this work to determine the key regions of interest, and the approval systems within each of these regions will be investigated. The different commercial marketing applications required in USA, Europe, China and Japan will be studied. The expedited approval systems and emergency approval systems in these regions will also be considered.

Part B which is to follow will be focused on the chemistry, manufacturing and controls (CMC) information necessary for market approval of small molecules, monoclonal antibodies and glycoconjugate vaccines in USA, Europe, China and Japan leading to a brief section on the non-clinical aspects.

2. Therapeutic areas and drug discovery process

2.1 Therapeutic Areas

Biopharmaceutical companies are driven by the need to improve quality of life of patients and this begins with looking at treatable causes of mortality and morbidity around the world. From **Figure 1,** it can be seen that circulatory system diseases and cancer are the most prevalent causes of treatable mortality across OECD countries in 2019. In most cases, medicinal products are used to extend the life of the patient compared to curing or preventing the mortality.

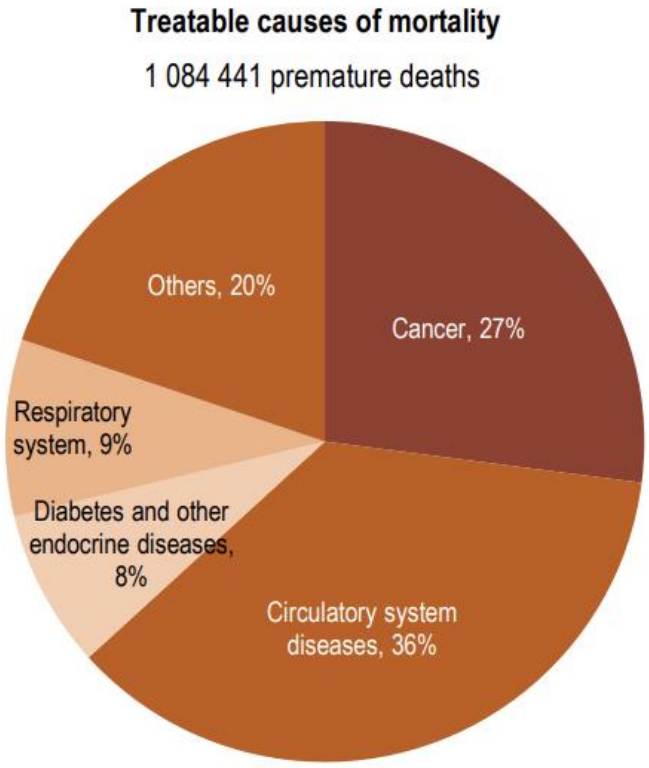

Figure 1. Main treatable causes of mortality across Organization for Economic Cooperation and Development (OECD) countries in 2019 (OECD, 2021). OECD countries refer to both developed and developing countries.

Cancer accounts for 27% of premature deaths across these countries and the approval of antineoplastic agents, which are medications used to treat cancer, have increased in the recent years. This was mainly evident in 2011-2015 as there was a significant increase in antineoplastic agent approvals (Santos *et al.*, 2017). The World Health Organisation (WHO, 2022) estimates the total deaths due to various types of cancers was to be approximately 10 million in 2020 worldwide. The global data for disability-adjusted life years (DALYs) in 2019 is shown by **Figure 2**, where DALYs include years lived with a disability as well as loss of life due to premature deaths. From this data it can be seen that cancer was globally responsible for 251.39 million losses of healthy life in 2019.

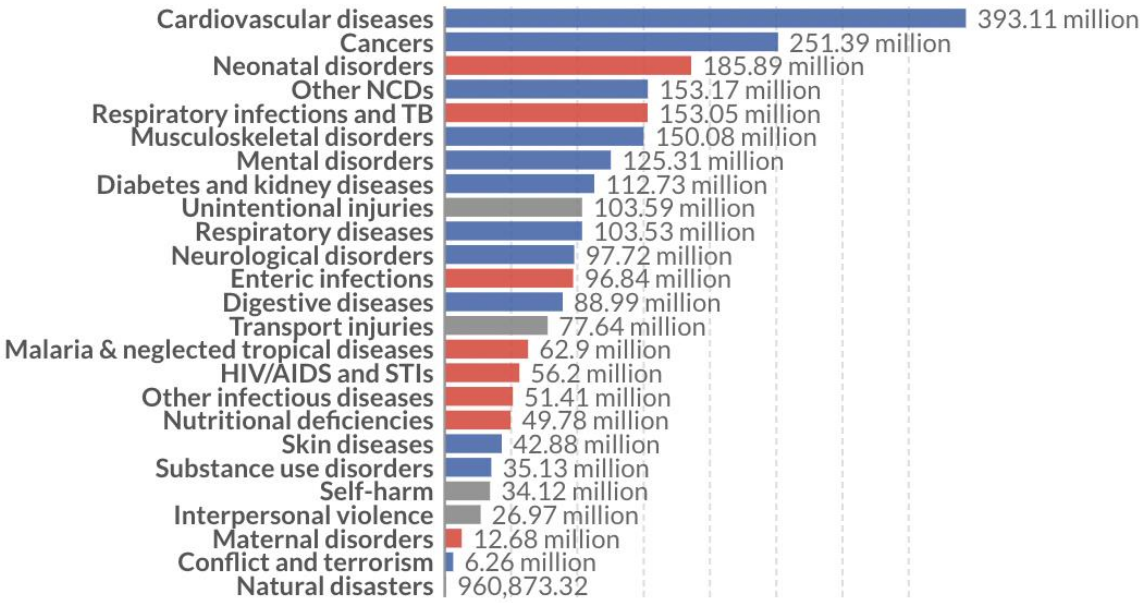

Figure 2. Global burden of disease by cause in 2019, adapted from Institute for Health Metrics and Evaluation (IHME) data. Taken from Roser, Ritchie and Spooner (2021) for educational purposes. Non-communicable diseases are coloured blue, injuries are coloured grey and communicable, maternal, neonatal and nutritional diseases are coloured red.

In 2022, oncology drugs continued to remain in lead for the United States Food and Drug Administration (FDA) approvals compared with the previous 5-year average (2017-2021) as illustrated by **Figure 3**. Each type of cancer requires a separate diagnosis and treatment strategy which can create a further challenge for biopharmaceutical companies in developing anticancer drugs (Bhutani et al., 2021).

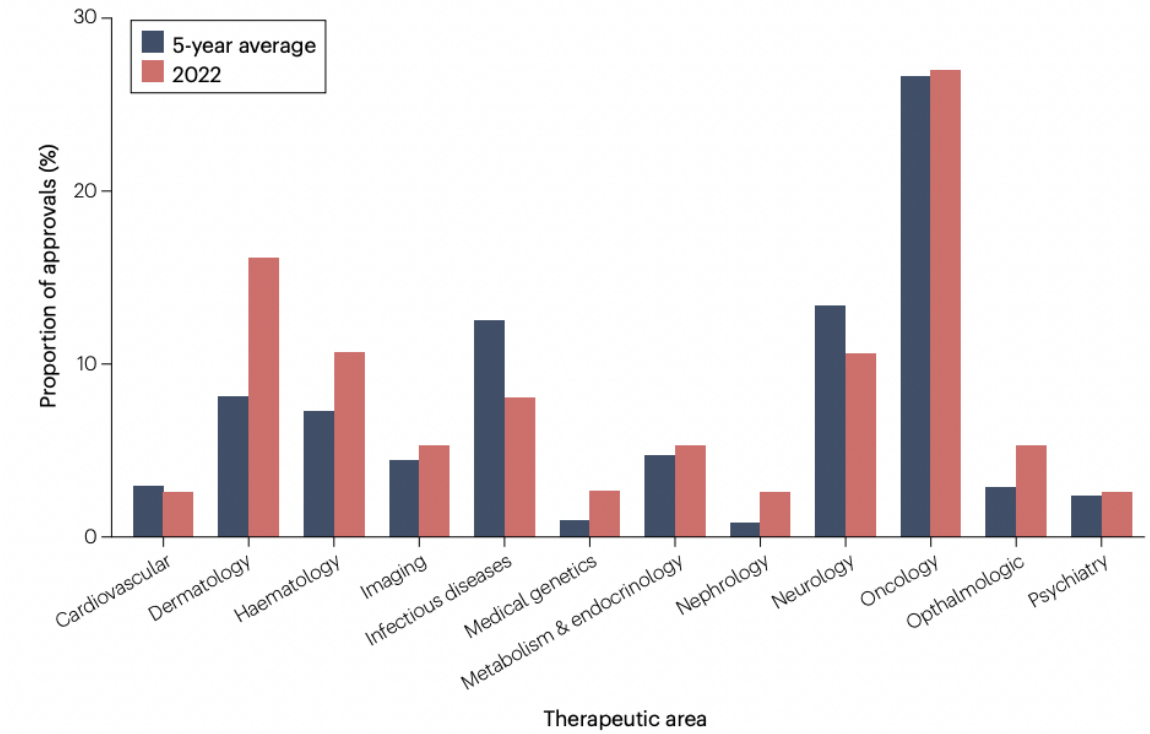

Figure 3. The therapeutic areas of approved drugs by FDA in 2022 compared against 5-year average of 2017-2021 (Mullard, 2023). This data only accounts for Centre for Drug Evaluation and Research (CDER) approvals and the biologics approval data of Centre for Biologics Evaluation and Research (CBER) is not included.

Some notable differences in **Figure 3** include the increase of approvals for dermatology and haematology drugs in 2022 compared to the previous 5-year average. There was a decrease in infectious diseases and neurology approvals in 2022 when evaluated against the previous 5-year trend. The primary approach to extend patient life, cure or prevent these diseases is through medication.

2.2 Small Molecules and Biologics

Small molecules and biologics are two major classifications of therapeutics that continue to be developed by pharmaceutical industry to fight these diseases and increase the life expectancy of humans. Small molecules are drugs typically generated by chemical synthesis or derived from natural products. Most patented drugs in the market and their generics belong to the small molecule category (Makurvet, 2021).

Synthesis of small molecules is commonly based around Lipinski's rule of five for bioavailability (Benet *et al*, 2016). Some examples of popular small molecule drugs include aspirin, penicillin, atorvastatin and diphenhydramine (Ngo and Garneau-Tsodikova, 2018). A generic drug product contains an active ingredient that is consistent in safety and efficacy to an already marketed drug (FDA, 2021).

Biologics are defined as medicines derived from living cells or through biological processes (FDA, 2018), and these molecules are complex. The characterisation, release and stability testing is defined for some biologic products such as monoclonal antibodies but remain in the process of being defined for other biologics such as cell-based therapies. Biopharmaceuticals belong to the broad term biologics and a biological product can be made up of sugars, proteins, nucleic acids or a complex combinations of these substances (FDA, 2018a). They can also be living entities such as cells and tissue (FDA, 2018a).

Examples of biologics include hormones, vaccines, blood products, gene and cellular therapies, monoclonal antibodies, recombinant therapeutic proteins and growth factors (FDA, 2018a). Advanced Therapy Medicinal Products (ATMPs) are deemed to be valuable as they are cures for diseases and can provide long-term management in areas of high unmet medical needs (NIHR, n.d.). Monoclonal antibody drug products such as adalimumab (Humira), pembrolizumab (Keytruda) and trastuzumab (Herceptin) are examples of popular biologics currently on the market.

The main difference between small molecule and biologics is their size as biologics usually tend to be bigger than 1 kDa whereas small molecules are at a size between 0.1 – 1 kDa (Makurvet, 2021). Small molecules are capable of targeting intracellular proteins, and currently there is research being performed surrounding RNA-targeting small molecules (Makurvet, 2021). **Figure 4** shows a size comparison between structures of baricitinib and monoclonal antibody Fab fragment of adalimumab. These drugs are both used to treat rheumatoid arthritis.

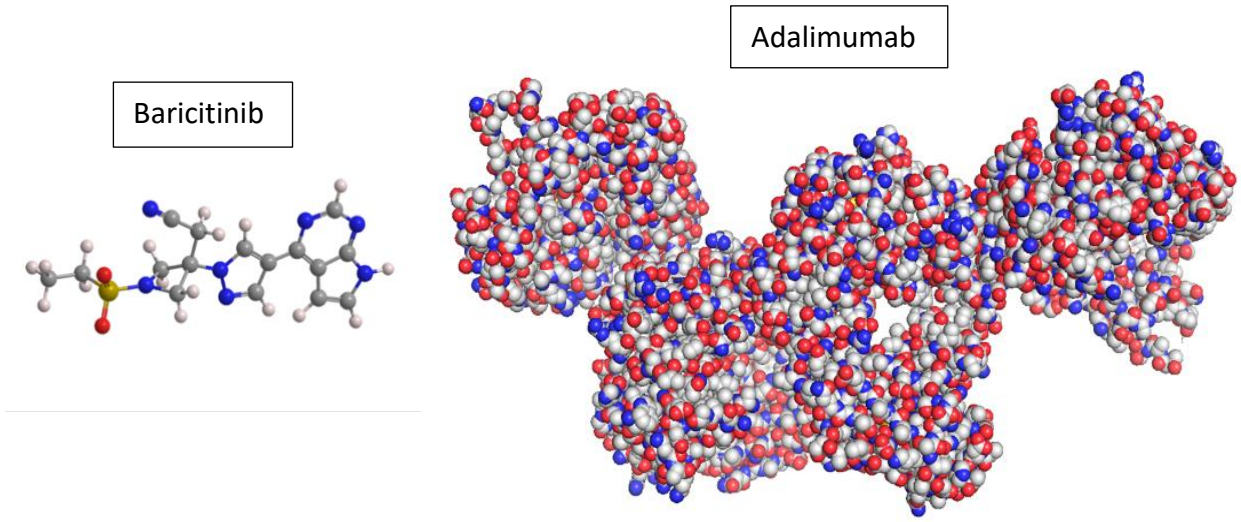

Figure 4. Structures of baricitinib (ACS, 2020) and adalimumab Fab fragment (PBD: 4NYL) (Fan, 2014). The atomic coding is as follows: carbon (grey), nitrogen (blue), oxygen (red) and hydrogen (white).

Small molecules are cost-effective in terms of production as biologics are incredibly complex; specifically surface glycosylation and folding patterns make the protein manufacturing process complicated (Ngo and Garneau-Tsodikova, 2018). Biological products tend to be more fragile and sensitive to degradation by physical conditions or enzymes therefore scaling up the manufacturing process and keeping batch-to-batch equivalence can also be a difficult practice (Ngo and Garneau-Tsodikova, 2018). Another challenge with developing biologics is that the patients can develop immune responses to drugs.

Biologics and biosimilars have garnered attention over the recent years as they play a significant role in fighting challenging diseases such as cancer, autoimmune and inheritable diseases. Biosimilars are also manufactured from living systems, similar to their reference products. A natural part of the manufacturing process is essential variation between manufacturing lots such as small changes in protein molecules (FDA, 2021).The introduction of abbreviated license pathway in 2005 has led to 55 biosimilars being approved by European Union as of 2019, and FDA has approved 33 biosimilar products as of 2021 of which only 22 are currently available within the US market (Goli and Butreddy, 2022).

Producing biosimilars are also hindered by secondary patents that include new formulations, manufacturing processes or new applications of existing active ingredients (Goli and Butreddy, 2022). However, as the technology evolves, the price of biologics can decrease with more cost-effective processes and there are already ongoing efforts to generate more stable biologics (Ngo and Garneau-Tsodikova, 2018).

