

Monopolies on Biologics, including Vaccines:

THE CASE FOR REFORM IN
INTELLECTUAL PROPERTY AND
PHARMACEUTICAL REGULATION

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Three more authors, who substantially contributed to this report, wish to remain unnamed due to a change in their professional circumstances over the course of this project and limitations thereof.

Ramya Sheshadri and Roshan John worked on Chapter 1 of this report; Chetali Rao and Gopakumar KM worked on Chapter 2 of this report. Achal Prabhala coordinated the project and worked on both chapters as well as on general aspects of the work, common to both chapters.

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Executive Summary

Context

This report, a collaborative effort from the AccessIBSA project and the Third World Network (TWN), examines monopolies on biologics, including vaccines, in India, and makes the case for reform of Indian laws and policies governing the management of intellectual property and pharmaceutical regulation. It does so through a deep dive into India's experience with biologics (a category that includes vaccines) over the last decade.

The first chapter of this report examines intellectual property monopolies, primarily through patents, on biologics. The second chapter of this examines monopolies created by pharmaceutical regulation, primarily through trade secrets.

Biologics are popularly referred to as macromolecules, which are large complex molecules originating from bacteria, yeast, insects, plants, and engineered mammalian cells, and is a category that includes both biotherapeutics and vaccines.

We began work before the Covid pandemic was declared a global health emergency in 2020, and its publication now coincides with a universal awareness of the importance of affordable and accessible biologics, especially vaccines – because, we are now fully aware of both the importance of non-vaccine biologics (such as monoclonal antibodies, popularly referred to as mAbs) for the treatment of Covid, as well as vaccines for the prevention and mitigation of Covid.

We could extend the argument further: there is now a better understanding of vaccine platform technologies, both traditional and new, such as the difference between traditional vaccines, produced with pre-pandemic technologies and generally with biological, cell-based material, as well as those made with cutting-edge mRNA, or messenger RNA technology, which employ a synthetic process of production, that involve routine lab-based biochemistry.

Intellectual Property

Intellectual property creates significant monopoly barriers to accessing biologics, including vaccines. Patent estates for biologics typically tend to be vast, often numbering several hundred, as well as dispersed across many technologies and sub-categories, thus distinguishing them from the relatively more compact patent estates of small molecule pharmaceuticals. They are harder to identify and also more difficult to separate into primary and secondary patent categories. They are also harder to identify per se, and as a result, without demanding categorisation from the patent application, it is harder for patent offices and examiners to create policies around the examination of such patents.

As a result, we found that even when a patent application could be rejected, the rejection was turned into a grant with the applicant tweaking the original claims. Additionally, there was significant inconsistency in the evaluation of comparable applications. Our findings suggest that if the patent office applied strict and consistent patentability criteria encoded in the law, to biologics, and set the high threshold level of patentability that our law requires, it is likely that many patent claims on biologics would be deemed ineligible for patent protection.

At this time, we do not have specific examination guidelines and regulations that govern the evaluation of biologic patent applications, resulting in what can only be described as an ad-hoc state of confusion. While there are patent examination guidelines for patents relating to biotechnology, this is an insufficient category to cover the complexity of biologics. This, in turn, calls into question the functioning of the Indian Patent Office and raises serious questions about its responsibility and accountability to the people it serves.

Lastly, we need to develop the tools to overcome intellectual property monopolies on biologics – and we need an expansion of the terms of compulsory licensing, in order to bring them in line with the terms of government use, so that the compulsory licensing process can cover products without a set of comprehensively identifiable patents, as well as technological platforms.

A system that identified intellectual property on biologics, which allowed for guidelines designed for evaluating patent applications around this category, combined with a broad and reflexive set of measures to overcome such intellectual property in the interests of public health, would not only create better access to biologics, but also access to other frontier technologies in crucial domains such as health and climate change, whenever they emerge.

Pharmaceutical Regulation

Compared to small molecules, vaccines and other biologics have a higher degree and range of entry barriers due to monopolies resulting from trade secrets and pharmaceutical regulation. These entry barriers lessen the number of competitors in the market and compromise the intensity of competition. As a result, biosimilars are fewer in number and in their ratio to originator biologics than is the case for small molecules, they take longer to come to market, and the price of biosimilars does not drop as much as it does when generic small molecules enter the market.

The role of trade secrets and regulatory barriers in creating monopolies around biologics, including vaccines, is perhaps not adequately understood or appreciated. In the case of small molecules, generic manufacturers do not have to repeat tests for safety and efficacy of the product, since these have been already established by the originator; they only need to show equivalence. Therefore, in jurisdictions where data exclusivity does not exist, that is, where the pharmaceutical regulatory agency is allowed to rely on originator data, a generic manufacturer only needs to show bio-availability and bio-equivalence, which are not time-consuming or expensive to carry out. By contrast, almost all countries require manufacturers of follow-on biologics to conduct clinical trials – either in full or part,

such as comparative clinical trials, which are both time-consuming and expensive – in order to be approved.

This requirement of clinical trials is largely due to the regulatory assumption that the process is the product, and therefore that the non-originator has to follow the manufacturing process of the originator. Biologic manufacturers have effectively used trade secrets as a tool to manage competition. Because of the perpetual time protection trade secrets offer, as against a limited 20-year patent term, they present an opportunity for biologics manufacturers to stonewall generic competition. Much of the technical and critical know-how that relates to the development of biologics is protected as a trade secret.

Biosimilars, which are non-licensed biologic products made by a manufacturer other than the originator, require animal studies as well as comparative clinical trials, that is, trials that use both the originator product and the biosimilar. However, new developments have led to a reconsideration of the biosimilar approval process. In 2021, the Medicines and Healthcare products Regulatory Agency in the UK changed its guidelines for the approval of biosimilars in the country by dropping the need for comparative clinical trials. In 2022, the WHO similarly amended its own guidelines for the approval and regulation of biosimilars, by doing away with the compulsory need for comparative clinical trials.

In the case of vaccines, however, which are a distinct category of biologics, there is no regulatory pathway whatsoever for non-originators, or generic or follow-on manufacturers. While there are tremendous benefits to be gained from having a faster, cheaper process for biosimilar approval, the covid pandemic laid bare the need to have similar reform instituted in the process of “generic” vaccine approval.

Within vaccines, there is a further problem, which is an inability – so far – to take advantage of the most significant milestone of the pandemic, which is the approval of mRNA-based vaccine technology for use in humans. We now have vaccine technology that eliminates the cell-based biological component, and therefore means that a range of equivalence pathways potentially open up.

Reassessing, and then fixing, the outsize role that trade secrets play in the pharmaceutical regulation of vaccines is a crucial step in fortifying ourselves against this pandemic, and those to come.

Introduction

Biologics—A Primer

In this report, we use the word 'biologics' to refer to biotherapeutics and vaccines. Biologics have been in existence for decades but the term 'biologics' emerged after the growth of the biotech industry in the United States. Broadly speaking, these are macromolecules either originating from living organisms or synthesised or semi-synthesised macromolecules, or a process involved in isolating them for treating, diagnosing or preventing diseases. There is no agreed definition of biologics; the USPTO and the FDA define biologics as including "a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins". Biologics include sugars, proteins, nucleic acids or a complex combination of these substances, or even living entities such as cells and tissues.³ Biologics may be isolated from a variety of natural sources - human, animal or microorganism - or these may be produced by biotechnological methods and other cutting-edge technologies. Gene-based and cellular biologics for example, are often at the forefront of biomedical research, and are widely used to treat a variety of medical conditions for which no other treatments are available.¹ Some prominent biologics are used for the treatment of Crohn's disease, rheumatoid arthritis, ulcerative colitis and other autoimmune diseases. They have also contributed to significant advances in the treatment of cancer.² There has been a continuous trend in the increase in the number of biologics approved by FDA, and a record 59 entities with at least 17 biologics were approved in the year 2018.³ For this study, we considered the following biologics - peptides, proteins, antibodies, nucleic acids, cells, sugars, vaccines and viruses. These are within the realm of IPC codes accepted as biologics as reported earlier.⁴

Biologics v/s Small Molecules: A Growing Trend

There are two classes of therapeutics in today's market - small molecules (<500 Da) and biologics (>5000 Da). In pharmacology, the difference between small molecules and biologics is exemplified by the occupancy of the target site. The effect of a drug on the body differs based on absorption, distribution, metabolism, and elimination (ADME) by the body, which in turn depends on the size and structural complexity of the therapeutic compound.⁵ The binding of a therapeutic compound to its target is akin to a lock and key model. The lock (biological target) would accept or accommodate a key (drug) receptive to the grooves on the key. The topology of the chemical groups are the grooves of a drug molecule and the affinity of these towards a biological target determines the efficacy and

¹ <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm>

² E Michael Lewiecki (2015) *Biological therapy: chronicling 15 years of progress*, *Expert Opinion on Biological Therapy*, 15:5, 619-621, DOI: 10.1517/14712598.2015.1009890

³ Beatriz G. de la Torre and Fernando Albericio, *The Pharmaceutical Industry in 2020. An Analysis of FDA Drug Approvals from the Perspective of Molecules*, *Molecules*, Vol. 26, 627, 2021
<https://www.mdpi.com/1420-3049/26/3/627>

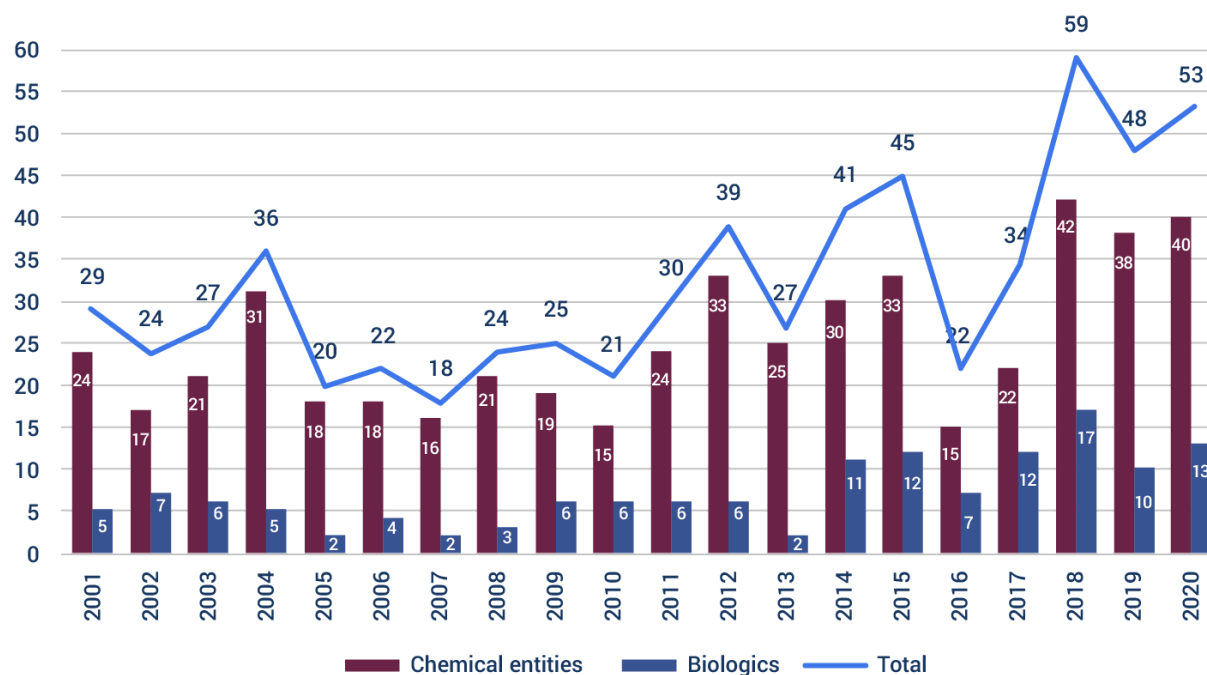
⁴ *A Patent Analytics Study on the Australian Pharmaceutical Industry, 2015*

<https://archive.industry.gov.au/industry/IndustrySectors/PharmaceuticalsandHealthTechnologies/Pharmaceuticals/Documents/PatentAnalyticsStudyOnTheAustralianPharmaceuticalIndustry.pdf>

⁵ Liang Zhao, Tian-hua Ren, Diane D Wang, *Clinical Pharmacology Considerations in Biologics Development*, *Acta Pharmacologica Sinica*, Vol. 33, 1339-1347, 2012.

potency of the compound or the lack of it to other side effects. This is relatively easier to understand in small molecules. However, macromolecules, especially proteins, also adopt a tertiary structure in addition to the presentation of chemical groups. A tertiary structure is an intertwined network of connections (non-covalent interactions) to preserve the water repelling chemical groups inside and water loving chemical groups outside the tertiary structure. The tertiary structure depends on aspects such as the environment around the molecule, temperature and so on.⁶

Small molecule v/s macromolecule comparison⁷



New chemical entities and biologics approved by the FDA in the last two decades

⁶ Bajaj M, Blundell T, *Evolution and the tertiary structure of proteins*. Ann Rev Biophys Bioeng 13:453–492, 1984

⁷ <https://www.mdpi.com/1420-3049/26/3/627>

Significance of Biologics

Biologics have become the most sought-after pharmaceuticals in the world; by 2017 seven out of the top 10 bestselling drugs are biologics in the United States of America.⁸

The Covid pandemic further underscored the central place of biologics, including vaccines, in our world, with revenues of the top vaccine manufacturers exceeding tens of billions of dollars on Covid vaccines alone.⁹

Active ingredient and therapeutic indication of bestselling biologics, 2020¹⁰

PRODUCT NAME	ACTIVE INGREDIENT	MAIN THERAPEUTIC INDICATION
Humira®	Adalimumab	Immunology (Organ Transplant, Arthritis etc.)
Keytruda	Pembrolizumab	Immunology (Melanoma, lung cancer, head and neck cancer)
Stelara	Ustekinumab	Immunology (Crohn's disease)
Eylea	Aflibercept	Ophthalmology
Opdivo	Nivolumab	Immunology (Cancer)
Dupilixent	Dupilumab	Dermatology
Enbrel®	Etanercept	Immunology (Organ Transplant, Arthritis etc.)
Pevnar 13	Pneumococcal conjugate vaccine	Prevention of Streptococcus pneumonia
Avastin®	Bevacizumab	Oncology
Trulicity	Dulaglutide	Diabetes

Humira® (adalimumab) continues to be one of the top selling drugs even in the year 2020.¹¹ This was followed by other key biological drugs used in the treatment of cancer, arthritis and diabetes.¹² Though biologics are hailed as the new medical breakthrough, IP protection has had an impact on the pricing, affordability and market access to these biologics in developed countries. There have been multiple measures that are being proposed to address this issue such as bills to regulate the pricing,

⁸ <https://www.pharmacompass.com/radio-compass-blog/top-drugs-by-sales-in-2017-who-sold-the-blockbuster-drugs>

⁹ <https://www.genengnews.com/a-lists/top-11-best-selling-covid-19-vaccines-and-drugs-of-h1-2021/>

¹⁰ <https://www.pharmacompass.com/data-compilation/top-drugs-by-sales-in-2020-who-sold-the-blockbuster-drugs>

¹¹ <https://www.pharmacompass.com/data-compilation/top-drugs-by-sales-in-2020-who-sold-the-blockbuster-drugs>

¹² <https://www.thebalance.com/top-biologic-drugs-2663233>

increasing transparency in regulatory process, curtailing patent term and patent litigation involving biosimilar drugs.¹³

It's not surprising that the IPO has been receiving an increasing number of patent applications for drugs in the field of biotechnology, which would include biologics. The following charts show the growing trends of patent applications filed and granted over the years in the fields of biotechnology, biochemistry, and microbiology.¹⁴

Patent applications filed in relation to biologics at the IPO

YEAR	BIO-TECHNOLOGY	BIOCHEMISTRY	MICROBIOLOGY
2012-2013	832	366	547
2013-2014	647	190	495
2014-2015	1035	384	308
2015-2016	887	372	316
2016-2017	876	258	253
2017-2018	992	331	297

Patent applications granted in relation to biologics at the IPO

YEAR	BIO-TECHNOLOGY	BIOCHEMISTRY	MICROBIOLOGY
2012-2013	144	17	27
2013-2014	220	56	21
2014-2015	262	66	41
2015-2016	185	52	44
2016-2017	333	73	81
2017-2018	505	142	108

¹³ <https://www.biosimilardevelopment.com/doc/legislation-to-watch-proposed-bills-impacting-biologics-patent-disputes-0001>

¹⁴ These categories are based on the IPO's classification of applications according to various 'fields of invention', which is an internal classification for segregating the applications for examination by the appropriate department within the IPO. The status of applications according to fields of invention can be viewed here: <https://iprsearch.ipindia.gov.in/DynamicUtility/DynamicStatus/INPROCESSDetail> (historical link used at the time of research here: <https://ipindiaservices.gov.in/DynamicUtility/DynamicStatus/INPROCESSDetail>). Please note that due to the frequent shifting of html links and rearrangement of databases at the Indian Patent Office, it can be difficult to provide a stable long-term link to the patents indexed within.