The approval process of generics include a demonstration of the generic drug bring bioequivalent to the reference drug whereas biosimilars must demonstrate high similarity to reference product excluding minor differences in clinically inactive components (FDA, 2021). The safety and effectiveness of the biosimilar with their reference product should not be clinically significant (FDA, 2021).

With the expiration of Humira patent, there are already five biosimilars currently available through NHS. This is an example of a scenario that can be expected from other biologics nearing their patent expiration dates. Biosimilars are cost-effective compared to their reference product and this is the main driving factor for global healthcare systems when purchasing biosimilars.

Small molecules also continue to be popular due to their simplicity in production and patient access because most biologics need to be administered intravenously which increases costs and risks for hospitals. Small molecules are also cheaper because there are more competitors in the market, which then increases the availability for number of generics of a drug. On the other hand, producing biosimilars is extremely challenging and the manufacturing processes are not readily available for some drugs which hinders prospective competitors from producing biosimilars (Destro and Barolo, 2022).

Small molecules and biologics have different origins and modes of actions which means understanding their drug discovery process is crucial. The drug discovery process also gives an insight into why the three different areas of regulatory affairs have been established.

2.3 Drug Discovery Process

The journey of a small molecule drug begins as a new molecular entity (NME) that contains an active moiety which has yet to be approved by regulatory authorities (FDA, 2022). The active moiety is referred to as active pharmaceutical ingredient (API) and is the defining factor of small molecules. The first step involves drug discovery and pre-clinical testing, and this part of the process can last between 3-6 years (Destro and Barolo, 2022). Modern drug discovery pipeline begins with target identification and target validation where once a drug target is identified, evaluation is carried out to see whether the modulation of target's function will yield desired clinical results (Rao and Srinivas, 2011).

During the HIT and lead identification part of the process, 'hit' compounds are identified through high-throughput screening (Rao and Srinivas, 2011). Then lead optimization is caried out to improve the characteristics of the compound that include absorption, distribution, metabolism and excretion (ADME), affinity and selectivity (Rao and Srinivas, 2011).

Pre-clinical testing involves in vitro and in vivo experiments and afterwards, the entities that seem promising are entered to development stage where investigational new drug applications (IND) and clinical trial applications (CTA) with respective regulatory authorities need to be submitted, which is shown in **Figure 5.** The clinical protocol, investigational medicinal product dossier (IMPD) and investigator's brochure (IB) can be submitted as part of an initial CTA (EMA, 2022).

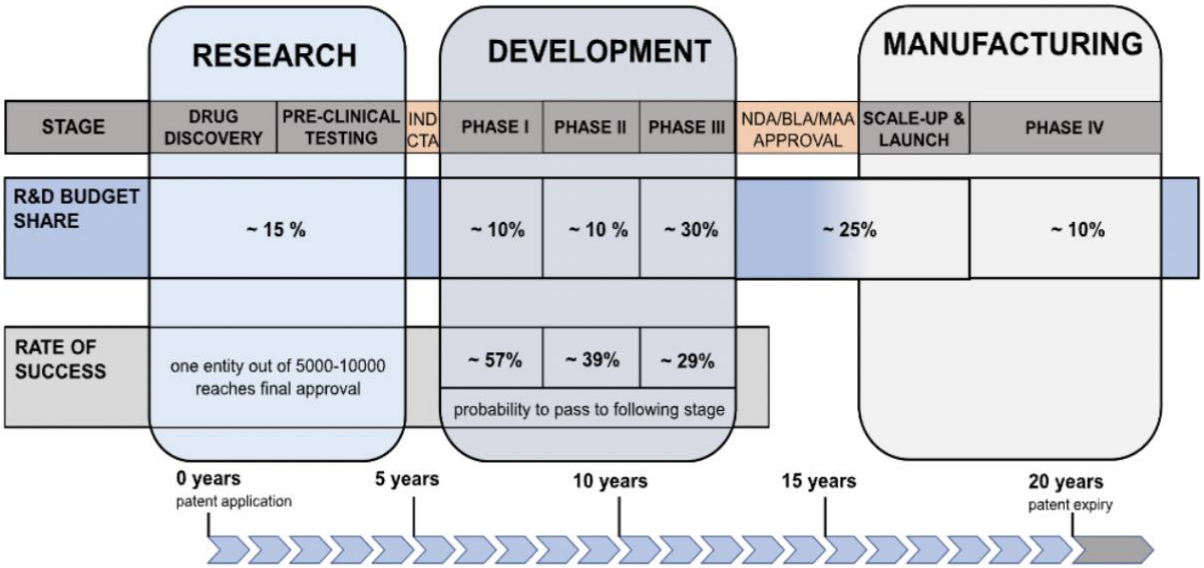

Figure 5. The different stages of drug discovery cycle with the regulatory applications that should be submitted during the process (Destro and Barolo, 2022).

Phase I clinical trials usually consist of 20-100 volunteers and the success rate for the next phase trial is around 57% (**Fig. 5**). Phase II clinical trials see an increase of volunteers to 100-500 and a placebo can also be introduced to compare treatments. After the success at this step, Phase III clinical trials are carried out with 1000-5000 volunteers. Phase II and Phase III trials can be randomised and double-blind where the volunteer and the researcher do not know which treatment is being used.

Phase III clinical trials tend to be the most expensive part of the process and API also increases from grams to hundreds of kilograms (Destro and Barolo, 2022). With the end of clinical trials, the process is scaled up therefore robustness of the process must be achieved to ensure manufacturing efficiency (Destro and Barolo, 2022). For compounds that successfully pass the clinical trials- new drug applications (NDA), biologics license applications (BLA) and marketing authorization applications (MAA) are submitted.

Phase IV is the post-marketing surveillance of a drug product and this is typically the last stage of drug discovery process. Monitoring the safety of a new drug product for humans continue after market approval by regulatory authorities, and the key purpose of this is to identify previously unrecognised adverse side effects as well as the positive effects (Raj *et al.*, 2019). The starting point of the drug discovery process for biologics is very similar to small molecules

with finding a drug target, but differ in establishing biomarkers, developing assays and routes for generating the modality (Breeze, 2020).

3.Overview of pharmaceutical market, drugs and regulatory affairs

3.1 Pharmaceutical markets

The drug discovery process is expensive and time-consuming. It can take around USD 1-5 billion to bring a drug to the market (Breeze, 2020). Furthermore, pharmaceutical companies typically only have a few years of patent life left to make return on investment. The IQVIA Institute (2021) has recorded USD 1.423 trillion for global biopharmaceutical market in 2021 and this is predicted to increase to USD 1.750–1.780 trillion by 2026.

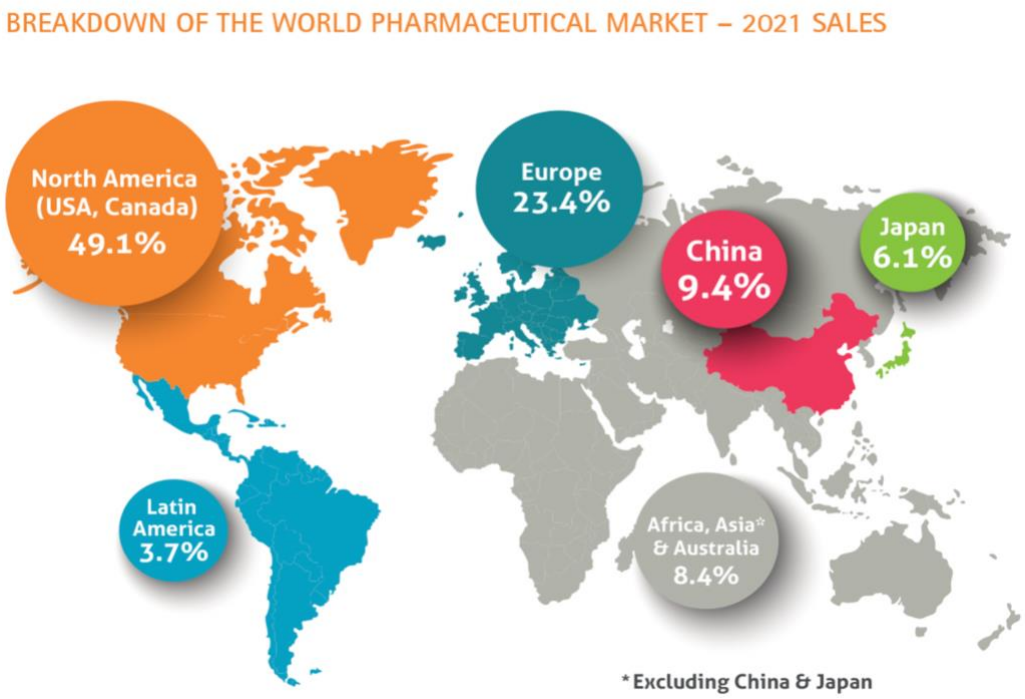

Figure 6. Overview of 2021 global pharmaceutical sales, adapted from IQVIA (EFPIA, 2022).

North America, Europe, China and Japan were the four major pharmaceutical markets in the world in 2021 as seen from the pharmaceutical sales information displayed in **Figure 6**. Therefore, these regions will be the main focus in this review and project when considering novel drug approvals by regulatory authorities. The pharmaceutical research and development expenditure for these regions from 1990-2020 is shown by **Figure 7** and it can

be seen that these costs have increased throughout the years. One of the regions that stand out is China since their pharmaceutical R&D expenditure significantly increased from 2010 to 2019. This change could be due to their membership with ICH as centralised procedures have reduced the time taken for market approval of a new medicinal product.

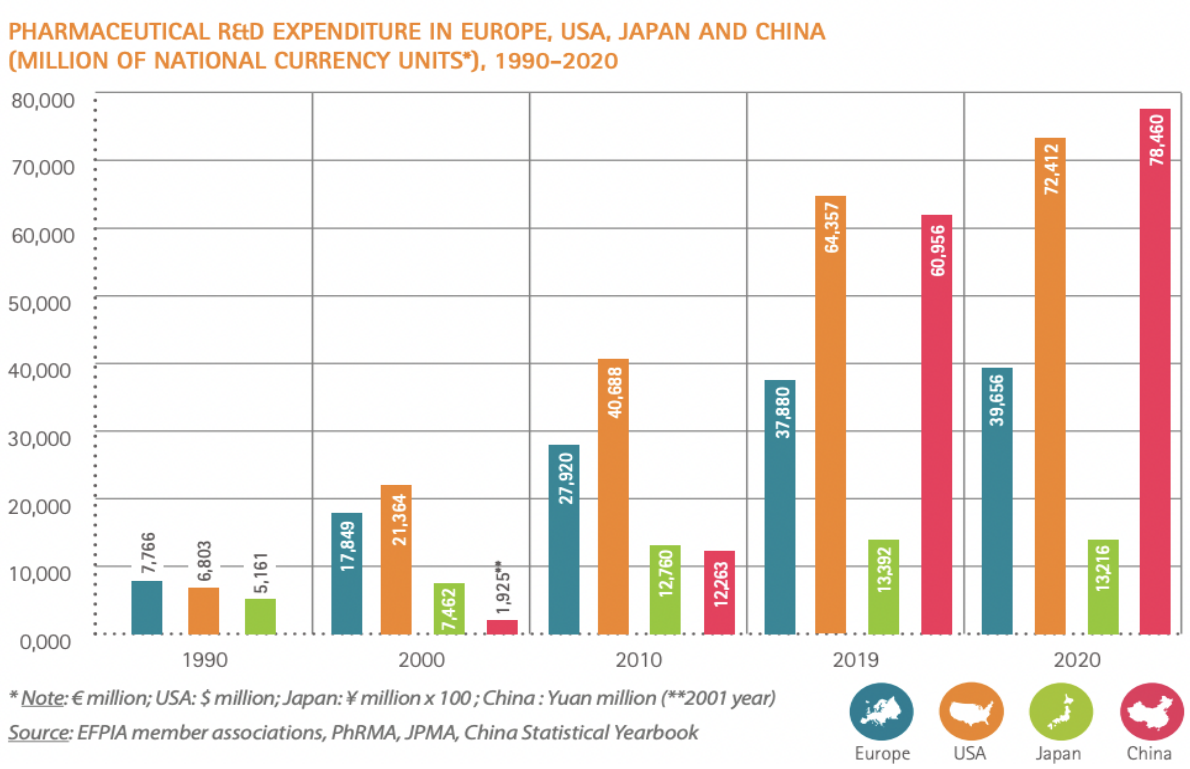

Figure 7. Research and development expenditure in Europe, USA, China and Japan from 1990-2020 (EFPIA, 2022).

The global drug sales can be studied to understand the leading classes of therapeutics currently available on the market. As expected, the top two best-selling drugs of 2022 were COVID-19 vaccines which is seen by **Figure 8**, but these sales are estimated to decrease with less demand in the upcoming years. Humira, Keytruda and Stelara are all monoclonal antibodies (mAbs) and there are also four small molecule drugs in this list that are used to treat a variety of diseases. Since vaccines, mAbs and small molecules are currently the top contributors in the sales for biopharmaceutical companies, these products can be considered significant in the present pharmaceutical market. It is evident that small molecules and biologics play an important part in treating diseases, and appropriate regulations are needed to be considered in their production.

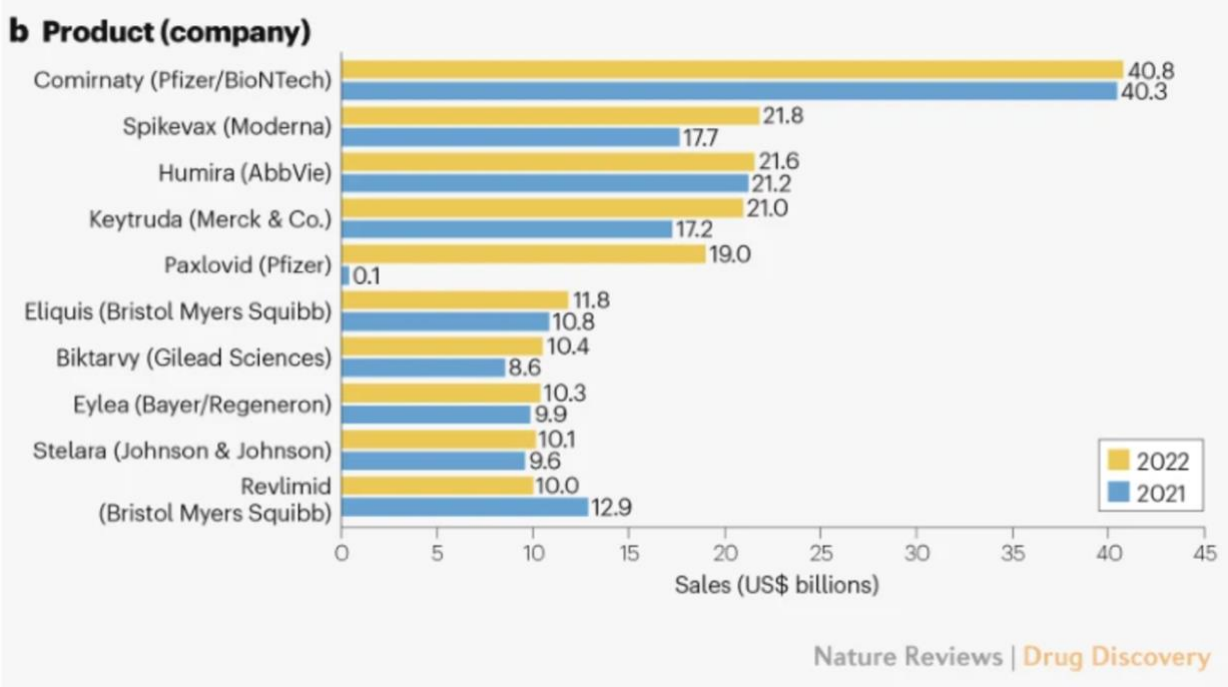

Figure 8. Top ten global drug sales of 2022, adapted from EvaluatePharma (Urquhart, 2023).

3.2 Regulatory Affairs

The regulatory affairs department in a biopharmaceutical company is crucial for bringing a drug to the market and there are three key areas of interest in regulatory affairs: chemistry, manufacturing and controls (CMC), non-clinical and clinical. CMC involves looking at safety and efficacy of pharmaceutical products where the development of the drug and process are investigated. Non-clinical regulatory aspects are associated with studies carried out on animals and clinical aspects relate to the studies carried out on humans.

The FDA defines a sponsor as a person who takes responsibility and initiates a clinical investigation, and this could be an individual or a company. It is expected that a sponsor will assure the regulation authority that the drug is made under controlled conditions and meets criteria of stability, potency, purity and stability. Information about the drug substance (the active pharmaceutical ingredient) and the drug product (the formulated drug ready for administration) are required in the submission (Chiodin *et al.*, 2019).

The drug substance part includes information about proper identification, quality, purity and strength of API. Similar to drug substance, the drug product information must also include data supporting the assays and acceptable results that are used for evaluating identity, strength, quality and purity (Chiodin *et al*., 2019). Evidence about stability of the drug substance and drug product is crucial, especially for clinical trials as product shelf-life and storage conditions will become important during the process (Chiodin *et al.*, 2019). If a placebo is utilised within clinical trials, then CMC information regarding the placebo must also be submitted (Chiodin *et al.*, 2019). Good manufacturing practices (GMP) must be employed by sponsor to meet quality standards when manufacturing the drug substance and drug product.

The principal aims of non-clinical studies are to identify pharmacological properties and understand the toxicological profile. The pharmacological properties of a drug are measured by pharmacodynamics (mode of action), pharmacokinetics (metabolism) and comparative physiology where animal data can be extrapolated to humans (EMA, 2011). Establishing a safe initial dose level for first human exposure, identifying parameters for clinical monitoring of adverse effects and special toxicity are all means of understanding the toxicological profile of the drug (EMA, 2011). Good laboratory practices (GLP) guidelines must be followed by sponsor during these non-clinical studies.

The CMC and non-clinical assessments are then briefly summarised and incorporated into a detailed plan on how the drug will be evaluated on humans (Chiodin *et al.*, 2019). The study population, dose selection and safety monitoring plan are all key aspects of the clinical protocol, and good clinical practices (GCP) must be implemented by the sponsor in this step of the process.

The number of new chemical and biological entities to have been approved has continuously increased over the years in each region according to **Figure 9,** in particular with USA from 2017-2021**.** Regulations in the pharmaceutical industry were first explored after fatal incidents such as Elixir sulphanilamide casualties that resulted in Food, Drug and Cosmetic Act 1938 in the USA, and thalidomide-related birth defects which led to the Kefauver-Harris Amendment in 1962 (Destro and Barolo, 2022).

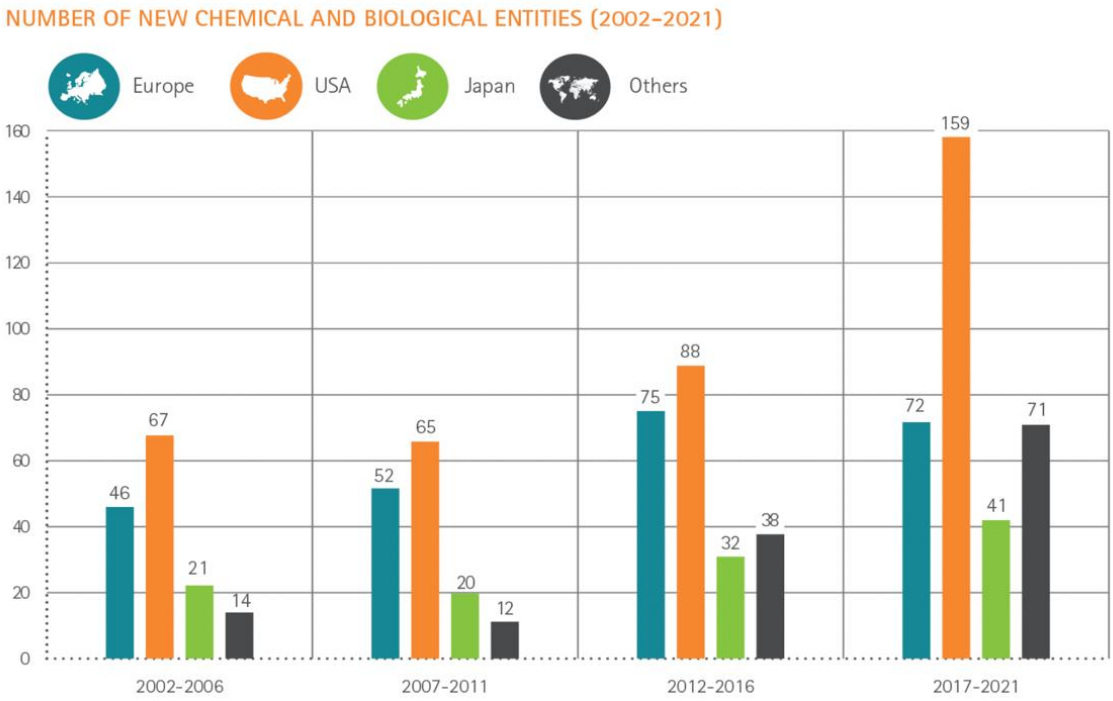

Figure 9. New chemical and biological entities in Europe, USA, Japan and China from 2002 to 2021 (EFPIA, 2022).

Prior to 1990, there was no harmonisation between countries in terms of pharmaceutical authorisation. Before a centralised procedure, the three major regulatory regions (USA, European Union and Japan) had their own set of guidelines and format for submission of a regulation dossier to obtain market approval for a new drug or a variation of an existing product registration (Jordan, 2014). In Europe it was required to submit Tabulated Summaries and Written Summaries, in USA there were guidance documents pertaining to NDA applications and in Japan a document known as GAIYO was required which organised and presented a summary of technical information (Jordan, 2014).

The procedure in Europe was further complicated as each region within EU had their own format of applications and guidelines which made making multiple submissions of an application to different countries time consuming and tedious for the pharmaceutical industry.

The ICH (International Council for Harmonisation) was set up by representatives of USA, Europe and Japan in 1990 to centralise the procedures, therefore these nations are known as the founding members. ICH provides guidelines for safety, quality and efficacy which the members should adhere to. The guidelines are extremely useful for harmonisation, consistency, transparency and guidance to industry and assessors (EMA, 2011). China only became a member of ICH in 2017, thus the regulations are still changing to improve the drug approval process.

In November 2000, the CTD (Common Technical Document) became the agreed upon format for drug regulation dossiers by ICH (**Fig.10**). This was another step to centralise the processes between different ICH regulatory authorities. This format is also known as M4 guideline in ICH procedures. The advantages of this format includes the implementation of good review practices and it has also eliminated the need for reformatting information that is submitted to different regulatory authorities by industries (ICH, n.d.). A centralised procedure is crucial for harmonised standards and with ICH members requiring a similar format in their submissions, it has been less time consuming for sponsors to obtain market approval in different regions.

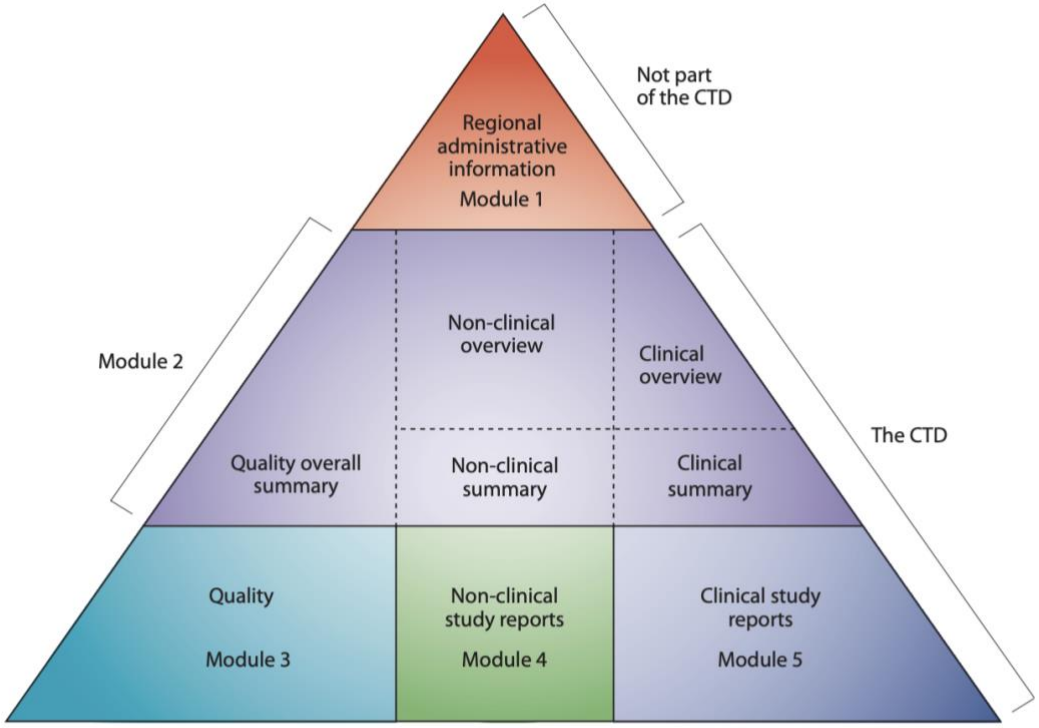

Figure 10. The Common Technical Document (CTD) format of that is followed in most new drug applications (ICH, n.d.).

The CTD format is shown in **Figure 10** and there are five modules which can be observed. Module 1 is administrative information that is specific to each region and does not normally count as part of the CTD. Module 2 starts with general introduction to the drug with pharmacological class, mode of action, proposed clinical use and then leads to an overview of CMC, non-clinical and clinical aspects that relate to quality, safety and efficacy (Jordan, 2014).

Module 3 is related to the quality of the drug and CMC reports are encompassed in the registration document. The nomenclature, structure, manufacturing process and process controls, impurities, analytical procedures, container closure system and stability data are examples of information required for drug substance and drug product sections in Module 3 (EMA, 2006a). The aim of this module is to convince the reviewer that the drug substance and drug product have been developed under controlled conditions, and the new drug meets all the requirements regarding identity and stability of the drug.

Module 4 involves the non-clinical reports included in the dossier and the main headings are pharmacology, pharmacokinetics and toxicology. This module assures the reviewer that the drug is safe to be used in humans from the extrapolation of non-clinical data, and the significance of any potential side effects should also be highlighted.

Module 5 presents the clinical study reports and each report must only appear in one section (Jordan, 2014). Examples of these reports include biopharmaceutic studies, pharmacokinetic studies using human biomaterials, human pharmacokinetic (PK) studies, human pharmacodynamic (PD) studies, efficacy and safety studies and reports of post-marketing experience (EMA, 2006b). Module 5 concerns efficacy and safety of the therapeutic product for intended population, and the benefit-risk assessment of the product should also be considered.

In July 2003, CTD became the mandatory format for new drug applications submitted in Japan and EU and the strongly recommended format for NDAs submitted to FDA (ICH, n.d.). China also implemented this format in February 2018. The CTD was replaced by its electronic counterpart eCTD and this has been the mandatory format for centralised procedure in EU since 2010 (Jordan, 2014).

3.3 Drug Approvals in USA

The USA has the oldest drug and biological product regulatory authority that was formed in 1908, therefore market specific discussions regarding FDA will be considered in this section. United States Pharmacopeia (USP) is a collection of pharmaceutical standards enforced by the FDA, and this is published annually. Novel drugs are approved as either NMEs under NDAs, or as therapeutic biologics under BLAs by the FDA (FDA, 2016). Novel drugs are classified as innovative products used to treat previously unmet medical needs or significantly improve patient care and public health (FDA, 2022).

In USA, an IND must be submitted to FDA before initiating clinical trials. The IND must contain information about the pre-clinical studies, manufacturing information as well as clinical protocols and investigator information. The sponsors that does not manufacture the drug

used in clinical trials must also submit a Drug Master File (DMF) (FDA, 2016). For small molecules, an NDA must be then submitted following the conclusion of clinical trials. This application is reviewed by Centre for Drug Evaluation and Research (CDER) after a review meeting with the sponsor. FDA takes 60 days to decide whether an NDA can be filed for a review, and the standard review process can take up to 10 months.

CDER oversees the approvals for over-the-counter and prescription drugs which also include biological therapeutics and generic drugs (FDA, 2019). The biological therapeutics that CDER oversee include products such as monoclonal antibodies, most proteins intended for therapeutic use (cytokines, enzymes) and immunomodulators (FDA, 2019).

In 2020, the Biologics Price Competition and Innovation Act (BPCI) mandated that all biological products must be submitted for approval through a BLA (Biologics License Application) as historically some protein products such as insulin were approved through NDAs. Centre for Biologics Evaluation and Research (CBER) is responsible for the regulation of biological and related products including blood, vaccines, allergenics, tissues and cellular and gene therapies (FDA, 2018a).

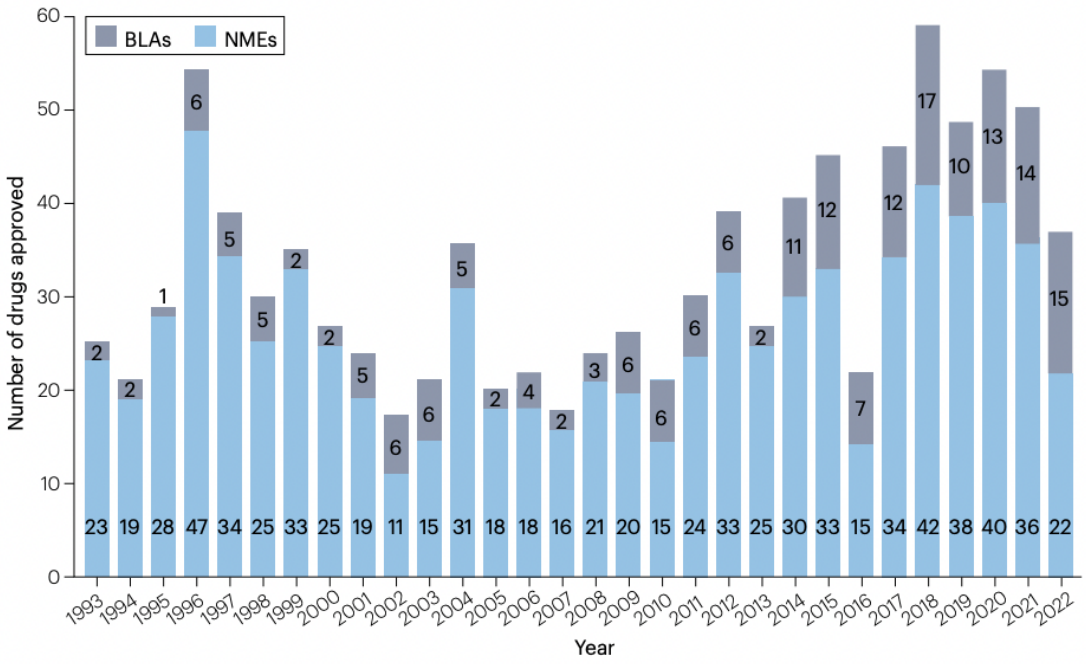

Figure 11. The FDA drug approvals by CDER since 1993. The BLA approvals for vaccines and gene therapies by CBER are not included in this graphical representation (Mullard, 2023).