1. | Monopolies on Biologics, including Vaccines, from Intellectual Property

Chapter 1: Monopolies on Biologics, including Vaccines, from Intellectual Property

Summary

In this section of the report, we analyse how the Office of the Controller General of Patents, Designs and Trademarks (generally known as the Indian Patent Office) has examined patent applications involving biologics. They are also popularly referred to as macromolecules, which are large complex molecules originating from bacteria, yeast, insects, plants, and engineered mammalian cells, and is a patent category that includes vaccines. We analyse the patenting trend of biologics in India, from 2012 to 2018.

Though work on this report began before the Covid pandemic was declared a global health emergency in 2020, its publication now coincides with a universal awareness of the importance of affordable and accessible biologics, especially vaccines. Through the pandemic, humanity at large has been repeatedly made aware of both the importance of non-vaccine biologics (such as monoclonal antibodies, popularly referred to as Mabs) for the treatment of Covid, as well as vaccines for the prevention and mitigation of Covid. Further, there is now a better understanding of vaccine platform technologies, both traditional and new, such as the difference between traditional vaccines, produced with pre-pandemic technologies and generally with biological, cell-based material, as well as those made with cutting-edge mRNA, or messenger RNA technology, which employ a purely synthetic process of production, that involve routine lab-based biochemistry, but not the actual use of cell-based biology.

Our findings on this increasingly crucial category of pharmaceuticals are as follows:

1. The patent estates for biologics typically tend to be dispersed across many technologies and sub-categories, thus distinguishing them from the relatively more compact patent estates of small molecule pharmaceuticals. Therefore, not only are they harder to identify – since, at the patent application stage, it can be hard to connect the different products and technologies that comprise the whole patent estate of a single biologic drug – they are also more difficult to separate into primary and secondary patent categories as is typical with the patents covering a small molecule pharmaceutical.
2. While there is a robust global commercial market for biologics, we have not developed specific patent classification codes either at the national or international level in order to categorise them accurately. One of the reasons it is so hard to identify patent applications relevant to a particular biologic is that patent examiners have no established guidelines to do so, no categories to mark the result of their findings, and also no universally established rules

by which to share such information across borders – unlike with other categories of technology, for which it is possible to accomplish these basic identification objectives. With biologics not being easily identifiable, it is difficult for patent offices and examiners to create policies around them.

3. Theoretically, we have existing provisions in Indian patent law that could cover the examination of patent applications relating to all biologics, including vaccines. But our existing guidelines and regulations do not effectively guide patent examiners as to how to interpret the law and evaluate biologic patent applications. (Though we have guidelines covering the broad category of biotechnology, these are insufficient.) Additionally, there are no clear precedents we can follow, since the same is largely true for most patent legislations elsewhere in the world, including in high-income countries. Without specific examination guidelines and regulations that govern the effective evaluation of biologic patent applications, the process is currently ad-hoc and fraught with misinterpretation, confusion and inconsistency, as evident in the report.
4. Given the difficulties in identifying or analysing patent applications on biologics, it is therefore also difficult to address these short-term patent monopolies during specific situations – such as with a particular form of cancer, for example, or a more widespread crisis such as the Covid pandemic. Our opportunities to address monopolies on biologics in the event of a crisis are quite specifically bound, therefore, to comprehensive, forward-looking compulsory licensing or government use exercises that cannot rely upon identifying a comprehensive set of specific patents, but rather allow for action to be taken around a specific product as a whole, or a technology in general.
5. It is imperative that we create the right tools to address intellectual property monopolies on biologics through an expansion of the terms of compulsory licensing, in order to bring them in line with the terms of government use. It is also imperative that we extend the principles and clauses enshrined in Indian patent law to specifically cover patent applications related to biologics, as well as create a system to ensure that we compulsorily evaluate other frontier technologies in crucial domains such as health and climate change, whenever they emerge.

Methodology

In order to identify the biologics patents granted by the IPO, we employed the methodology described below.

Methodology: Rejected Biologics

We adopted a 4-step methodology to identify biologics from a set of biological applications for patents. The IPO database has a section titled 'Dynamic Patent Utilities', which allows a user to search for applications across 23 different streams of technologies, based on the field of invention.¹⁵ The field of invention is an internal classification done by the IPO for segregating the applications for examination by the appropriate department within the IPO. Applications can be searched for under five headings, namely 'In Process', 'Granted', 'Refused u/s (15)', 'Abandoned u/s 21(1)', and 'Withdrawn after 15 Month'. The database classifies the applications based on the field of invention from 1 July 2012 to 25 May 2018. We followed the four-step analysis below to identify biologics:

1. We selected 'Granted' and 'Refused u/s (15)' categories under four fields of inventions, that is, Biotechnology, Biochemistry, Biomedical Engineering, and Microbiology.
2. We retrieved bibliographic details, including IPC codes of all the above selected applications through a commercially available patent search and analysis tool, PatBase.¹⁶ We limited our dataset to only those applications for which details could be retrieved through PatBase. All other applications were not considered for our analysis.
3. We mapped the applications to IPC codes A61K, A61P, C07C, C07D relevant for drugs/medicines.
4. Patent applications relating to biologics were manually classified by reading the abstract, description and claims of the patent applications.

We retrieved 4616 filed patent applications relating to biological inventions from the 'Dynamic Patent Utilities' database. Using the above mentioned four-step analysis we were able to identify 544 biologics, of which 250 were rejected by the IPO.

¹⁵ Agrochemical, Biotechnology, Chemical, Civil, Communication, Electrical, Electronics, Food, General Engineering, Mechanical Engineering, Pharmaceuticals, Textile, Computer Science, Physics, Bio-Chemistry, Polymer Technology, Microbiology, Metallurgy, Biomedical Engineering, Agriculture Engineering, Traditional Knowledge Biotechnology, Traditional Knowledge Chemical, and Traditional Knowledge Mechanical. The list of different fields of technology is available in Dynamic Patent Utilities maintained by the IPO, available at <https://ipindiaservices.gov.in/DynamicUtility/DynamicStatus/Index>. Please note that due to the frequent shifting of html links and rearrangement of databases at the Indian Patent Office, it can be difficult to provide a stable long-term link to the patents indexed within.

¹⁶ <https://minesoft.com/our-products/patbase/>

Methodology: Rejected Patent Applications Related to Biologics

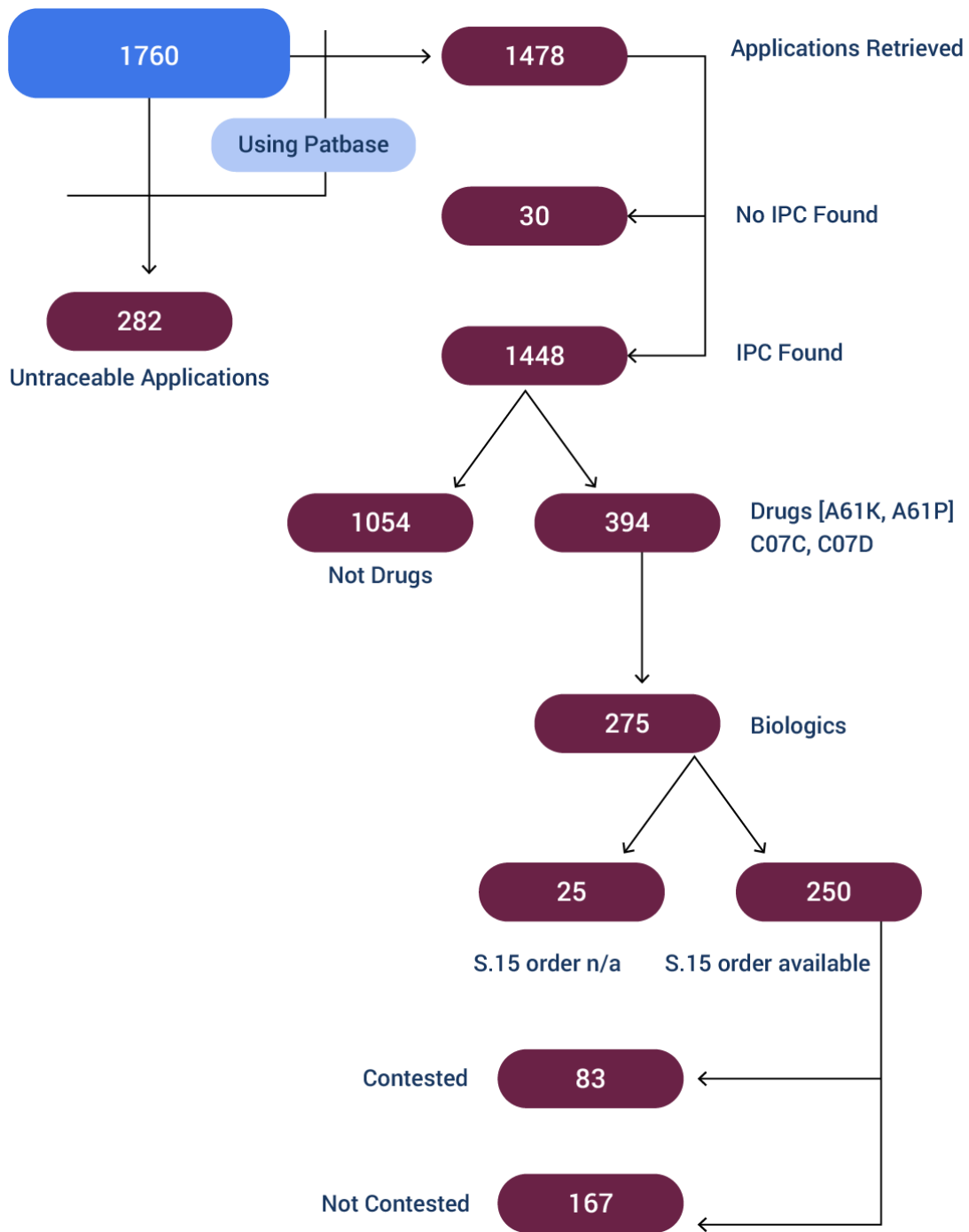
We followed the steps below to identify patent applications for biologics rejected by the IPO in the Dynamic Patent Utilities' database.