The FDA drug approvals by CDER from 1993 -2002 are shown by **Figure 11** and it can be seen that in 2022, there was a drop in number of NDAs approved compared to past 5 years. However, this number was still higher than the average of combined previous years. This drop could be due to the impact of COVID-19 and companies not submitting as many NDA applications compared to previous years.

Beasley (2023) report that drug companies have favoured biotech medicine over small molecule pills due to Inflation Reduction Act (IRA) that causes inequality in 'fair price' implementation between small molecules and biologics in USA. The act dictates that selected biologics will undergo price negotiation after 13 years which gives a longer time period compared to small molecules that will have their prices negotiated after 9 years (Beasley, 2023). The article cites that since small molecules will have a shorter time period for return on investment, biopharmaceutical companies are discouraged from pursuing small molecule drugs. However emerging biological therapeutics have already increased their presence on the market therefore it is unlikely this new legislation is entirely responsible for the reduced interest in small molecule drugs by industry.

Another noticeable trend in **Figure 11** is the steady increase of BLA approvals over the years. Most of the approved BLA applications by the FDA in 2022 were monoclonal antibodies with bispecific antibodies closely following. **Figure 12** also shows how small molecules still continue to dominate FDA approvals and mAbs were the most approved biologics. There is a lot more variation observed in biological approvals compared to small molecules, and this could be due to the lack of specificity in small molecule classification.

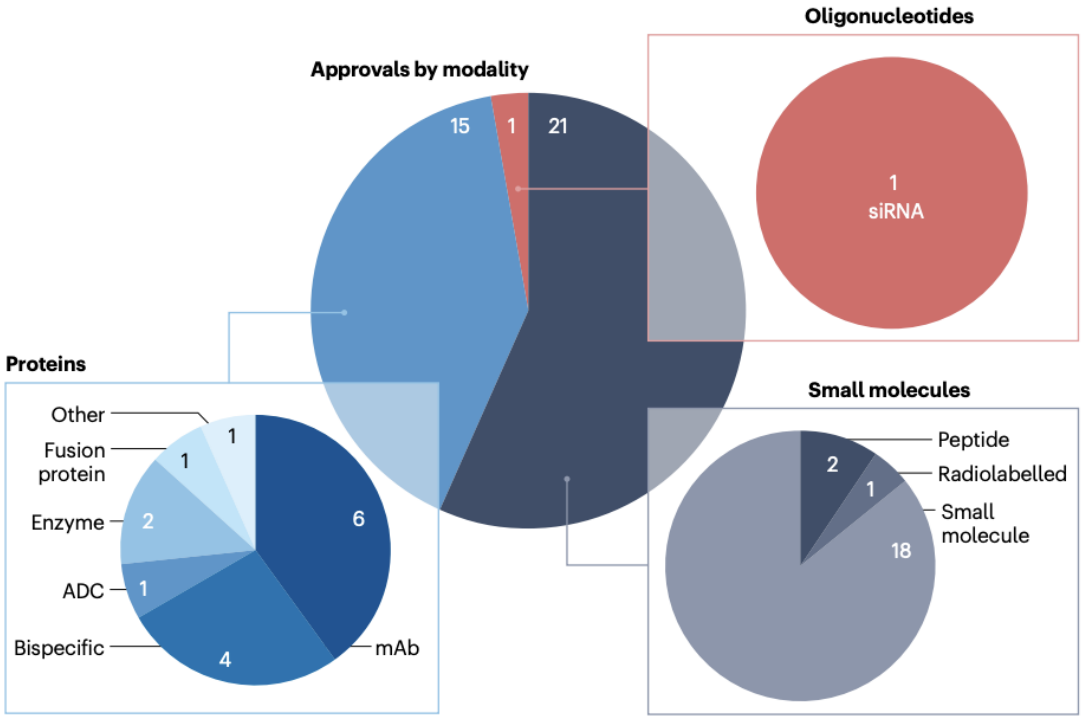

Figure 12. Approved small molecules and protein-based candidates (biologics) by CDER in 2022 (Mullard, 2023).

In terms of the future of drug approvals, it is worth noting that **Fig.11** and **Fig.12** does not include vaccine, gene and cell therapy approvals by CBER, and a total of five gene and cell therapies were approved in 2022. This is advancing on the number of mAb approvals in the same year. There are currently 26 total FDA approved gene and cell therapy products, and these numbers are only expected to grow as FDA predicted in 2019 that they will be looking at approving 10-20 gene and cell therapy products a year by 2025 (FDA, 2019).

Approvals for antibody-drug conjugates (ADC) have also increased since 2015 and ADCs are highly selective and allow specific delivery of cytotoxic agents to intended cancer cell targets as they are based on 'magic bullet' concept conceived by Paul Ehrlich more than 100 years ago (Bhutani *et al.*, 2021; Wu *et al.*, 2022). ADCs are particularly interesting as they target specific cells by delivering monoclonal antibodies and small molecules in a pattern. Peptide drug conjugates (PDCs) also share a similar concept to ADCs but PDCs have enhanced tumour penetration, reduced immunogenicity and lower production costs and although progress of PDCs are still at an early stage- they show promising potential (Wu *et al.*, 2022).

3.4 Drug Approval Process in Europe, Japan and China

There are a few differences in the commercial market authorisation of a medicinal product in Europe and USA. In Europe, the regulatory procedure includes submitting a Marketing Authorization Application (MAA) through European Medicines Agency (EMA). The standard assessment of the application by Committee for Human Medicinal Products (CHMP) can take up to 210 days. European committee (EC) is the authorizing body for all centrally authorised product who assumes decisions based on EMA recommendations, and EC takes 67 days to reach a decision. The decision is then a legally binding authorisation.

IMPDs must be submitted as part of initial CTA in Europe, and an MAA is submitted for commercial marketing authorisation following the conclusion of clinical trials. Previously, sponsors were expected to submit CTAs separately to national competent authorities (NCAs) and ethics committee associated with each country in Europe to obtain regulatory approval to carry out a clinical trial but from 31st January 2023, this procedure has become centralised. Sponsors must now submit CTAs via CTIS (Clinical Trial Information System) and this clinical trial regulation (CTR) ensures high standards for public transparency and safety for the clinical trial participants (EMA, 2023). European Pharmacopeia is a collection of texts regarding pharmaceutical standards specific to Europe.

The Ministry of Health, Labour and Welfare (MHLW) and Pharmaceutical and Medical Device Agency (PDMA) are responsible for the approval of NDA applications in Japan. For the basic review process in Japan the process stars with screening non-clinical study, which then leads to clinical trials where a clinical trial notification (CTN) is submitted to PDMA to initiate a clinical trial. The review process for NDA can take up to 12 months. ICH guidelines are the basis for NDA assessment but some domestic guides are not covered by ICH guidelines (PDMA, 2021). Japan also has its own book of official pharmaceutical standards known as Japanese Pharmacopeia (JP).

In August 2015, the China State Council issued its guidance 'Opinions on the Reform of Review and Approval Process for Drugs and Medical Devices' which greatly improved China's regulation process (Xu et al, 2018). Since China's ICH membership in 2017, the regulatory authority was renamed as National Medical Products Administration (NMPA) and the

regulatory process for overseas drugs has improved. Chinese Pharmacopeia is the set of pharmaceutical standards enforced by NMPA.

The Centre for Drug Evaluation (CDE) is responsible for evaluating drug CTAs, NDAs, supplementary applications and registration renewal applications of drugs manufactured overseas. The NDA approval time in China has significantly reduced from 2 years to around 15 months after the regulatory changes in 2017 (Su *et al.*, 2023). As a recent member of ICH, the regulatory guidelines in China are expected to change in the upcoming years as the authority starts implementing more ICH guidelines.

3.5 Expedited Approval Systems

The FDA possess a Fast Track programme that is designed to facilitate and expedite the development of drugs to treat serious conditions and fill an unmet medical need. Some examples of these serious conditions include AIDS, Alzheimer's disease, heart failure, cancer, epilepsy and diabetes (Cox et al., 2020). Fast Track applications may include non-clinical data to demonstrate superior efficacy and safety, improved outcome of diagnosis and decreased clinically significant toxicity when compared to standard therapy (Cox et al., 2020).

The FDA also has another accelerated pathway named Breakthrough Therapy Designation (BTD). An investigational new drug qualifies for BTD if it demonstrates preliminary clinical evidence indicating significant improvement for treatment of serious or life-threatening disease over existing therapies on a clinically significant endpoint (FDA, 2018b). The clinically significant endpoint measures an effect on irreversible morbidity, mortality or on symptoms that embody serious consequences of the disease (FDA, 2018b).

Priority review decreases application review time and to qualify for this review system, the new drug product must demonstrate significant improvements in the safety and effectiveness in the treatment, diagnosis or prevention of a serious condition (FDA, 2018c). The priority review does not guarantee approval and any major issues will lead to timeline extensions. CDER used at least one of these expedited programs to speed approval of 65% of all novel drugs approved in 2022 (FDA, 2023b).

The EMA also has a priority review system named PRIME which was launched in 2016, and for an application to be qualified for PRIME it has to meet two requirements: the investigational drug targets conditions where there is an unmet medical need and the investigational drug illustrated potential to address the unmet medical need (Cox et al., 2020). Accelerated assessment by EMA reduces the normal 210 day review time to 150 days and to qualify for this system, the applicant needs to demonstrate 'major public health interest' for the drug product (Cox et al., 2020).

There are four types expedited regulatory pathways in Japan known as priority review, orphan disease, conditional early approval and SAKIGAKE (forerunner designation). Priority Review is for severe diseases, and the NDA application review process can take 9 months. Severity of target disease and clinical utility are the required criteria for Priority Review (PDMA, 2021). Orphan Drugs and Conditional Early Approval systems are performed in addition to Priority Review system.

The conditions required for Orphan Drugs pathway are that the number of patients is less than 50,000 or the target disease is an 'Intractable Disease' in Japan, as well as feasibility of the development of the product (PDMA, 2021). These conditions must be met in addition to the Priority Review criteria. Similarly, Conditional Early Approval entails conditions such as the conduct of clinical trials is impracticable due to small population subject, and results of clinical studies that suggest a certain level of efficacy and safety (PDMA, 2021). Priority Review, Orphan Drugs and Conditional Early Approval review systems take 9 months, which is advantageous over the time period of 12 months taken during the standard pathway.

SAKIGAKE includes innovative medical products for serious diseases. The development process and NDA submission are both expected to be in Japan and effectiveness is anticipated from non-clinical and early phase clinical studies (PDMA, 2021). The typical review process for this market authorisation application is much shorter compared to other review systems at 6 months. All of these systems are subjected to a re-examination period that can last between 8-10 years.

China has also introduced expedited regulatory programmes such as Priority Review, Conditional Approval, Breakthrough Therapy and Urgently Needed Overseas Drugs (Su *et al.*, 2023; Li *et al*., 2021). The approval times for these programmes are currently working towards keeping up with FDA's benchmark, and Priority Review has a review time period of 130 days compared to the standard 200 working days (Li *et al*., 2021). Applications that meet Conditional Approval and Breakthrough Therapy are eligible for Priority Review designation time period. The Urgently Needed Overseas Drugs review process can take 3-6 months, and NDA filling is allowed with limited or no data in Chinese population (Li *et al*., 2021).

3.6 Emergency Approvals Case Study: COVID-19

In 2020, the COVID-19 pandemic led to an increase in the development of vaccines and drugs used to combat the disease. Although there were already expedited approval pathways already in place, rapid approval systems for these products was necessary to swiftly treat large amounts of population. As the best-selling drugs in 2022 were COVID-19 vaccines (**Fig.8**), the approval systems that were used to expedite these therapeutics in USA, Europe, China and Japan will be considered in this case study.

Emergency Use Authorization (EUA) is a regulatory pathway by FDA that is used for the permit of unapproved medical countermeasures to diagnose, treat, prevent serious or life-threatening disease related to public health, military or domestic emergency (FDA, 2023d). This was a pathway that had been in place since 2004 after Anthrax attacks in USA, and it was used to approve therapeutics and vaccines for COVID-19 pandemic. EUAs are granted in less than a month.

Under the EMA Article 5(3) of Regulation 726/2004, the Executive Director of the agency or the Commission representative could request review of COVID-19 treatments (EMA, 2021a). The timeline for the development of medicinal products in the treatment of COVID-19 was shortened, and EMA utilised rolling review process where they evaluated data for a promising medicine as data continued to emerge (EMA, 2020). Once the quality, safety and efficacy data were ready, the sponsor could apply for a commercial marketing application. EMA first approved Remdesivir for COVID-19 through a Conditional Marketing Authorisation, and this was the system used to expedite the approval of other COVID-19 vaccines and medicines

(EMA, 2021b). A prerequisite of conditional marketing authorisations is that they are only valid for one year but can be renewed annually (EMA, 2021b).

Since 2010, Japan has been using Special Approval for Emergency (SAFE) system to approve emergencies arising in Japan, and this was used to first approve Remdesivir in 2020 for COVID-19 (Maeda, 2022). A condition for granting SAFE approval is that the drug must be approved in other countries that have corresponding approval systems to Japan. For the approval of Comirnaty vaccine, MHLW evaluated data from Phase II and Phase III international trials, whilst the Japanese data was derived from Phase I and Phase II trials of a small Japanese population (Maeda, 2022).

In 2020, China granted official conditional approval for the first time in the treatment of COVID-19 for Sinopharm vaccine (NMPA, 2020). This vaccine had already been in use for several months in emergency use by frontline healthcare workers before the official approval (NMPA, 2020). This vaccination and others that were used before official approval were all in Phase III clinical trials.

During pandemics, vaccines are the most effective form of intervention in controlling the spread of an infectious disease. COVID-19 was a great example of the need for international collaboration between different regulatory authorities in evaluating vaccines and therapeutics.

4. *Future of therapeutic interests and drug delivery*

Glycoconjugate vaccines in particular are cost-effective and play a crucial role in preventing infectious diseases (Adamo, 2021). The most successful human vaccines have been glycoconjugate vaccines and they have an advantage over other vaccines due to being suitable for most human populations (Kay, Cuccui and Wren, 2019). Glycobiology maintains an important part in cancer studies as glycosylation profiles vary between healthy and malignant cells therefore these modifications can lead to tumour development and progression (Sorieul *et al.*, 2022).

Different strategies of cancer glycans for vaccine design have been explored at pre-clinical and clinical levels, and with the advancement of glycan-specific mAbs, it can be forecasted that new strategies to improve the efficacy of carbohydrate-based cancer vaccines will also emerge (Sorieul *et al.*, 2022). Therapeutics targeting cancer has continuously been leading the FDA approvals throughout the years, and it is one of the prevailing treatable causes of mortality (**Fig.1)**, therefore glycoconjugate vaccines can play an important part in the future direction of cancer treatments. Since glycoconjugate vaccines are very successful in treating infectious diseases, regulations regarding their development will also be considered in this work.

A recent webinar by a medicinal chemist from AstraZeneca reveals that PROteolysis TArgeting Chimeras (PROTACs) are currently being researched by multiple biopharmaceutical companies give a promising look into the future of small molecule drug discovery for the treatment of various diseases including cancer (Scott, 2023). Currently there are no approved PROTAC drug compounds due to limited bioavailability, however the PROTACs ARV-110 (NCT03888612) and ARV-471 (NCT04072952) have both moved on to phase II trials (Békés, Langley and Crews, 2022). Small molecules that can be used as facilitators for cell and gene therapy, and RNA-targeting small molecules are also being researched by industry and academia for treatment of diseases (Beck *et al*., 2022).

Therefore, it can be assumed that small molecules are still very much essential to pharmaceutical companies and attempts to increase their selectivity are being explored. The low cost in production, easy administration and their ability to reach targets through cell membranes also means small molecules will continue to have a presence in the pharmaceutical market. Small molecules also were responsible for majority of the FDA approvals in 2022 (**Fig.12**). Thus, the regulations considering market approval of small molecule drugs will be considered for this project.

Despite the approval increase of other biologics, mAb approvals by FDA have continued to accelerate over the years and mAbs are currently the leading class of biopharmaceuticals on the market (**Fig.13**). They accounted for 54% of total FDA approvals in 2020-2022, and an advantage of mAbs is that they offer specificity and affinity for both secreted and cell-surface

targets (Mullard, 2021). From Phase I to approval, mAbs have a 22% rate of overall success, and they are twice as likely to succeed in clinical trials compared to small molecules (Mullard, 2021). Therefore, it is evident that mAbs are still important for treating diseases and will be looked at in further detail to understand the regulations that are in place regarding their market approval.

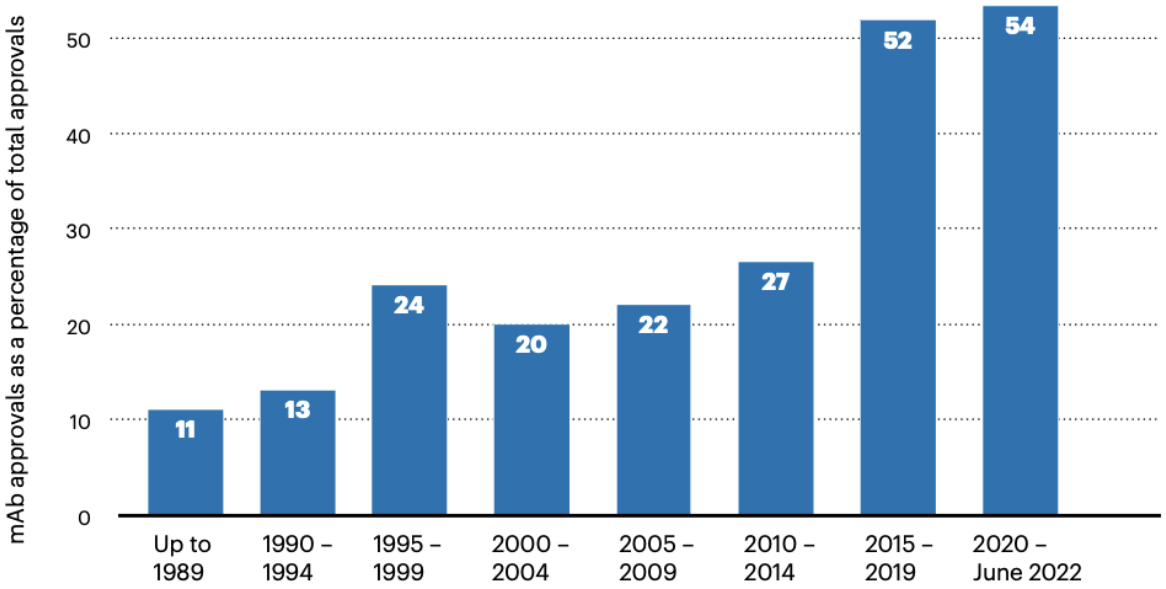

Figure 13. MAbs as a percentage of total approvals of FDA throughout the years (Walsh and Walsh, 2022).

The oral administration of a drug product is attractive to both patients and manufacturing processes but this remains a challenge for biologics such as vaccines and mAbs. Biologics are mainly administered intravenously due to their complex macromolecular structures that interfere with preservation of the bioactivity as well as interaction with biological barriers (Durán-Lobato, Niu and Alonso, 2020). The gastrointestinal tract (GIT) composed of oral cavity, oesophagus, stomach, small intestine and colon is designed for compound digestion and processing. GIT presents several biological barriers and has a harsh pH environment for biologics leading to complications with oral drug delivery.

With the evolving landscape of technology, the future of drug delivery systems can be also expected to advance. Some examples of future drug delivery systems include improving targeting efficiency through tissue and cellular levels by delivering drugs through skin or brain

barriers, improving drug pharmacokinetics by long-acting delivery technology and pulsatile release systems, developing personalized therapies and merging artificial intelligence (AI) and machine learning (ML) in drug delivery (Gao *et al.*, 2023). Although AI has been making waves in the drug discovery process with target identification hypotheses and industry collaboration (Kirkpatrick, 2022), it is still too early to tell whether AI can be a feasible endeavour in drug delivery attempts.

5. Conclusion

Various diseases are responsible for premature deaths and morbidity across populations, and biopharmaceutical companies are interested in developing different medicinal products for the treatment of these diseases. The main focus over the recent years has been medications used to treat cancer. Small molecules and biologics are classes of medicines that are manufactured by the industry to fight these diseases. The drug discovery process is complicated and time-consuming which means adhering to regulations enforced by different regulatory authorities is essential.

In therapeutic context, the perfect drug would be effective and easily administered with no side effects. Small molecule drugs tend to struggle with bioavailability and specificity whereas the administration of biologics tend to be complicated due to their structures. Safety, quality and efficacy are essential components for a medicine.

To bring these drugs to market, they must be approved through a regulatory agency in each region. Currently USA, Europe, Japan and China hold the biggest pharmaceutical sales in the world, therefore the regulations in place by the authorities in these regions for different classes of drugs will be explored further. All of these regions are members of ICH, which was formed harmonise guidelines regarding quality, safety and efficacy of a medicinal product. CMC, non-clinical and clinical aspects related to the drug and development process must be present in a centralised format termed CTD for drug registration. In order to investigate the regulations more in depth, only CMC and non-clinical aspects will be considered in the continuation of this work.

The clinical trial applications and commercial marketing authorisations differ in regions, and each regulatory authority has different review systems for these applications in place. The expedited approval pathways and emergency approval systems are also diverse for each region which makes making multiple submissions of an application to separate authorities a difficult process. Hence, the centralised CTD format and harmony between regulatory authorities has made this procedure easier for sponsors.

Small molecules are still essential to pharmaceutical industry due to cost-effectiveness and simplicity in administration therefore the regulations considering their market approval will be studied extensively for this project. MAbs are the leading class of biopharmaceuticals and they continue to dominate the global drug sales list. This means their presence in the pharmaceutical market is important and regulations considering their market approval will also be looked at thoroughly in the continuation of this work. Glycoconjugate vaccines are cost-effective and successful in treating human infectious diseases, therefore the regulation guidelines regarding these vaccines will be considered in the next part of this work.

In the following Part B of this dissertation, the CMC regulatory information regarding small molecules, mAbs and glycoconjugate vaccines in USA, Europe, China and Japan will be the main focus with a brief overlook on the non-clinical aspects.

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References

ACS (2020) *Baricitinib*, *American Chemical Society*. Available at: https://www.acs.org/molecule-of-the-week/archive/b/baricitinib.html (Accessed: 02 April 2023).

Adamo, R. (2021) 'Glycoconjugate vaccines: classic and novel approaches', *Glycoconjugate Journal*, 38(4), pp. 397–398. Available at: https://doi.org/10.1007/s10719-021-09997-5.

Beasley, D. (2023) *Drug companies favor biotech meds over pills, citing new U.S. law*, *Reuters*. Available at: https://www.reuters.com/business/healthcare-pharmaceuticals/drug-companies-favor-biotech-meds-over-pills-citing-new-us-law-2023-01-13/ (Accessed: 07 May 2023).

Beck, H, Harter. M., HaB, B., Schmeck. C. and Baerfacker. L. (2022) 'Small molecules and their impact in drug discovery: A perspective on the occasion of the 125th anniversary of the Bayer Chemical Research Laboratory', *Drug Discovery Today*, 27(6), pp. 1560–1574. doi:10.1016/j.drudis.2022.02.015.

Békés, M., Langley, D.R. and Crews, C.M. (2022) 'PROTAC targeted protein degraders: the past is prologue', *Nature Reviews Drug Discovery*, 21(3), pp. 181–200. Available at: https://doi.org/10.1038/s41573-021-00371-6.

Benet, L. Z., Hosey, C. M., Ursu, O., & Oprea, T. I. (2016) BDDCS, the Rule of 5 and drugability. *Advanced Drug Delivery Reviews*, *101*, 89-98. Available at: https://doi.org/10.1016/j.addr.2016.05.007

Breeze, A. (2020) The biopharma Drug Development Pathway (Webinar). (Online). Biochemical Society, 24-09-2020. Available at: https://www.biochemistry.org/about-us/resources-and-videos/video-library/the-biopharma-drug-development-pathway/ (Accessed: 14 April 2023).

Bhutani, P., Joshi, G., Raja, N., Bachhav, N., Rajanna, P.K., Bhutani, H., Paul, A.T. and Kumar, R. (2021) 'U.S. FDA Approved Drugs from 2015–June 2020: A Perspective', *Journal of Medicinal Chemistry*, 64(5), pp. 2339–2381. Available at: https://doi.org/10.1021/acs.jmedchem.0c01786.

Chiodin, D., Cox, E.M., Edmund, A. V., Kratz, E. and Lockwood, S.H. (2019) 'Regulatory Affairs 101: Introduction to Investigational New Drug Applications and Clinical Trial Applications', *Clinical and Translational Science*, 12(4), pp. 334–342. Available at: https://doi.org/10.1111/cts.12635.

Cox, E.M., Edmund, A. V., Kratz, E., Lockwood, S.H. and Shankar, A. (2020) 'Regulatory Affairs 101: Introduction to Expedited Regulatory Pathways', *Clinical and Translational Science*, 13(3), pp. 451–461. Available at: https://doi.org/10.1111/cts.12745.

Destro, F. and Barolo, M. (2022) 'A review on the modernization of pharmaceutical development and manufacturing – Trends, perspectives, and the role of mathematical modeling', *International Journal of Pharmaceutics*, 620, p. 121715. Available at: https://doi.org/10.1016/j.ijpharm.2022.121715.

Durán-Lobato, M., Niu, Z. and Alonso, M.J. (2020) 'Oral Delivery of Biologics for Precision Medicine', *Advanced Materials*, 32(13), p. 1901935. Available at: https://doi.org/10.1002/adma.201901935.

EFPIA (2022) *World Pharmaceutical Market*, *EFPIA Homepage*. Available at: https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-economy/world-pharmaceutical-market/ (Accessed: 06 May 2023).

EMA (2006a) *M 4 q common technical document for the registration of pharmaceuticals ...* Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m-4-q-common-technical-document-registration-pharmaceuticals-human-use-quality-step-5_en.pdf (Accessed: 03 June 2023).

EMA (2006b) *M 4 e common technical document for the registration of pharmaceuticals ...* Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m-4-e-common-technical-document-registration-pharmaceuticals-human-use-efficacy-step-5_en.pdf (Accessed: 04 June 2023).

EMA (2011) *Non-clinical assessment requirements - European medicines agency*. Available at: https://www.ema.europa.eu/en/documents/presentation/presentation-non-clinical-assessment-requirements_en.pdf (Accessed: 04 May 2023).

EMA (2020) *EMA public stakeholder meeting COVID 19 - EU's regulatory process for evaluation and approval, YouTube.* Available at: https://www.youtube.com/watch?v=eItRLe1Jq98&t=390s (Accessed: 05 June 2023).

EMA (2021a) *EMA issues advice on use of antibody combination (bamlanivimab / etesevimab)*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-issues-advice-use-antibody-combination-bamlanivimab-etesevimab (Accessed: 13 May 2023).

EMA (2021b) *Conditional marketing authorisation*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (Accessed: 05 May 2023).

EMA (2022) *FAQs - european medicines agency*. Available at: https://www.ema.europa.eu/en/documents/other/faqs-how-evaluate-initial-clinical-trial-application-assessment-decision-ctis-training-programme_en.pdf (Accessed: 03 June 2023).

Fan L.J. et al (2014) Crystal Structure of Adalimumab FAB fragment. Available at: https://doi.org/10.2210/pdb4NYL/pdb

FDA (2016) *Early clinical trials with live biotherapeutic products: Chemistry ...* Available at: https://www.fda.gov/media/82945/download (Accessed: 05 June 2023).

FDA (2018a) *What are 'biologics' Questions and answers*, *U.S. Food and Drug Administration*. Available at: https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers (Accessed: 19 April 2023).

FDA (2018b) *Breakthrough therapy*, *U.S. Food and Drug Administration*. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy (Accessed: 03 June 2023).

FDA (2018c) *Priority review*, *U.S. Food and Drug Administration*. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review (Accessed: 03 June 2023).

FDA (2019) *Frequently asked questions about CDER*, *U.S. Food and Drug Administration*. Available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/frequently-asked-questions-about-cder#1 (Accessed: 19 April 2023).

FDA (2021) *Biosimilars info sheet - Food and Drug Administration*. Available at: https://www.fda.gov/media/154912/download (Accessed: 08 May 2023).

FDA (2022) *Compilation of CDER new molecular entity (NME) drug and new biologic ...* Available at: https://www.fda.gov/media/135308/download (Accessed: 05 May 2023).

FDA (2023a) *CFR - Code of Federal Regulations Title 21*, *accessdata.fda.gov*. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.3 (Accessed: 03 May 2023).

FDA (2023b) *CDER New Drug Therapy Approvals 2022.* Available at: https://www.fda.gov/media/164429/download (Accessed: 02 May 2023).

FDA (2023c) *U.S. Food and Drug Administration*. Available at: https://www.fda.gov/media/164429/download (Accessed: 11 May 2023).

FDA (2023d) *Emergency use authorization*, *U.S. Food and Drug Administration*. Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization (Accessed: 03 May 2023).

Gao, J., Karp, J.M., Langer, R. and Joshi, N. (2023) 'The Future of Drug Delivery', *Chemistry of Materials*, 35(2), pp. 359–363. Available at: https://doi.org/10.1021/acs.chemmater.2c03003.

Goli, V.A.R. and Butreddy, A. (2022) 'Biosimilar monoclonal antibodies: Challenges and approaches towards formulation', *Chemico-Biological Interactions*, 366, p. 110116. Available at: https://doi.org/10.1016/j.cbi.2022.110116.

ICH (no date) *Ich official web site*, *ICH*. Available at: https://www.ich.org/page/ctd (Accessed: 23 March 2023).

IQVIA Institute (2021). *Global Medicines Use in 2022:Outlook to 2026*. Available at: https://www. iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicines-2022 (Accessed: 06 May 2023).

Jordan, D. (2014) 'An overview of the Common Technical Document (CTD) regulatory dossier', *Medical Writing*, 23(2), pp. 101–105. Available at: https://doi.org/10.1179/2047480614Z.000000000207.

Kay, E., Cuccui, J. and Wren, B.W. (2019) 'Recent advances in the production of recombinant glycoconjugate vaccines', *npj Vaccines*, 4(1), p. 16. Available at: https://doi.org/10.1038/s41541-019-0110-z.

Kirkpatrick, P. (2022) 'Artificial intelligence makes a splash in small-molecule drug discovery', *Biopharma Dealmakers* [Preprint]. Available at: https://doi.org/10.1038/d43747-022-00104-7.