1. From each of the four fields of inventions, that is, Biotechnology, Biochemistry, Biomedical Engineering, and Microbiology, we selected the "refused u/s 15" category and found 1760 applications.

CATEGORY	REFUSED
Biotechnology	1197
Biochemistry	227
Biomedical Engineering	108
Microbiology	228
TOTAL	1760

2. From the 1760 applications, we retrieved bibliographic details of 1478 applications using PatBase. The remaining 283 applications were not available on PatBase. Additionally, IPC codes were not available for 30 applications. This process identified 1448 applications across the above four fields of inventions.
3. The objective was to study biologics relating to drugs/medicines for the remaining 1448 applications. We mapped the IPC codes A61K, A61P, C07C, C07D relevant for drugs/medicines and found 394 applications.
4. Based on the definition of biologics for the purposes of this report, we found 275 relevant patent applications out of 394 applications.
5. For the 275 applications, we looked for the Controller's decision under section 15 of the Patents Act, 1970 to conduct a detailed analysis of the refusal of a patent application. We found 250 such decisions and these patent applications form the core dataset of our report, as reported earlier in this narrative.

Refused applications from IPO dynamic utilities



Methodology: Granted Patent Applications Related to Biologics

We identified all granted patents from the Indian patent office for the period 1 January 2012 to 31 December 2018. Once all the records for patents granted by the IPO were retrieved, the bibliographic details associated with each record helped us in identifying all granted patents.

We had to use contrasting methodologies considering the variability in the access of refused and granted biologics, The refused cases were easily accessible by applying filters to retrieve data under the dynamic utilities section from the IPO website, whereas for the granted biologics all the granted patents from the IPO site were retrieved and other patents were filtered out to access the biologics patents.

We followed the three-step methodology below to identify patents related to biologics from a master list of approximately 12000 patents:

Step 1: Remove irrelevant records, by applying the following filters on the Field of Invention column - "Electrical/Agrochemical/Agro products/Textile/General Engineering/Traditional Knowledge-Chemical/Traditional Knowledge-Biotech", which showed close to ~25 applications, which could be quickly filtered out by reading title/abstract.

Step 2: Select IPC codes related to Biologics, C07K/C12N/C12Q/C12P/C07H (C07K: Peptides; C12N: Microorganisms or enzymes or compositions thereof; C12Q: Measuring or testing processes involving enzymes; C12P: Fermentation or enzyme used processes to synthesise a chemical compound; C07H: Sugars/derivatives/nucleotides/nucleic acids).

Step 3: Select these codes individually and filter the applications by IPC codes and colour code them according to – C07K, C12N, C12Q, C12P, C07H and save the file. Colour coding would help in the later stages to eliminate any overlaps.

Step 4: Select IPC codes related to pharmaceutical patents, A61K/A61P/C07C/C07D (A61K: Preparations for medical/dental; A61P: Specific therapeutic activity of chemical compounds or medicinal preparations; C07C: Acyclic or carbocyclic compounds; C07D: Heterocyclic Compounds).

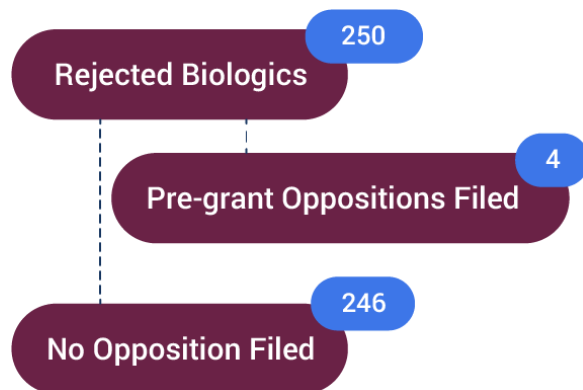
The file from Step 2 would carry different colour codes along with IPC codes of Step 3. Select these codes individually, for example, A61K) to check for any overlaps, and eliminate applications that are exclusively selected as pharmaceutical patents (using the data from the previous report on pharmaceutical patents).

The final dataset of patents (granted to biologics) consists of 1827 patents. These 1827 patents granted were further categorised into different types of biologics as seen below:

CATEGORY	NUMBER OF PATENTS
Antibody	329
Cells	109
Nucleic Acid	310
Peptide	198
Protein	472
Sugars	16
Vaccine	91
Virus	80
Others	222
TOTAL	1827

An Analysis of Rejected and Granted Biologics Patent Applications

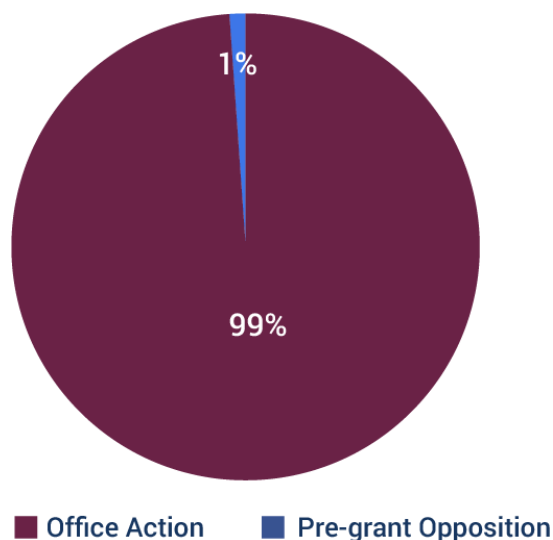
Our final dataset consists of 250 applications, which we have categorised as biologics, and which also have a section 15 order by the Controller. Of the 250 applications, 167 applications were abandoned by the applicants, which then resulted in a rejection, while the remaining 83 applications were contested by the applicants, and later rejected by the Controller.



Types of Rejection Proceedings

The Controller rejected most of the patent applications due to the objections raised initially by the IPO in the first statement of objections. Objections were raised by a third party in only four of the cases, of which two applications were abandoned by the applicants themselves. In essence, the rejection of the patent application was due to the result of the pre-grant opposition proceedings only in two cases. All the other 248 applications were rejected by the IPO without the intervention of a third party (99 percent of the total 250 applications). This is primarily because of the practice of looking into the pre-grant oppositions after the patent applicant overcomes the objections raised by the IPO.

Rejection Distribution: Office Actions v. Pre-grant Opposition



The rejections by the IPO are raised mostly in section 15 proceedings, which gives the Controller the power to refuse the application if it doesn't comply with the requirements of the Patents Act and the rules. However, before proceeding to dispose of the application under Section 15, the Controller calls for a hearing under Section 14 seeking clarifications from the applicant on the objections raised. In cases where the applicant fails to remedy the objections raised, the Controller rejects the application under Section 15. In four cases, the Controller rejected the patent application solely based on Section 16, that is, the application did not qualify as a divisional application under the Act. Section 16 was otherwise quoted nine times along with other sections.

Pre-Grant Opposition in Biologics

The dismal number of pre-grant oppositions could be because of the lack of expertise in biologics related inventions. The pre-grant opposition is a vital function of the patent examination process, which ensures sufficient information is supplied to the IPO leading to acceptance or rejection of a patent. However, we found that only a fraction of applications were challenged using this route. This could be attributed to the nascent market of biologics with very little or no competition. The competitors may not have much knowledge about the invention or prior patents related to the invention. Moreover, the tedious process of regulatory approval makes it even more difficult to bring biosimilars or follow-on biologics. With regard to third party intervention, there are only two cases where the patent was rejected based on the pre-grant opposition filed by a third party under section 25(1). Although there were four pre-grant oppositions filed in total, in two cases, the application was abandoned, thereby not necessitating the need to hear the pre-grant oppositions and the applications were eventually refused under Section 15 by the IPO. In all these cases, the pre-grant oppositions were filed by a single opponent. These oppositions were filed by companies, professional bodies, and non-governmental organisations. Pre-grant oppositions provide the IPO the much-required prior knowledge, which the IPO would have otherwise not raised (through the first statement of objections).