Li, G., Liu, Y., Xie, C., Zhou, Q. and Chen, X. (2021) 'Characteristics of expedited programmes for cancer drug approval in China', *Nature Reviews Drug Discovery*, 20(6), pp. 416–416. Available at: doi:10.1038/d41573-021-00080-0.

Maeda, H. (2022) 'Japan's Special Approval for Emergency System During the COVID-19 Pandemic', *Clinical Pharmacology & Therapeutics*, 111(3), pp. 551–558. Available at: https://doi.org/10.1002/cpt.2310.

Makurvet, F.D. (2021) 'Biologics vs. small molecules: Drug costs and patient access', *Medicine in Drug Discovery*, 9, p. 100075. Available at: https://doi.org/10.1016/j.medidd.2020.100075.

Mullard, A. (2021) 'FDA approves 100th monoclonal antibody product', *Nature Reviews Drug Discovery*, 20(7), pp. 491–495. Available at: https://doi.org/10.1038/d41573-021-00079-7.

Mullard, A. (2023) '2022 FDA approvals', *Nature Reviews Drug Discovery*, 22(2), pp. 83–88. Available at: https://doi.org/10.1038/d41573-023-00001-3.

Ngo, H.X. and Garneau-Tsodikova, S. (2018) 'What are the drugs of the future?', *MedChemComm*, 9(5), pp. 757–758. Available at: https://doi.org/10.1039/C8MD90019A.

NIHR (no date) *Advanced therapy medicinal products*, *NIHR*. Available at: https://www.nihr.ac.uk/explore-nihr/innovation-areas/advanced-therapy-medicinal-products.htm (Accessed: 04 May 2023).

NMPA (2020) *China grants conditional approval for first COVID vaccine*. Available at: http://english.nmpa.gov.cn/2020-12/31/c_579192.htm (Accessed: 02 May 2023).

OECD (2021). *Health at a Glance 2021*. Available at: https://doi.org/10.1787/ae3016b9-en.

PDMA (2021) *(Review) expedited regulatory pathways in Japan - PMDA-ATC e-learning*, *YouTube*. Available at: https://www.youtube.com/watch?v=P6z3MGDhYh4&t=165s (Accessed: 20 March 2023).

Raj, N., Fernandes, S., Charyulu, N.R., Dubey, A., G. S., R. and Hebbar, S. (2019) 'Postmarket surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada', *Therapeutic Advances in Drug Safety*, 10, p. 204209861986541. Available at: https://doi.org/10.1177/2042098619865413.

Roser, M., Ritchie, H., Spooner, F. (2021) 'Burden of disease', *Our World in Data*. Available at: https://ourworldindata.org/burden-of-disease (Accessed: 02 June 2023).

Santos, R., Ursu, O., Gaulton, A., Bento, A.P., Donadi, R.S., Bologa, C.G., Karlsson, A., Al-Lazikani, B., Hersey, A., Oprea, T.I. and Overington, J.P. (2017) 'A comprehensive map of molecular drug targets', *Nature Reviews Drug Discovery*, 16(1), pp. 19–34. Available at: https://doi.org/10.1038/nrd.2016.230.

Scott. J. (2023) Protein Degradation: Small Molecule and PROTAC Approaches. Targeted Protein Degradation Series (Webinar). (Online). Sygnature Discovery, 10-05-2023.

Sorieul, C., Papi, F., Carboni, F., Pecetta, S., Phogat, S. and Adamo, R. (2022) 'Recent advances and future perspectives on carbohydrate-based cancer vaccines and therapeutics', *Pharmacology & Therapeutics*, 235, p. 108158. Available at: https://doi.org/10.1016/j.pharmthera.2022.108158.

Su, L., Liu, S., Li, G., Xie, C., Yang, H., Liu, Y., Yin, C. and Chen, X. (2023) 'Trends and Characteristics of New Drug Approvals in China, 2011–2021', *Therapeutic Innovation & Regulatory Science*, 57(2), pp. 343–351. Available at: https://doi.org/10.1007/s43441-022-00472-3.

TOPRA (no date), *About topra*, *TOPRA*. Available at: https://www.topra.org/TOPRA/TOPRA_Member/What_is_regulatory_affairs.aspx (Accessed: 22 April 2023).

Urquhart, L. (2023) ‘Top companies and drugs by sales in 2022’, *Nature Reviews Drug Discovery*, 22(4), pp. 260–260. Available at: https://doi.org/10.1038/d41573-023-00039-3.

Walsh, G. and Walsh, E. (2022) ‘Biopharmaceutical benchmarks 2022’, *Nature Biotechnology*, 40(12), pp. 1722–1760. Available at: https://doi.org/10.1038/s41587-022-01582-x.

WHO (2022) *Cancer*, *World Health Organization*. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer (Accessed: 13 May 2023).

Wu, M., Huang, W., Yang, N. and Liu, Y. (2022) ‘Learn from antibody–drug conjugates: consideration in the future construction of peptide-drug conjugates for cancer therapy’, *Experimental Hematology & Oncology*, 11(1), p. 93. Available at: https://doi.org/10.1186/s40164-022-00347-1.

Part B: A comparison of the CMC regulatory submission requirements in Europe and USA for Small Molecules and Biologics

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Contents Page

Abstract

The European Medicines Agency (EMA) requires an Investigational Medicinal Product Dossier (IMPD) to be submitted for the initiation of a clinical trial for a medicinal product in Europe. In the USA, an Investigational New Drug (IND) application needs to be submitted. The harmonised Common Technical Document (CTD) format set by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has made it easier for the multiple submissions of these applications to different regulatory authorities.

Module 3 of the CTD relates to quality of the medicinal product and this is separated into two parts: drug substance and drug product. The body of data concerning Module 3 of the CTD for small molecules and biologics are the same, but the information required for these medicinal products due to the guidelines set by the EMA and the FDA. The Chemistry, Manufacturing and Controls (CMC) information needs to be updated at the beginning of each phase of a clinical trial. Generally, basic information is supplied at Phase I and the CMC requirements needed for Phase I application submissions to the Europe and USA are specifically considered in this second part of Review of Regulatory issues, building on the more general Review of Part A.

For small molecules, the Module 3 requirements by the EMA and the FDA are similar with differences arising around the information required for Manufacture and Stability sections of the drug substance and the drug product parts. This was observed for the biological medicinal products as well, and it was also seen that usually the EMA requires detailed information in some sections compared to the FDA. The content and format of the IND guidance for Phase I studies set by the FDA has not updated since 1995, therefore the information required for IND applications is basic with no future amendment requirements for some sections of the IND. In contrast, the EMA continues to update their guidance documents regularly. Although the applications can be submitted simultaneously to different regulatory authorities with a standardised format, the information requested by these authorities are different for each medicinal product.

1. Introduction

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) created guidelines pertaining to Module 3 of the Common Technical Document (CTD) in 2002. This is also known as M4Q(R1) guideline since Module 3 relates to the quality of the medicinal product. This guideline allows the structure of CTD to be in a standardised format for the submission of the different clinical trial applications to separate regulatory authorities.

The structure of Module 3 remains the same for the format of applications regarding small molecule and biological medicinal products, but each regulatory authority requires the information provided in these sections to adhere to regional guidelines. Module 3 is divided into two sections: drug substance and drug product. The drug substance refers to Active Pharmaceutical Ingredient (API), whereas the drug product refers to the finished dosage form that contains the active drug substance and generally one or more other ingredients (FDA, 2023). The complete requirements regarding the substance part of Module 3 are split into seven sections as shown by **Table 1** and this table shows the information required regarding the drug substance according to ICH guidelines.

For a drug product that contains more than one drug substance, the data required in the '**S**' part should be provided for each of the drug substance (ICH, 2002). **S.1** entails general information about the drug substance such as nomenclature, structure and general properties that include physicochemical properties and biological activity depending on the nature of the medicinal product.

Table 1. Full requirements for the drug substance section of CTD Module 3 (ICH, 2002).

Substance	Content
S.1	**General Information** S.1.1 Nomenclature S.1.2 Structure S.1.3 General Properties
S.2	**Manufacture** S.2.1 Manufacturer S.2.2 Description of Manufacturing Process and Process Controls S.2.3 Control of Materials S.2.4 Controls of Critical Steps and Intermediates S.2.5 Process Validation and/or Evaluation S.2.6 Manufacturing process development
S.3	**Characterisation** S.3.1 Elucidation of Structure and other Characteristics S.3.2 Impurities
S.4	**Control of Drug Substance** S.4.1 Specification S.4.2 Analytical Procedures S.4.3 Validation of Analytical Procedures S.4.4 Batch Analyses S.4.5 Justification of Specification
S.5	**Reference Standards or Materials**
S.6	**Container Closure System**
S.7	**Stability** S.7.1 Stability Summary and Conclusions S.7.2 Post-approval Stability Protocol and Stability Commitment S.7.3 Stability Data

The manufacture information is required for **S.2**, and this usually involves a description and flow diagram(s) describing the manufacturing process. The materials used during the process must be listed and where the material was used during the manufacture should also be identified. The tests and acceptance criteria at the critical steps of the manufacturing process needs to be included to assure that the process is controlled. Process validation and evaluation studies are required for aseptic processing and sterilisation of chemical entities, and for biologics these studies are needed to establish the suitability of the manufacturing process for the proposed purpose (ICH, 2002).

The characterisation of the drug substance and any impurities information should be provided in the **S.3** section and references to individual ICH guidelines can be made in this section

regarding chemical and biological medicinal products. The analytical procedures used for the testing of the medicinal product and batch analyses information is included in the **S.4** section. Specification refers to a list of tests, and the qualification data of the drug substance must demonstrate that the quality of the product is not compromised and is fit for process. The process validation is required to evaluate the robustness and accuracy of the process. Evidence of any reference standards or materials used for the testing of the drug substance needs to be submitted under the **S.5** drug substance section.

The materials used to construct the primary packaging component of the drug substance should be identified in the **S.6** section and their description and identification specifications should also be included (ICH, 2002). The choice of materials, protection from light and moisture as well as the compatibility of materials used to construct the packaging and the drug substance should be discussed in this section to assess the safety of the materials (ICH, 2002).

In the **S.7** section, the stability data should be summarised with the types of studies conducted, protocols used and the results of these studies. The results from studies such as degradation studies and stress conditions can be entered in the summary (ICH, 2002). Conclusions in respect to the to storage conditions, re-test date or shelf-life can also be made. The time period at which a drug substance or drug product is anticipated to stay within the approved specifications is defined as shelf-life (ICH, 2003). Re-test date is different to shelf-life as this is the date after which samples of the drug substance should be investigated to confirm that the material is still in accordance with the specification and therefore is suitable for to be used in the manufacture of a drug substance or drug product (ICH, 2003). The results of the stability studies can be displayed in an acceptable format such as tabular, graphical, or narrative according to ICH guidelines (ICH, 2002).

Compared to the contents of drug substance information, more detailed explanations are required regarding the drug product part of Module 3. A description and composition of the drug product is required in the **P.1** section and this means all the components of the dosage form should be listed, including drug substance and excipients. Excipients are substances other than the active drug substance in the dosage form (ICH, 2002). As shown by **Table 2**,

the **P.2** Pharmaceutical Development section should contain information on the development studies performed to determine that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and the usage instructions are suitable for the application of the drug product (ICH, 2002). All this information encompassed in this section must demonstrate the stability of the drug product.

Table 2. Full requirements for the drug product section of CTD Module 3 (ICH, 2002).

Product	Content
P.1	**Description and composition of drug product**
P.2	**Pharmaceutical Development** P.2.1 Components of the Drug Product P.2.2 Drug Product P.2.3 Manufacturing Process Development P.2.4 Container Closure System P.2.5 Microbiological Attributes P.2.6 Compatibility
P.3	**Manufacture** P.3.1 Manufacturer P.3.2 Batch Formula P.3.3 Description of Manufacturing Process and Process Controls P.3.4 Controls of Critical Steps and Intermediates P.3.5 Process Validation and/or Evaluation
P.4	**Control of Excipients** P.4.1 Specifications P.4.2 Analytical Procedures P.4.3 Validation of Analytical Procedures P.4.4 Justification of Specifications P.4.5 Excipients of Human or Animal Origin P.4.6 Novel Excipients
P.5	**Control of drug product** P.5.1 Specification(s) P.5.2 Analytical Procedures P.5.3 Validation of Analytical Procedures P.5.4 Batch Analyses P.5.5 Characterisation of Impurities P.5.6 Justification of Specification(s)
P.6	**Reference Standards or Materials**
P.7	**Container Closure System**
P.8	**Stability** P.8.1 Stability Summary and Conclusion P.8.2 Post-approval Stability Protocol and Stability Commitment P.8.3 Stability Data

The manufacturer, batch formula and description of the manufacturing process should be described in detail in the **P.3** section, as well as the control of critical steps and intermediates. As with the drug substance section, this information is used to ensure the manufacturing process is controlled. The excipient information including their specifications, analytical procedures and the validation of the analytical procedures must be submitted in the **P.4** section. Information regarding excipients of human or animal origin should be provided under the **P.4.5** section (ICH, 2002). In the **P.4.6** section, for the excipients used first time in a drug product by a new route of administration- the complete details of manufacture, characterisation and controls with cross references to supporting safety data should be supplied following the drug substance format (ICH, 2002).

Similarly, to the **S.4** Control of Drug Substance section, the same information regarding the drug product is required in the **P.5** section and ICH guidelines can be followed for the required information. The information on the reference standards or materials used to test the drug product should be provided in the **P.6** section if they were not previously provided in the **S.5** section (ICH, 2002). A description of the container closure systems, identity of materials used in the construction of each primary packaging component and its specification should also be provided in the **P.7** section**.** Corresponding with **S.7** stability data of the drug substance, the same information regarding the drug product is required in the **P.8** section.

It can be seen that the information required regarding drug substance and drug product sections of Module 3 is not completely identical although there are similarities in some sections. More detailed information regarding the drug product is generally required, and this is because substances alongside the active drug substance are added to the drug dosage form. Generally, basic information is supplied at Phase I and Phase II regarding the quality of the medicinal product with detailed information supplied at Phase III submissions. An Investigational New Drug (IND) must be submitted to the US Food and Drug Administration (FDA) to initiate a clinical trial and an Investigational Medicinal Product Dossier (IMPD) must be submitted to the European Medicines Agency (EMA). The information required for Phase I clinical trial submissions of these applications to the EMA and the FDA with one batch of clinical materials will be considered further in detail.

2. CTD Module 3 Small Molecule Requirements in Europe and USA

2.1 Drug Substance Requirements for Small Molecules

For the submission of an IND application to the FDA, a brief narrative of the drug substance with selected evidence to support the chemical structure is sufficient for one batch of clinical materials, and this is the same for the IMPD requirements requested by the EMA. According to ICH guidelines, the information that can be supplied to support the chemical structure is the structural formula, relative and absolute stereochemistry, molecular formula and relative molecular mass (ICH, 2002). Physicochemical and other relevant properties can also be listed in the **S.1.3** section of the document as shown by **Table 3**. As this general information stays consistent throughout Phase I, Phase II and Phase III, sponsors that wish to initiate a clinical trial can supply the full information at Phase I application submission.