Rejection Trends Based on Different Types of Biologics

Category-wise distribution of biologics

CATEGORY	NUMBER OF APPLICATIONS
Antibody	46
Cells	31
Nucleic Acid	22
Peptide	29
Protein	73
Sugars	02
Vaccine	29
Virus	15
Others	03
TOTAL	250

Grounds of Rejection

GROUND OF REJECTION	NUMBER
Section 3	205
Abandonment	167
Sufficiency of Disclosure under Section 10	107

Of the 250 applications rejected by the IPO, in 211 cases, the Controller rejected the application on the grounds that the application did not meet the requirements of an invention under the Act. The Controller cited provisions on lack of novelty or inventive steps under Section 2(1)(j) or Section 2(1)(ja) respectively. This was the most frequently used provision to reject a patent application. In addition to above mentioned grounds, Section 3 was used to reject applications in 205 cases. In one case, the application was rejected without any intervention by the Controller as the application was withdrawn by the applicant under Section 11 B.

Patentable Invention

An invention is considered patentable under the Patents Act if the application satisfies the requirements of patentability as mentioned under Section 2(1)(j), that is, the invention which is a product or process is new (novelty), involves an inventive step, and is capable of industrial application. The Patents Act has added new definitions of 'new invention' and 'inventive step' through an

amendment in 2005. Section 2(1)(l) defines a new invention as “any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e., the subject matter has not fallen in public domain or that it does not form part of the state of the art”. In 140 cases, the Controller has raised an issue of novelty and stated that the invention mentioned in the present application has been disclosed earlier before the date of filing of the application. Section 2(1)(ja) defines inventive step as “a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art”. The Controller has used this provision in 124 cases as a ground for rejection of a patent application, on the basis that the invention disclosed would have been obvious to a person skilled in the art.

Statutory Exceptions to Patentability

Section 2(1)(j) and Section 2(1)(ja) were the most cited provisions by the Controller while rejecting a patent application. After these sections, we found that Section 3 was the most widely used by the IPO to reject a patent application (in 81% of the cases either alone or in combination with other provisions of the Act). Of the 250 applications, Section 3 was used by the IPO in 203 cases to reject an application. Section 3 discusses the inventions that are not patentable and has many sub-sections. The applications were rejected on the grounds of Section 3(c), Section 3(d), Section 3(e), Section 3(i), and Section 3(j).

Of these, Section 3(d) was the most cited statutory exception to patentability (nearly 55% of the 205 cases involving Section 3).

Rejections Due to Applicants’ Inaction

The Controller allows the applicant an opportunity to present their arguments against the objections raised, either in writing or in a hearing. 83 applications were contested, whereas in 167 cases the application was abandoned by the applicant due to - (1) Abandonment by giving notice to the IPO, which occurred in 82 cases (2) Abandonment by being absent for hearing, which happened in 85 cases. In one case, the application was rejected because the applicant had withdrawn his application by making a written request to the Controller.

We found 28 applications which were abandoned after the FER raised objections on Section 3(b) and 3(c). This meant that the applicant did not bother to rebut these objections and abandoned them. These grounds include – ‘contrary to public order’ and ‘discovery of living thing occurring in nature (again applied for genes)’. This list amounts to more than 10% of the number under study and we consider this a significant trend.

Written Description (Section 10)

An invention is disclosed in the complete specification of a patent application, which should satisfy the requirements mentioned under the Act. The specifications begin with a title that sufficiently indicates the subject matter of the invention, fully and particularly describe the invention, disclose the best method of performing the invention, and include an abstract. The reason for filing a complete specification is to disclose the invention and enable a person skilled in the art to recreate the invention.

The Controller rejected patent applications in 107 cases on the grounds of not fulfilling the written description criteria mentioned under Section 10. Additionally, whenever an objection under section 10 was raised, 86% of the applicants preferred to abandon the application, rather than contesting it in a hearing before the Controller. The major grounds that can be raised under Section 10 are:

1. Sufficiency of disclosure

- a. Every complete specification of a patent application shall fully and particularly describe the invention and its operation or its use and the method by which it is to be performed.
- b. The specification shall also disclose the best method of performing the invention known to the applicant for which he is entitled to claim protection.

2. Scope

- a. The complete specification shall end with a set of claims defining the scope of the invention for which protection is sought

3. Clear and succinct

- a. The claims shall not be too broad and vague. It should have clarity and conciseness.
- b. The claims shall be fairly based on the matter disclosed in the specification.

4. Unity of invention

- a. The claims of a complete specification shall relate to a single inventive concept or to a group of inventions linked so as to form a single inventive concept.

It becomes difficult to overcome an objection under Section 10 if the applicant is not able to show that the invention cannot be reproduced by a skilled person. We do not consider unity of invention as a major ground for rejection of a patent application under Section 10 as it can always be overcome by filing a divisional application under Section 16. However, the other grounds of objection under Section 10 are critical and overcoming the objection requires serious effort from the applicant.

Grounds of objections under Section 10

APPLICATION	SUFFICIENCY OF DISCLOSURE	SCOPE	CLEAR AND SUCCINCT
Rejected (83)	8	10	13
Abandoned (167)	32	67	72
TOTAL	40	77	85

Grants

The 1827 identified patents granted (as described earlier) were further categorised into different types of biologics as seen below:

CATEGORY	NUMBER OF PATENTS
Antibody	329
Cells	109
Nucleic Acid	310
Peptide	198
Protein	472
Sugars	16
Vaccine	91
Virus	80
Others	222
TOTAL	1827

Each of these granted patents was analysed to examine the grounds raised by the IPO in the examination reports and the submissions made by the applicant to overcome the objections raised by the patent office to seek patent protection.

The objections raised by the patent office against biologics applications were predominantly over lack of written description and statutory exceptions to patentability. In particular Section 3 was raised and applicants were able to overcome these objections successfully and were able to obtain patents.

Detailed Analyses of a Few Categories of Biologics

We were interested in understanding how statutory exceptions to patentability under Section 3 applied to biologics patent applications. In particular, we wanted to know the extent to which exceptions under Sections 3(d), 3(e) and 3(i), which are also known as anti-evergreening provisions, were relevant to examination of biologics. In previous reports, we have discussed the significance of these provisions in keeping a check on frivolous patenting for pharmaceuticals.^{17,18} Specifically, we had looked at the extent to which secondary patents,¹⁹ which seek to extend protection for already patented drugs, were granted/refused by the patent office.

In these previous reports, we relied on guidance from a body of existing scholarly literature that extensively described the practice of secondary patenting for pharmaceuticals to identify patents as primary or secondary patents. Additionally, the wording in the explanation of Section 3(d), which specified possible alternative forms of pharmaceutical compounds, also aided classification of patents as primary/secondary. However, similar guidance for biologics was unavailable and the explanation under Section 3(d) is only concerned with alternative forms of small molecule drugs, and these are of little relevance to biologic drugs. Thus, we lacked a framework that could help us identify secondary patents for biologics in a similar manner as was done for pharmaceuticals.

Any attempt to identify secondary patents for biologics in the absence of such a framework would be fraught with uncertainty. Therefore, we decided to focus our efforts on studying the patent office's approach to applying statutory exceptions in practice, with a view of identifying limitations as well as inconsistencies. We undertook a detailed analysis of the prosecution history of about 1268 applications to identify contexts that triggered objections under Section 3 (particularly 3(d)/(e)/(i)). Once such contexts were identified we looked for other applications with similar contexts, but where a relevant Section 3 objection was not raised, to highlight inconsistencies in the patent office's approach. We also reviewed applicant responses to these objections, in order to understand how applicants either overcame objections (in case of granted patents) or failed to do so (for rejected applications).