The FDA requires the name and full street address of the manufacturer in the **S.2** section, whereas the EMA requires details of all manufacturers, contractors and sites involved in the manufacture and testing of the drug substance. Flow diagrams and flow charts can be submitted to both regulatory authorities describing the manufacturing process as defined in **Table 3**. If the non-clinical manufacturing studies data is not comparable with the clinical batch data, then in the **S.2.6** section, another flow chart illustrating the manufacturing process of the drug substance is required by the EMA (EMA, 2022a). This information can also be used for the FDA submission. Brief characterisation information can be submitted in the **S.3** section for both the FDA and the EMA, and for the drug substances that comply with European, EU member state, US or Japanese pharmacopeia- no further details on impurities is required. For the **S.4** Control of the Drug Substance section**,** full description of the analytical procedures is not necessary and only the appropriate analytical methods that were used needs to be confirmed (EMA, 2022a). A primary standard must be laid down to demonstrate that the drug substance has been suitably characterised and this information needs to be submitted under the **S.5** section for both of the regulatory authorities. The same information can be submitted about the packaging material used for immediate packaging of the drug substance for the EMA and the FDA in the **S.6** section.

However separate information needs to be submitted to the FDA and the EMA in **S.7** section as the EMA requires details regarding potential degradation pathways and re-test periods for

small molecule medicinal products as well as the stability data. The FDA only requires a short narrative of the stability study, the test methods used to observe the stability of the drug substance and the storage conditions (FDA, 1995). This means there are no future amendments in this section of the IND. The FDA does not require detailed stability data nor stability protocols for Phase I application submissions. As the IND guidelines for the FDA has not changed since 1995 there is flexibility in the CMC information that can be submitted for the drug substance section of Phase I application submission compared to the EMA guidelines. The summary of the information required by the EMA and the FDA for drug substance section of the Phase I applications is displayed by **Table 3**.

Table 3. Summary of the drug substance Phase I information required for Module 3 of IMPD (EMA, 2022a) and IND (FDA, 1995) applications for small molecule medicinal products.

Drug Substance	**Europe (EMA)** **IMPD**	**USA (FDA)** **IND**
S.1	Structural formula, molecular weight, chirality/stereochemistry. A list of physico-chemical and other relevant properties that can include solubilities, pKa, polymorphism, isomerism, log P, permeability and more.	Brief narrative of the drug substance. Some evidence to support the predicted chemical structure.
S.2	The names and addresses of all the manufacturers, contractors and each planned site that are responsible for the manufacture and testing of the drug substance. Brief summary and a flow chart that describes each step with the starting materials, intermediates, solvents, catalysts and critical reagents used in the synthesis process. A flow chart describing the manufacturing process for the drug substance used in non-clinical studies needs to be submitted if the manufacturing process is different from the batches used for non-clinical studies.	The name and full street address of the manufacturer. A brief description of the manufacturing process with a list of reagents, solvents and catalysts. Flow diagrams recommended to present this information.
S.3	Brief description of the characterisation of the drug substance and the structure should be defined with appropriate methodology and relevant data. For drug substances that comply with European, US, Japanese or an EU Member State pharmacopoeia- no further details on impurities is required as long as adequate control of active substance quality from the source is discussed.	A brief characterisation of the drug substance. Information used from the EMA guidelines regarding impurities.

S.4	The specification, tests used and their acceptance criteria for the batch of drug substance used in the clinical trial. Tests regarding identity, impurities and assay are compulsory and upper limits need to be set for impurities. Impurity profiles of the batches used in non-clinical and clinical studies can be used to support the limits, and if European pharmacopeia or ICH guidelines are met then no limit justification is anticipated. References can be made to European, US, Japanese or an EU Member State pharmacopoeia for substances that comply with them, but the acceptance criteria for any relevant residual solvent or catalyst should be included in the specification. The analytical methods need to be described for all tests included in the specification, and the suitability of the analytical methods should be confirmed. Tabulated form recommended to present the acceptance limits and the parameters for performing the validation of the analytical methods. Batch results should be in a tabulated form or certificate of analysis can be submitted for the clinical batch to be used in the clinical trial as well as batches used in non-clinical studies. List of the batch number, batch size, manufacturing site, manufacturing date, control methods, and the test results should be submitted. Brief justification of the specifications and the acceptance criteria for impurities and other substances that can affect the drug product performance should be considered for substances that cannot be referenced to European, US, Japanese or an EU Member State pharmacopoeia.	Simple analytical data that can be used to support the acceptable limits of the batch of clinical materials should be submitted. The copy of the certificate of analysis can also be provided.
S.5	Parameters that have been used to characterise the batch of drug substance that was determined as the reference standard should be submitted.	Information used from the EMA guidelines.
S.6	The material used for immediate packaging of the drug substance should be identified. If materials that have not previously been approved are used, a description and specifications should be given.	Information used from the EMA guidelines.

S.7	The stability data available for Phase I clinical trial should be submitted, and chemical and physical sensitivity parameters that are essential for stability of the drug substance need to be provided. Description of potential degradation pathways should be submitted. Re-test period should be given based on available stability data. Stability data and a re-test period should be provided for drug substances covered by a Certificate of Suitability (CEP) as they do not include a re-test date.	Short narrative of the stability study and test methods used for observing the stability of the drug substance can be provided. Tabulated form of preliminary data from representative material can be submitted.

2.2 Drug Product Requirements for Small Molecules

The EMA and the FDA both require qualitative and quantitative composition of the investigational drug product. However, a brief summary of the composition of the investigational new drug can be submitted to the FDA, whilst the EMA requires a complete composition of the investigational medicinal product (IMP) in the **P.1** section. As there are no official requirements listed on the FDA IND guidance document regarding the **P.2** section, the information from the EMA requirements such as a short description of the formulation development and information on any excipients can be used for the IND submission in Phase I clinical trials.

Similar to the drug substance part, the information regarding the manufacturers for the FDA and the EMA can be provided in the **P.3** section as described in **Table 4**. Process validation is not required at this stage. There are differences in the **P.3.1** requirements for the EMA and the FDA as the EMA requires a drug product that is manufactured overseas to be imported and registered first in EEA before clinical trials. The drug release must also be carried out by a Qualified Person (QP). The FDA on the other hand does not require any registering or release information regarding an imported drug product.

Reference to European, Japanese, US or an EU Member State pharmacopeia can be made for excipient specifications in the **P.4** section for the EMA requirements. The FDA IND guidance also requires a list of all excipients and the manufacturing process information for any

excipients used in the dosage form for the first time (novel excipients). The EMA requires further details on the characterisation of the novel excipients and control of excipients in relevance to product safety (EMA, 2022a).

The full requirements for the **P.5** section of Module 3 for the EMA is listed in **Table 4** and more information regarding degradation products is required compared to the FDA. For **P.6** Reference Standards or Materials section, references can be made to the **S.5** information and the EMA requires information concerning the parameters surrounding characterisation of the reference standard to be submitted. As this information is comparable between the EMA and the FDA, the same information can be used in the submission of the IND. The intended and immediate packaging and if applicable, the outer packaging to be used for the IMP in the clinical trial information should be submitted under the **P.7** section of the IMPD application. For the **P.8** section, only the storage conditions alongside the stability data are required for the submission of the IND at Phase I clinical trials. Detailed stability data and the stability protocol should not be submitted to the FDA. This is different compared to the IMPD requirements where shelf-life as well as storage conditions of the IMP needs to be defined based on the stability profile of the drug substance and the available data (EMA, 2022a). The ongoing stability program for Phase I clinical trials should also be confirmed and a fourfold extrapolation of the stability data is suitable up to a shelf-life of 12 months (EMA, 2022a).

In the the drug product part of Module 3 for small molecules, the information that needs to be submitted to the EMA and the FDA is similar with minor differences in the **P.3, P.4, P.5** and **P.8** sections. In the instances where the IND guidance document does not include detailed requirements, references can be made to the IMPD guidelines. This information has been summarised in **Table 4**.

Table 4. Summary of drug product Phase I clinical trial information required for Module 3 of the IND (FDA, 1995) and the IMPD (EMA, 2022) applications for small molecule medicinal products.

Drug Product	Europe (EMA) IMPD	USA (FDA) IND
P.1	Complete qualitative and quantitative composition of the IMP should be defined. Table or a short statement of the dosage form and the function of each excipient should be provided.	All compounds used in the manufacture of the investigational drug product should be listed. A brief composition summary of the investigational new drug product should be submitted.
P.2	Short description about the formulation development which includes justification of any new pharmaceutical form or excipient, should be submitted.	Information used from the EMA guidelines.
P.3	Names, addresses and responsibilities of all manufacturers including contractors and each proposed site involved in the manufacture, packaging/assembly and testing should be submitted. The sites that are responsible for the import of the drug product and Qualified Person (QP) release in the EEA should be provided. If relevant, it is sufficient to indicate that re-packaging and or re-labelling is carried out at another site such as a hospital, a health centre or a clinic. Batch formula for the batch of clinical materials used in Phase I clinical trial should be presented. The successive steps of the manufacturing process including components used for each step and any relevant in process controls should be presented in a flow chart. A brief narrative description needed for the manufacturing process.	Names and full street addresses of the manufacturers of the clinical trial drug product can be provided. A brief written description of the manufacturing process and a flow diagram describing the manufacturing process should be submitted.
P.4	Reference to the European, US, Japanese or an EU Member State pharmacopoeia for excipients to be indicated. For excipients not covered by any of the mentioned pharmacopoeias- references can be made to the relevant food-chemical regulations (e.g., FCC) or an in-house monograph should be provided with the analytical methods used. Details needed for the manufacturing process, characterisation and control in relevance to product safety for novel excipients.	A list of should be submitted regarding excipients and the quality of the inactive ingredients should be cited. The inactive substances used in the manufacture that may appear in the drug product and those which may not be included but are used in the manufacturing process should also be listed. Additional manufacturing information required for novel excipients.

P.5	Specifications of the chosen release and shelf-life should be provided, with the test methods and acceptance criteria. Tests on the identity, assay and degradation products should be provided. Upper limits can be set for individual degradation products and the sum of degradation products. The impurity profiles of the batches used in non-clinical studies of the drug substance should support these limits. All tests included in the specification should have a description of analytical methods. Detailed description of the analytical procedures not necessary. The suitability of the analytical methods used should be established. A tabular form of acceptance limits and parameters for validation of the analytical methods should be submitted. Tabulated form of batch results or certificates of analysis for the batch to be used in the Phase I clinical trial should be presented. A list containing the batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results to be provided. Any additional impurities or degradant seen in the IMP but not included in section **S.3.2** need to be listed. Brief justification the specifications and the acceptance criteria for degradation products and other parameters that is important to the drug product performance.	Brief narrative of the proposed acceptable limits and analytical methods that are utilised to assure the identity, strength, quality, and purity of the drug product should be submitted. The copy of the certificate of analysis of the clinical batch can also be submitted.
P.6	Parameters for characterising the reference standard should be submitted. References can be made to **S.5**.	Information used from the EMA guidelines.
P.7	Immediate intended packaging and if relevant, the outer packaging used for the IMP should be submitted. If materials that have not previously been approved are used, or the drug product is packed in a non-standard administration device, a description and specifications should be presented.	Details of proposed container/closure system should be submitted.
P.8	The stability profile of the active substance and the available data on the IMP can be used to define the shelf-life and storage conditions of the IMP. A tabular form should be used to present the stability data. If stability studies are conducted in parallel with clinical studies through its entire duration, then extrapolation may be used. The confirmation that an ongoing stability program will be carried out	Short narrative of the stability study and test methods used for observing the stability of the drug product in the recommended closure system and storage conditions can be provided. Tabulated form of the preliminary data based on representative material can be submitted.

	with the relevant batch for Phase I clinical trials and studies under accelerated and long-term storage conditions will be initiated prior to the start of the clinical trial should be given. Results summary to be submitted in a tabulated form.	

3. CTD Module 3 Biological Requirements in Europe and USA

3.1 Active Substance Requirements for Biologics

The term 'drug' is commonly used to describe chemical entities, therefore the '**S**' mentioned for biologics in this portion of the review will be considered as active substance. It can be difficult to assure the quality of biological medicinal products because they usually contain number of product variants and process related impurities whose safety and efficacy profiles that are challenging to predict (EMA, 2022b). For biologics, a brief description regarding the predicted structure should be submitted with the glycosylation sites or other post-translational modifications indicated in the schematic amino acid sequence for the **S.1** section of the IMPD application. The relative molecular mass, physicochemical properties and other relevant properties including the biological activity should also be provided in this section. All of this information can also be applied to the IND requirements regarding a brief narrative of the active substance.

The manufacturer information in **S.2.1** is similar to the requirements asked by the EMA for chemical entities in the IMPD application, but for biologics batch release information is required as well. The manufacturing process which usually starts with one or more vials of the cell bank and includes cell culture, harvest(s), purification, modification reactions and filling needs to be adequately described for biologics (EMA, 2022b). A flow chart describing process parameters should be given in the **S.2.2** section. The control strategy is concentrated on the safety relevant in-process controls (IPCs), and acceptance criteria for critical steps needs to be determined for Phase I material (EMA, 2022b). The control limits are dependent on a limited number of development batches, in this case one batch of clinical materials, therefore they are considered preliminary and as further process knowledge is obtained,

further details of IPCs should be presented and the acceptance criteria should be evaluated (EMA, 2022b).

In the **S.2.3** Control of materials section, a brief description along with a flow chart on development of the Master Cell Bank (MCB) should be provided. This involves source and generation of the cell substrate, an analysis of the expression vector used to genetically modify the cells and included in the parental / host cells (EMA, 2022b). The preparation of MCBs and working cell banks (WCBs) is displayed by **Figure 1** and a WCB is not always established.

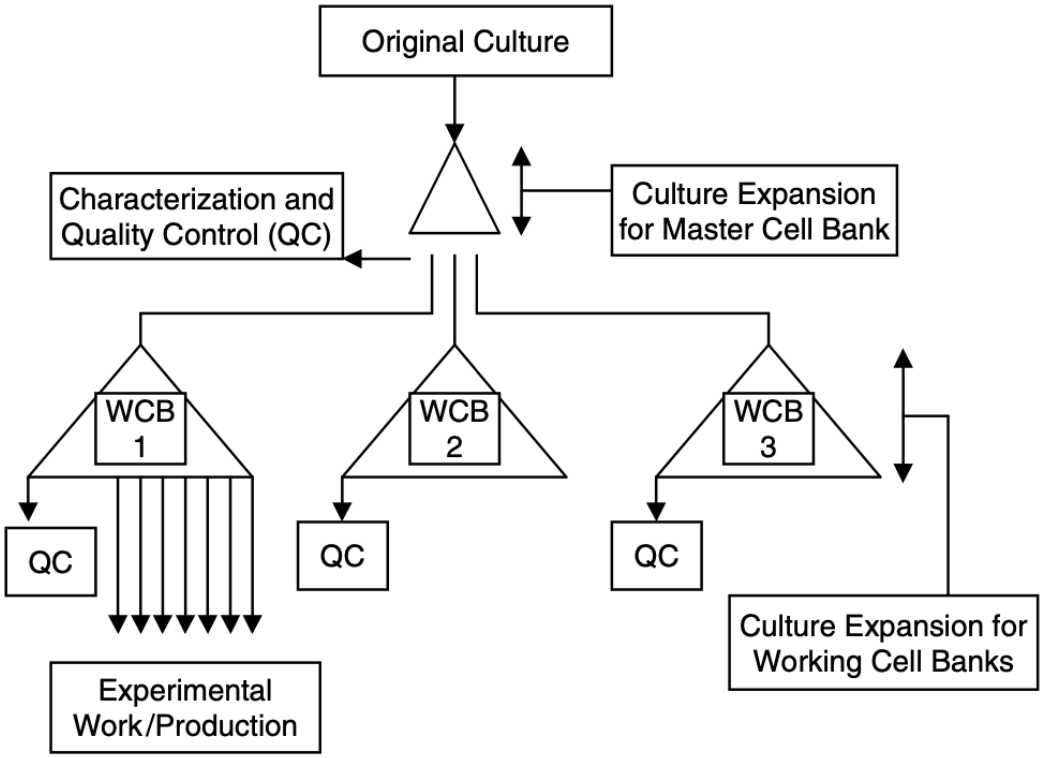

Figure 1. The preparation of master cell banks (MCBs) and working cell banks (WCBs) from cell culture (Stacey, 2004). The MCB is an aliquot of a single pool of cells that has been prepared from the selected cell clone and dispensed into multiple containers under defined conditions, and the MCB is used to derive all WCBs (ICH, 1997).