We focused our analysis on groups of biologics that have similar subject matter, to streamline the identification of similar contexts for comparisons. We selected three categories of biologics as

¹⁷ Dr. Feroz Ali, Dr. Sudarsan Rajagopal, Dr. Venkata S. Raman & Roshan John, *Pharmaceutical Patent Grants in India: How our safeguards against evergreening have failed, and why the system must be reformed*; <http://accessibsa.org/media/2018/04/Pharmaceutical-Patent-Grants-in-India.pdf>

¹⁸ Dr. Feroz Ali, Dr. Sudarsan Rajagopal, Mohamed Mustafa and Chinnasamy Prabhu, *Rejected in India: What the Indian Patent Office got right on pharmaceuticals patent applications (2009-2016)*; <http://accessibsa.org/media/2017/12/Rejected-in-India.pdf>

¹⁹ Such secondary patents for pharmaceuticals attracted scrutiny under anti-evergreening provisions as follows:

- patents for alternative forms of previously known drugs – these could be objected to under Section 3(d), and the explanation under this statute specifically listed out various alternative forms for pharmaceuticals (salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives);
- patents for formulations/compositions, where a known active ingredient is present as an admixture with excipients – objectionable under Section 3(e); and
- patents concerning methods of treatment, e.g. seeking protection for the manner of administering particular drugs to individuals/patients for treating diseases – objectionable under Section 3(i).

representative subsets for our detailed analysis – antibodies, proteins/peptides and vaccines, which together account 58.6% of all biologics from our dataset. Moreover, these categories also represent leading classes of biotherapeutics (antibodies and proteins/peptides) and are of immense significance to global public health (vaccines).

The following sections outline the results of analyses across these categories, with each section including an introductory primer on the category of interest.

To note, our analysis in the sections to come is illustrative of the problems we define in this report, and therefore, confined to the scope of the defined problems themselves. Our analysis provides clear instances of how the problems defined within the scope of this report play out in the process of patent examinations of biologic pharmaceuticals in India.

Antibodies

Introduction

Antibodies are naturally occurring protein components in the human body and are an integral part of the immune system. Over the years antibodies have been extensively researched for use in the biomedical field for multiple uses including in the treatment of various medical conditions.

A basic structure of an antibody comprises two heavy and two light chains with two main functions in different regions of the structure. The fragment of antibody that binds to the antigen is Fab, while the Fc region interacts with the other elements of the immune system. The Fab domain has two variable fragments (Fv), which provide antigen specificity and two constant domains which provide a structural framework for the antibody. The complementary determining regions (CDRs) are located in the variable domain as three hypervariable loops that are responsible for eliciting specific antigen recognition. The hypervariability²⁰ of the CDRs allows antibodies to recognise a large number of antigens.

There are five main isotypes or classes of antibodies in mammals - IgA, IgD, IgE, IgG and IgM classified based on the heavy chain they contain and the difference in the sequence and constant domain, hinge structure and valency of the antibody.²¹

Predominantly IgG immunoglobulin accounts for 70-85% of the total immunoglobulin pool in normal human serum.²²

An immune response is triggered by an antibody through engagement of different parts of the immune system. These include ligand-receptors or cell lysis through activation of the classical complement pathway CDC (complement dependent cytotoxicity). The antibodies act as a link between the antibody-mediated (humoral) and cell-mediated immune responses by engaging the Fc receptors which is a key immune regulatory receptor.

Due to the high specificity and selectivity of different antibodies and with variability in the amino acid sequence of the variable regions, they are used as biochemical tools for a wide range of applications.

Antibodies are broadly categorised into two groups- polyclonal antibody (pAbs) which are heterogeneous mixture of antibodies binding to various epitopes on the same antigen and monoclonal antibody (mAbs) possessing specificity for one particular epitope on an antigen. Due to their specificity, mAbs have extensive applications in the area of research, diagnostics and therapeutics.

²⁰ Hypervariability (HVR) - A location in the nuclear DNA in which base pairs of nucleotides repeat or consist of substitutions; these changes or repeats in the hypervariable region are highly polymorphic. For further information can refer https://link.springer.com/referenceworkentry/10.1007%2F3-540-29662-X_1303

²¹ Valency of an antibody is the number of antigenic determinants that an antibody molecule can bind. For further information refer to <https://www.microbiologybook.org/mobile/m.immuno-4.htm#:~:text=The%20valency%20of%20antibody%20refers,and%20in%20some%20instances%20more>

²² <https://absoluteantibody.com/antibody-resources/antibody-overview/antibody-isotypes-subtypes/>

Since the discovery of production of mAbs through hybridoma technology,²³ attempts have been made to engineer them to make them suitable for therapeutic use in humans. Over the years technology has evolved to produce fully human antibodies with the expression of isolated human variable domain genes in E.coli through phage display technology and expression of human antibody repertoire in transgenic mice.

Ever since the first approved monoclonal antibody in 1986, more than 100 antibodies have been discovered and approved for various indications and many more mAbs (monoclonal antibodies) are under review.²⁴ The discovery of mAbs in the 1970s led to multiple advancements, both in diagnostic and therapeutic fields in addressing various challenges in the treatment of new age diseases. The first ever therapeutic mAb, Muromonab-CD3 (Orthoclone, OKT3) was approved by the FDA for kidney transplant treatment in 1986.²⁵

Given the ability of mAbs specificity towards an antigen, they can be designed to bind and identify antigens, used in immunotherapy and used in diagnostic fields to detect numerous diseases in early stages. MAb are internal components in over-the-counter tests for ovulation, pregnancy, menopause, detection of heart attack and they are also used in screening blood to detect infectious diseases and AIDS. They are also vital in the process of typing blood for transfusion and organ transplantation.²⁶

Antibody Patents

The first ever patent on monoclonal antibodies was for the method of producing tumour antibodies.²⁷ Over the years, the production of monoclonal antibodies has evolved and the market for therapeutic antibodies continues to expand. Many mAbs are approved for use in the treatment of cancer, metabolic disorders, autoimmune diseases, and so on.²⁸

In view of the vast application and importance of antibodies it is important to emphasise the need to accord patent protection for genuine inventions, which advances research and development in harnessing therapeutic benefits. Thus, there is a need to ensure patent protection does not lead to price barriers in accessing these wonder drugs, as seen in the case of grant of multiple patents to Humira (adalimumab).²⁹

²³ Hybridoma Technology - A method to produce monoclonal antibodies by immunising laboratory animals with target antigen and undertaking fusion of B cells extracted from immunised lab animals with myeloma cells, cells cultured on a medium to obtain desired monoclonal antibodies from hybrid cells. For further information refer to <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255167/>

²⁴ <https://www.antibodysociety.org/resources/approved-antibodies/>

²⁵ The Evolution of Therapeutic Monoclonal Antibodies – 14 August 2018;

<https://www.pharmamanufacturing.com/articles/2018/the-evolution-of-therapeutic-monoclonal-antibodies/>

²⁶ <http://blog.yalebooks.com/2015/08/06/monoclonal-antibodies-mabs-little-known-life-savers/>

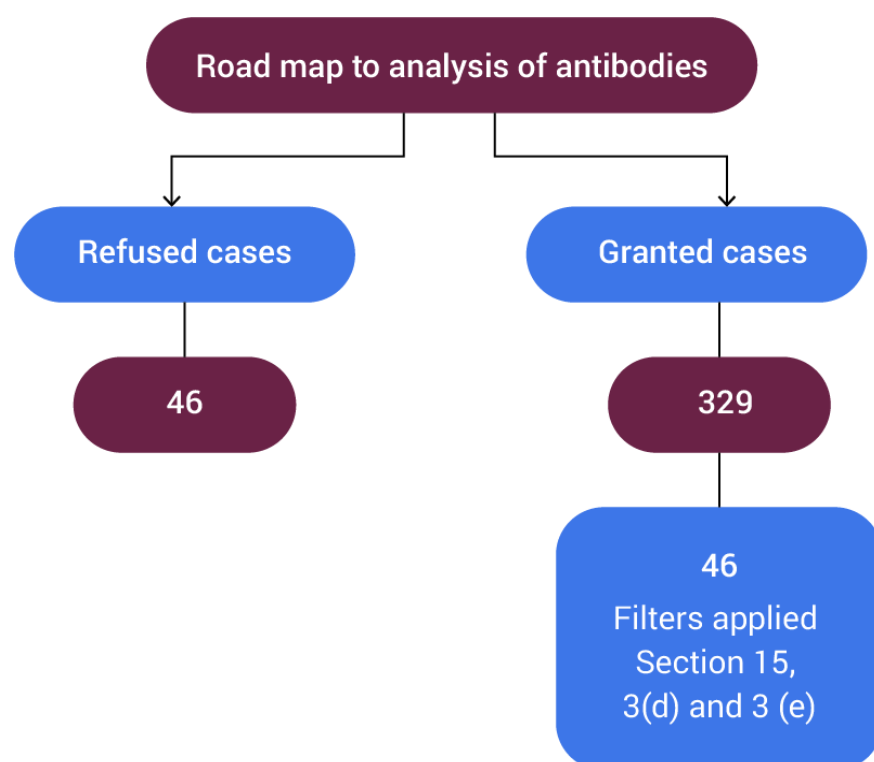
²⁷ <https://patents.google.com/patent/US4172124A/en?q=4172124>

²⁸ Leu et al, *Development of therapeutic antibodies for the treatment of diseases*; Journal of Biomedical Science (2020) 27:1

²⁹ <https://www.i-mak.org/wp-content/uploads/2020/10/i-mak.humira.report.3.final-REVISED-2020-10-06.pdf>

Types of Claims in Applications for Antibodies

Antibody patent applications include claims directed to a wide range of antibody components / elements, or antibody composition or formulation or combination. These patent claims may cover antigens, epitopes, nanobody, polyclonal antibody, fusion protein, Fab or Fv fragments,³⁰ scFV peptide,³¹ nucleic acid code of antibody region, bispecific antibody, modified antibodies and epitope (antigenic determinant) on antigens and paratopes (antigen binding site) on antibodies. Further claims cover domain antibodies.³² and conjugated antibodies,³³ chimeric, humanised and human antibodies. In our dataset we identified 329 granted patents and 46 refused patent applications related to antibodies.