The MCB needs to be established before the beginning of Phase I trials and the characterisation of cell banks is necessary for appropriate phenotypic and genotypic markers in the confirmation of identity, viability, and purity of cells used for creation of the MCB (EMA, 2022b). Brief description of the manufacturing process with a flow diagram should also be given for the IND application. There is limited data available at Phase I regarding the tests and acceptance criteria for the control of critical steps in the **S.2** section, therefore only the existing data should be submitted in the IMPD. There are no requirements regarding the process validation data in the submission of the IMPD but the data should be gathered throughout development process (EMA, 2022b).

In the **S.2.6** Manufacturing Process Development section of the IMPD for biologics, the EMA requires descriptions of the manufacturing processes used to produce each batch of materials used in non-clinical and clinical studies and this is because an appropriate link must be established between pre-change and post-change batches (EMA, 2022b). If changes were introduced during the development to the manufacturing process, then a comparability exercise should also be carried out to demonstrate that the quality of active substance has not been impacted (EMA, 2022b). The further information required for biological drugs in the IND application can be utilised from the EMA requirements, and the aim is to convince the FDA regulators that the active substance has been generated under controlled conditions.

Adequate characterisation is required for both the EMA and the FDA in the **S.3** section and the biological activity should be determined before Phase I studies. Process related impurities such as host cell proteins, host cell DNA, media residues and column leachables should be discussed (EMA, 2022b). Any product related impurities such as precursors, cleaved forms, degradation products, aggregates need to also be considered (EMA, 2022b). Since only one batch of clinical materials has been manufactured, test results from appropriate clinical and non-clinical batches should be given as comparability of the data and materials is required in the **S.4** section for the IMPD application. The consistency between different batches is confirmed by a well-characterised reference material and a primary standard needs to be laid down. Therefore, this information should be provided in the **S.5** section of the IMPD and then can also be used for the IND application.

Relevant immediate packaging material used for the active substance can be submitted in the **S.6** section, and any potential interactions between the active substance and the packaging should also be considered for the EMA and the FDA. For the EMA, a stability protocol that contains the recommended storage period of the active substance should be provided in the **S.7** section. Since most biological medicinal products are known to be labile, shelf-life is established rather than a re-test period which is different to the requirements of small molecule medicinal products (EMA, 2022b). At least 3-months stability data and 6-months shelf-life data with non-substantial changes is required for the EMA, whereas the FDA does not require any information regarding the shelf-life of biologics.

Detailed requirements are needed for the EMA in the Module 3 active substance section of biologics compared to the FDA and this information has been summarised in **Table 5**. The EMA requires further information regarding the **S.2**, **S.4**, **S.5**, **S.6** and **S.7** sections for biologics compared to the FDA.

Table 5. Summary of the active substance Phase I information required for Module 3 of the IND (FDA, 1995) and the IMPD (EMA, 2022b) applications for biological medicinal products.

Active Substance	Europe (EMA) IMPD	USA (FDA) IND
S.1	Brief general information and description of the anticipated structure. Information of higher-order structure, schematic amino acid sequence that indicates any glycosylation sites or other post-translational modifications along with the relative molecular mass should be submitted. The biological activity, physico-chemical and other relevant properties of the active substance should be listed. The proposed mechanism of action should also be discussed.	Brief description of the investigational medicinal product, including biological characteristics. During early development, the structure information can be limited.
S.2	The name and address of all the manufacturers, including contractors and each planned site involved in the manufacture, testing and batch release. One or more vials of cell bank is usually used to start the manufacturing process and this includes cell culture, harvest(s), purification, modification reactions and	Name and full street address of manufacturer with a flow diagram describing the manufacturing process. More information required for biological products which can be utilised from the EMA guidelines.

	filling. A summary of storage and shipping conditions should be provided. A flow chart containing all relevant process parameters and in-process-testing to be provided. Control strategy should focus on safety relevant in-process controls (IPCs) and acceptance criteria for critical steps in the manufacture of Phase I material. Batch and scale defined. Materials used in manufacture of active substance identified. Master Cell Bank (MCB) should be established before the initiation of Phase I trials and a Working Cell Bank might not always be determined. The data concerning generation, qualification and storage of cell banks is necessary. Results of the tests and characterisation of MCB and WCB required. Information on the generation, qualification and storage of the cell banks is also required. Information on the nucleic acid sequence of the expression cassette and sequence of the coding region needs to be confirmed before the initiation of clinical trials. Submission of the available tests and acceptance criteria of the control of critical steps in the manufacturing process is required. Descriptions of the manufacturing processes of non-clinical and clinical batches used in studies can be utilised to establish a connection between pre-change and post-change batches. A flow chart and lists can be used to present the process changes. Representative to the IMP used in non-clinical studies should be utilised for comparability testing if changes are introduced to manufacturing process.	
S.3	Brief characterisation of the biotechnological or biological substance and satisfactory characterisation to be completed in the development phase prior to Phase I clinical trial. Relevant information on higher-order structure, including glycoforms and other modifications of the active substance should all be submitted. Biological activity should also be	Brief characterisation and information on impurities.

	determined. Process related impurities and product related impurities should be identified.	
S.4	Tests and defined acceptance criteria are compulsory for the quantity, identity and purity of active substance. Test for biological activity is required or otherwise justified. In early clinical development, the suitability of the analytical methods should be confirmed. A tabular form of the acceptance limits and parameters for performing validation of the analytical methods should be presented. Only one of clinical batch of materials has been manufactured, therefore the test results from appropriate clinical and non-clinical batches should be presented. List of information regarding batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results along with the use of the batches is required. Justification of the specifications required.	Simple analytical data that can be used to support the acceptable limits of the batch of clinical materials should be submitted. The copy of the certificate of analysis can also be submitted.
S.5	Well characterised reference material is needed, and the manufacturing process of the reference material should be submitted.	Information used from the EMA guidelines.
S.6	The material used for immediate packaging of the drug substance should be provided. Any potential interactions between the drug substance and the packaging should also be discussed.	Information used from the EMA guidelines.
S.7	Stability data for at least one batch and limited storage conditions. Tabulated form for relevant stability data is required. The batches tested, date of manufacture, process version, composition, storage conditions, time-points, test methods, acceptance criteria and results are to be included. Real-time stability studies need to be performed monthly for first 3 months and at 3-month intervals for shelf-lives of one year or less. Drug substances with proposed shelf-lives of more than 1 year, the stability studies need to be performed every 3 months during the first year of storage, every 6 months during the second year, and annually afterwards.	Short narrative of the stability study and test methods used for observing the stability of the active substance can be provided. Tabulated form of preliminary data from representative material can be submitted.

3.2 Medicinal Product Requirements for Biologics

As previously mentioned, the term 'drug' is commonly used to describe chemical entities, therefore the '**P**' mentioned for biologics in this portion of the review will be considered as medicinal product. In the **P.1** section as with the small molecule drug product requirements, a total qualitative and quantitative composition of the IMP is required for the IMPD application whilst the FDA only requires a brief summary of the quantitative composition and a complete qualitative composition of the dosage form. A summary of the type of container and closure used for the dosage form should also be provided for the biological IMPD application (EMA, 2022b).

In the **P.2** section, a brief description of the formulation development and justification for any excipients should be submitted for the EMA. There also needs to be a demonstration of the stability of the molecule and that proposed formulation and packaging will not affect the correct dosing in the **P.2** section for the IMPD application. The information used in this section can also be applied to the IND application. **Table 6** describes the information required for the **P.3** section of Module 3 in the applications and a flow chart that includes relevant IPCs (process parameters and in-process-tests) is required for the IMPD application. An aseptic process is used to manufacture monoclonal antibodies and this is considered a non-standard manufacturing processes (EMA, 2022b). Therefore, this manufacturing process needs to be described in sufficient detail for monoclonal antibody medicinal products in the application. Tests and acceptance criteria for the control of critical steps in the manufacturing process can be reduced at Phase I due to limited data availability.

The excipients of human or animal origin information should be provided in the **P.4.5** section of the IMPD application and viral safety data according to the EMA guidelines should also be provided. This information can also be used for the IND application. Same principles from the active substance section can be applied in the **P.5** section for the medicinal product. Analytical methods and their limits as well as the bioactivity are required to ensure a correct dosing and upper limits needs to be set for impurities not covered in the active substance section (EMA, 2022b). The considerations for characterisation of the reference standard can be provided with references made to **S.5** where applicable for the EMA and the FDA. The intended primary

packaging to be used for the IMP in the clinical trial should also be described in the **P.7** Container closure system section. More details can be requested by the EMA for biological products that are for parenteral use as there is possibility of interactions between the product and the container closure system (EMA, 2022b).

The same requirements needed in the active substance section are also utilised to the medicinal product **P.8** Stability section for the EMA and the FDA. The medicinal product section concerning the EMA and the FDA requirements of biologics has been summarised in **Table 6**. The information required for this section is similar for the regulatory authorities but the EMA does require more information regarding the medicinal product compared to the FDA in the **P.1**, **P.2, P.3, P.4** and **P.8** sections of Module 3.

Table 6. Summary of drug product Phase I information required for Module 3 of IND (FDA, 1995) and IMPD (EMA, 2022b) applications for biological medicinal products.

Medicinal Product	**Europe (EMA)** **IMPD**	**USA (FDA)** **IND**
P.1	Complete qualitative and quantitative composition of the IMP should be defined in a short statement or tabular form. The type of container and closure used for the dosage form should be outlined.	All compounds utilised in the manufacture of the investigational medicinal product should be listed. A brief composition outline of the investigational new medicinal product should be provided.
P.2	Brief description of formulation development and justification for any excipients. Demonstration of the stability of the molecule and that intended formulation and packaging will not affect the correct dosing.	Information used from the EMA guidelines.
P.3	The name and address of all the manufacturers, including contractors and each planned site involved in the manufacture, testing and batch release. Batch formula and flow chart describing all manufacturing steps should be provided. Relevant IPCs (process parameters and in-process-tests) and a brief process description to be included. Aseptic non-standard processes should be illustrated in necessary detail.	Name and full street address of the manufacturer of the clinical trial medicinal product should be provided. A flow diagram with a written description describing the manufacturing process should be provided.
P.4	Reference to the European, US, Japanese or an EU Member State pharmacopoeia for excipients to be specified. For excipients not	A list of usually no more than 1 or 2 pages of written pages should be submitted and the quality of inactive

	covered by any of the mentioned pharmacopoeias- references can be made to an in-house monograph with the analytical methods used should be provided. The safety evaluation information should be given for excipients of human or animal origin. Details needed for the manufacturing process, characterisation and control in relevance to product safety for novel excipients.	ingredients should be cited. Additional manufacturing information required for novel excipients.
P.5	Tests for content, identity and purity are mandatory and biological activity test should be included. Preliminary acceptance criteria for safety considerations. Upper limits need to be set for impurities not covered in the drug substance section. Analytical methods for all tests should be described. Only one of clinical batch of materials has been manufactured, therefore the test results from appropriate clinical and non-clinical batches should be presented. A list of batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results to be provided. Any additional impurities or degradant observed in the IMP but not included in section **S.3.2** should be listed. Justification of the product specification should be submitted.	Brief narrative of the proposed acceptable limits and analytical methods that are utilised to assure the identity, strength, quality, and purity and biological activity of the medicinal product should be submitted. Preliminary specifications for adequate assessment of the bioactivity of the medicinal product should be submitted. The copy of the certificate of analysis of the clinical batch can also be submitted.
P.6	Parameters for characterising the reference standard should be provided. References can be made to **S.5**.	Information used from the EMA guidelines.
P.7	Immediate intended packaging and if appropriate, reference to relevant pharmacopoeias can be made. If materials that have not previously been approved are used or the drug product is packed in a non-standard administration device, there is a requirement of a description and specifications. More details required for products that are for parenteral use.	Details of the proposed container closure system.
P.8	Same requirements needed in the active substance section concerning stability is applied in this section.	Short narrative of the stability study and test methods used for observing the stability of the medicinal product in the recommended closure system and

		storage conditions can be provided. Tabulated form of the preliminary data based on representative material can be submitted.

4. Conclusion

Since different applications are required for the clinical filing of a medicinal product, the CTD has helped sponsors with arranging the required CMC information in Module 3 in a standardised format. An IND application needs to be submitted to the FDA to initiate a clinical trial and an IMPD needs to be submitted to the EMA. These applications stay the same for small molecule and biological medicinal products, however the content required in these applications are different due to the nature of the medicinal product. The requirements for the drug substance and the drug product parts of Module 3 are split into separate sections, and some required information can be limited at Phase I clinical trial stage. Manufacture, Characterisation and Stability are examples of the sections that can be provided in more detail at Phase II and Phase III stages.

Although the dossiers can be submitted simultaneously to each regulatory agency the information they request can be different, for example the FDA does not require any shelf-life data regarding the stability of the drug substance or the drug product for biologics, but the EMA requests a minimum of 3-month self-life data. Another example where they differ is in the Manufacturer information provided in the **P.3.1** section as the EMA requires a medicinal product produced overseas to be registered first and released by a qualified person. On the other hand, the FDA does not require the medicinal product to be registered first or any further release information. It has been a recurrent theme in this review where the EMA requires further details in the substance and the product sections for medicinal products compared to the FDA.

The IND guidance document has also not updated since 1995, which means it can be advantageous when drafting the application as there is flexibility in the information that can be provided to convince the FDA regulators. Alternatively, the EMA continues to update their guidance documents regularly with the most recent update being in 2022 for chemical entities as well as biologics. This means that further information regarding the medicinal product needs to be submitted to the EMA. Although there are guidelines set by the ICH and the regulatory authorities regarding the information that can be submitted in these clinical trial applications, the main objective of a sponsor is to convince the regulators that the medicinal product has been produced under controlled conditions and is safe to be used in the clinical trials with sufficient evidence.

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References

EMA (2022a) *Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.* Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en-1.pdf (Accessed: 16 August 2023).

EMA (2022b) *Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials*. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal_en-2.pdf (Accessed: 16 August 2023).

FDA (1995) *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.* Available at: https://www.fda.gov/media/72057/download (Accessed: 14 August 2023).

FDA (2023) *CFR - Code of Federal Regulations Title 21.* Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.3#:~:text=Drug%20substance%20is%20an%20active,in%20the%20synthesis%20of%20such (Accessed: 14 August 2023).

ICH (1997) *Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.* Available at: https://database.ich.org/sites/default/files/Q5D%20Guideline.pdf (Accessed: 14 August 2023).

ICH (2002) *THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY – M4Q(R1).* Available at: https://database.ich.org/sites/default/files/M4Q_R1_Guideline.pdf (Accessed 06 July 2023).

ICH (2003) *STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2).* Available at: https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf (Accessed: 29 August 2023).

Stacey, G. (2004) 'Fundamental issues for cell-line banks in biotechnology and regulatory affairs.' Life in the frozen state. CRC Press.