Some of the patents granted for antibodies identified in our dataset include monoclonal antibodies such as Sarilumab, Pembrolizumab, Caplacizumab, Secukinumab, Apomab and Cetuximab. Applications for monoclonal antibodies such as Adalimumab, Pertuzumab, combination of Bevacizumab & Cetuximab, anti-CD20 Orelizumab, Veltuzumab, Ofatumumab, anti-C5 antibody eculizumab, pexelizumab and so on were identified in the rejected dataset.

³⁰ Fab - fragment antigen binding or Fv - variable fragment. For further information refer <https://absoluteantibody.com/antibody-resources/antibody-overview/antibody-structure/>

³¹ scFV peptide - single chain fragment variables are engineered antibodies generated by fusion of the heavy chain and light chain linked through a short polypeptide. For further information refer to <https://www.mdpi.com/2073-4468/2/2/193/html>

³² Domain antibodies - composed of variable domain of heavy chain with antigen binding portion and is completely devoid of light chain. Due to their small size they are also termed as Nanobodies. <https://www.frontiersin.org/articles/10.3389/fimmu.2017.01802/full>

³³ Conjugated antibodies are antibodies attached to a substrate like an enzyme, inorganic compound termed as tagged or loaded or labelled antibody used predominantly in immunological assays.

#	PATENTED ANTIBODIES	DISEASE / CONDITION
1	Sarilumab [6373/CHENP/2008]	Rheumatoid Arthritis
2	Pembrolizumab [7435/CHENP/2009]	Cancer – lung, head and neck
3	Caplacizumab [1914/MUMNP/2007]	Acquired thrombocytopenic purpura (aTTP)
4	Secukinumab [250/DELNP/2007]	Psoriasis
5	Cetuximab [3293/CHENP/2008]	Cancer – Colon and rectum
6	Apomab [1730/DELNP/2007]	Cancer

#	REJECTED ANTIBODIES	DISEASE / CONDITION
1	Adalimumab [8655/DELNP/2005]	Rheumatoid Arthritis, Psoriatic arthritis
2	Pertuzumab [4840/DELNP/2007]	Breast cancer (HER2 positive)
3	Cetuximab and Mab h425 [2603/KOLNP/2006]	Cancer – head and neck
4	Bevacizumab [4693/DELNP/2009]	Cancer – colorectal, non-small lung cancer, glioblastoma
5	Ocrelizumab, Veltuzumab, Ofatumumab [1192/MUMNP/2010]	Autoimmune disorders
6	Eculizumab, pexelizumab [7366/DELNP/2008]	Blood disorders – Paroxysmal nocturnal hemoglobinuria (PNH) Atypical Hemolytic Uremic Syndrome (aHSU) Acute myocardial infraction

Statutory Exceptions and Examination of Applications

What kind of objections are usually raised? What contexts are they raised in?

Section 3(d) states mere discovery of a new form of a known substance with no enhancement in the efficacy of the claimed substance over the known substance, mere discovery of new property or new use for a known substance or mere use of a known process without resulting in any new product or if the process does not involve new reactant are all considered as inventions which would fail under Section 3(d).

Mere Discovery of New Forms of Known Substance in Absence of Efficacy Data

Patent application claims covering the variants of an antibody in the Fc region are considered as a new form of a known substance. A patent application [2347/CHENP/2008] claiming an anti-glypican 3 antibody involving substitution of amino acid residues in the Fc region was filed. However, both the anti-glypican 3 antibody and the claimed amino acid substitutions position in the Fc region were disclosed in the prior art. Further, the possibility of enhancing the activity of antibody-dependent cellular cytotoxicity (ADCC) through the claimed substitutions was also known. The applicant amended the claims to cover specific positions of the Fc region wherein the amino acid substitutions were made in the anti-glypican 3 antibody. The applicant argued that the claims should not be considered as a new form of known substance, as the application mentioned that the substitutions in the Fc region of the anti-glypican 3 antibody improved antibody-dependent cellular cytotoxicity (ADCC) activity.

However, the patent office refused the application for the lack of inventive step and Section 3(d), considering it as a new form of a known substance. In particular it was noted that the applicant failed to submit any experimental data of the claimed Fc variant of anti-glypican 3 antibody enhanced ADCC activity in comparison to the disclosed antibody. The applicant did not submit any working examples proving the enhanced efficacy over the known efficacy of anti-glypican antibody.

In [5745/CHENP/2010], an antibody variant specifically binding to human CSF-1R (colony stimulating factor 1 receptor) comprising a humanised antibody derived from CXIIIG6 was claimed. The applicant claimed that certain CDRs in sequence ID 11 - 16 led to unexpected superior properties over known anti-CSF-1R antibodies in the prior art. The partial inhibition of the CSF-1 binding by the claimed antibody and its ability to bind to an epitope located far from the CSF-1 binding site led to an improved safety profile.

In this case the patent office refused the application under Section 3(d) as the applicant failed to submit working examples to illustrate the advantage of the claimed antibody or its variants with selected CDRs over the disclosed antibody in the prior art. Further, the application was also rejected for failing to provide the specific amino acid substitutions within the claimed antibody.

In [2792/DELNP/2008], claims covering a combination of known antibodies (cetuximab or bevacizumab or trastuzumab and irinotecan) with hyaluronan (HA) were formulated together with a second or third therapeutic antibody. In light of the disclosure in the prior art documents, the patent office noted the lack of novelty and inventive step and raised an objection under Section 3(d) as claims were found to be a mere discovery of a new form of a known substance. The applicant contested that none of the prior art documents disclosed or taught a formulation comprising a therapeutic antibody and hyaluronan (HA) with a specific molecular weight range and display of enhanced efficacy of a therapeutic antibody when used in combination with HA. The surprising finding of use of HA, enhanced the efficacy of therapeutic antibody whose synergistic effect was independent of the specificity of the antibody. Further, the applicant argued that the examples listed in the specification demonstrated an improvement in efficacy and therefore, the Section 3(d) objection did not apply.

However, the patent office rejected the application and maintained the objections raised in the examination report on the basis that examples in the specification failed to demonstrate the efficacy of the claimed formulations to overcome the Section 3(d) objection.

In cases where the combination of known antibodies is claimed, they are objected to as mere discovery of a new form of a known substance.

In applications where claims cover antibody drug conjugates (ADC)³⁴ a new form of a known substance objection under Section 3(d) was raised. In [1352/DEL/2006] a claim was made of a recombinant antibody cPiPP conjugated with curcumin for better delivery of the conjugate to the target site. Since all the components of the claimed antibody drug conjugate were already known in the prior art, and as the applicant failed to submit any data on the improved technical features and efficacy of the claimed antibody conjugate over the disclosure made in the prior art, the application was rejected.

Mere Discovery of a New Use of a Known Substance

When assessing claims of a pharmaceutical composition, the use of antibodies in the treatment of a particular disease and dosage related claims of antibodies are objected to under Section 3(d) as mere discovery of new use of a known substance. Patent applications covering combinations of known antibodies in the absence of efficacy data or in comparison to the disclosure made in the prior art have been rejected by the Indian Patent Office (IPO).

In an application [2603/KOLNP/2006] claims covering highly concentrated liquid formulation of antibodies Cetuximab and Matuzumab (EMD 72000) obtained through ultrafiltration technique in a concentration of 60-180 mg/ml or 100 – 150 mg/ml were objected to under Section 3(d). The claimed composition was considered as a new use of a known substance, apart from being objected to for lack of novelty and inventive step over the disclosure made in the prior art. Since the application failed to demonstrate the advantage of the claimed composition over the cited prior art documents in terms

³⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6359697/>

of efficacy data, novelty and inventive step, the application was rejected.

The applicant in [7710/DELNP/2006] submitted that the use specific composition claim consisting of radiolabelled anti-CD20 antibody is for B-cell lymphoma patients. The claimed composition is for patients who have received chemotherapy and show no sign of relapse. These patients were not treated with radio-labelled anti-CD 20 antibodies prior to this invention. The addition of radio-labelled anti-CD20 antibodies in the chemotherapy regimen of B-cell lymphoma patients with use-specific compositions and whose cancers are non-refractory and have no relapse was claimed to increase response and survival rates over and above the extent of chemotherapy. The applicant submitted that this overcame the objection under Section 3(d) of this composition, whereas in the FER it was considered as a new form of known substance.

Another application [8655/DELNP/2007] with claims concerning a composition comprising Adalimumab to treat erosive polyarthritis was also rejected. The claims were objected to for lack of novelty, inventive step and under Section 3(d) as new use of a known molecule. Additionally, the composition did not exhibit any data with regard to improved efficacy.

To summarise, the key objections raised under Section 3(d) against applications covering antibodies as compositions and formulations of a known antibody, were identified as a new form of a known substance. This is noted irrespective of variation or changes made in the antigenic binding site of the known antibody [Fc region, CDR in specific] and covers modifications in the Fab region of a known antibody.

Objections Under Section 3(e)

Patent claims covering compositions are objected to under Section 3(e). This section states that a substance obtained by mere admixture leading to only aggregation of the properties of the components or a process for producing such substance is not considered as an invention.

In the reject patent dataset claims of known antibodies along with other pharmaceutically acceptable excipients, the following reasons are considered as mere admixture resulting only in the aggregation of properties with no synergistic effect demonstrated by the claimed composition - claims of composition without the description of ratio or percentage of individual components, combination of known antibodies, and conjugate of antibodies.

In most of the applications which were rejected, claims covering antibody composition comprising conjugates, immunoliposomes complex³⁵ of antibodies, formulation claims were also objected to under Section 3(e).

In an application [2792/DELNP/2008], claims covering a combination of known antibodies (cetuximab or bevacizumab or trastuzumab and irinotecan) with hyaluronan (HA) were formulated together with a second or third therapeutic antibody. In light of the disclosure in the prior art documents, the patent

³⁵ Immunoliposomes complex – antibody molecules are conjugated directly to the lipid bilayer either in presence or absence of PEG chains.

office noted the lack of novelty and inventive step and raised an objection under Section 3(e) for - absence of relative ratio or percentage of the individual components. The applicant complied by submitting the missing information by including the specific quantities of hyaluronan (HA) and therapeutic antibody in the claims. Further since the dose of the therapeutic antibody formulated with HA will depend on antibody factors such as target epitope, binding specificity and proposed application of the claimed composition, Section 3(e) objection should be waived off.

This application [7710/DELNP/2006] claimed the composition of a radio labelled anti-CD20 antibodies - Y-ibritumomab tiuxetan and tositumomab. Since the claimed antibodies were already known and disclosed in the prior art for use in the treatment of non-Hodgkin's lymphoma (NHL), the application was objected to for - lack of novelty, inventive step and under Section 3 including 3(e) for absence of definitive ratio of the ingredients in the claimed composition and absence of synergistic data as supporting examples in the specification. The applicant submitted that the Section 3(e) objection should be waived off as the claims are for a composition of a radiolabelled anti-CD20 antibody and is a single ingredient composition. Therefore, the definition of specific ratio is not required as the chemotherapeutic compound is not documented in the claim and the antibody's identity and dosage is immaterial to the patentability of the composition.

However, the patent office rejected the application and maintained that the objections raised in the examination report under Section 3(e) by noting the complete specification failed to provide any data demonstrating the synergistic effects produced by formulations covered in the claims.

An application [3426/KOLNP/2008] initially filed as method of treatment claims was amended to composition claims comprising a known antibody IMC-A12 and androgen deprivation therapy [orchiectomy]. This application was rejected by the patent office for the lack of inventive step, further under Section 3 and the amended claims were not allowed under Section 59. The applicant argued that none of the cited prior art documents disclosed that the combination of IMC-A12 antibody and castration would lead to improved and durable tumour regression, thereby demonstrating a greater than additive effect. The applicant submitted that the amended pharmaceutical composition was capable of inhibiting or preventing the transition of an androgen dependent cancer to an androgen independent cancer. However, the patent office rejected the application noting that the amended claims were treatment claims disguised as composition claims.

In another application [5567/DELNP/2006] the claims covering a pharmaceutical liquid composition comprising the anti- $\alpha 5\beta 1$ integrin antibody along with pharmaceutical excipients such as citrate, sodium chloride, polysorbate was rejected on the grounds of lack of inventive step and Section 3(e). The applicant submitted that since the claimed pharmaceutical liquid formulation exhibited improved long-term stability, the composition is synergistic and is not a mere admixture. However, since the applicant did not attend the hearing, the application was refused.

Section 3(i) states that processes involved in the medicinal, surgical, curative, prophylactic including diagnostic therapeutic or other treatment of human beings or similar processes in the treatment of animals are considered as inventions falling under the ambit of Section 3(i).

In the reject patent dataset one of the common practices adopted by patent applicants to overcome the objection under Section 3(i) against antibody claims - covering the method of treatment, method of assaying / detection, diagnostic kits, administration of antibody to humans and so on - was to usually amend them into composition claims. However, in most cases the amended method of treatment claims to composition claims were further objected to under Section 3(e) and were also flagged by the patent office.

In one particular rejected case [4981/DELNP/2008], the claim was objected to for being a method of assaying or detection under Section 3(i) in the first examination report. The applicant amended the claims as an *in vitro* method for detecting fragmentation of an adiponectin receptor for detecting the presence or absence of soluble C-terminal fragment of the adiponectin receptor in bodily fluids. Though the patent office acknowledged the novelty and inventive step of the amended claims, since the claims pertained to diagnosis of a diseased state, the application was rejected under Section 3(i). Further, the patent office also noted that since section 3(i) encompasses all types of diagnostic and methods of treatment of human / animal to render them free of diseases, it does not differentiate between *in vitro* and *in vivo* methods. Therefore, the applicant's submission that claims pertain to the *in vitro* method alone was rejected.

Section 3(c) states that the mere discovery of a scientific principle or mere discovery of any living thing or non-living substance occurring in nature are considered as inventions that are not patentable.

An appeal is filed and pending against a decision for rejecting an application on the sole ground of Section 3(c). In the [5808/CHENP/2007] rejected application, claims cover a nucleotide sequence encoding the antibody or antibody fragment of anti-PDGFR α antibody (IMC-3G3), which inhibits the binding of PDGFR α to a ligand of PDGFR α or which neutralises PDGFR α . The claims cover an isolated antibody or antibody fragment specific for human PDGFR α , for use in the treatment of bone cancer through administration of PDGFR α antagonist and neutralising the activation of PDGFR α , all of which is disclosed in the prior art. Since certain claims are directed towards entities which are already present in nature and the applicant has only isolated these antibodies through standard methods or known techniques it was objected to, under Section 3(c). The submission that the claimed antibody is not isolated from nature and IMC-3G3 is generated by immunising transgenic mice through recombinant technology, was not accepted by the patent office.

In [2911/CHENP/2010], the IPO stated that under Section 3(c) non-living substances occurring in nature are not patentable subject matter. In [1253/KOLNP/2010], claims covering a monoclonal antibody specific to Vascular Endothelial Growth Factor (VEGF) or a fragment with an antigen binding portion binding to pro-angiogenic VEGF isoforms were objected to under Section 3(c). Further claims covering isolated human monoclonal anti-mesothelin antibody 6A4 or an antigen binding fragment conjugated to cytotoxin were objected to as a mere discovery of a non-living thing occurring in nature.

Wherever the term isolated antibodies are used in the claims, a Section 3(c) objection is raised.

How Applicants Overcome Objections Under Section 3

In an application [2339/CHENP/2009], the applicant was able to overcome the objection under the inventive step by claiming that since the antibody possessed unique and unexpected properties like enhanced affinity, effectively inhibiting the activity of the IL-4, it thereby exhibits unexpected technical advantage. The applicant argued that since these features render the claimed subject matter inventive over a known antibody and as the novelty of the claims was acknowledged, Section 3(d) objection does not apply to these claims. The applicant referred to the examples in the specification to overcome the objection of lack of inventive step. The same examples were cited to prove technical advantage of claims over a prior art antibody having the same CDRs. The patent office accepted the applicant's reasoning, and the Section 3(d) objection was overcome.

In an application [454/DELNP/2007] a pharmaceutical composition comprising a glycosylated variant of a known antibody (pertuzumab), which also included additional amino acids in the antibody sequence, was granted a patent. The filed claims were objected for lack of novelty, inventive step and under various subsections of Section 3. The patent office noted that since HER2 targeting antibodies such as trastuzumab and pertuzumab were already known and disclosed in the prior art, the applicant has to submit the efficacy of the claimed composition to overcome Section 3(d) objection. The claims were objected to for being a mere admixture in absence of ratio / percentage of the components in the composition under Section 3(e).

The applicant then submitted an amended set of claims to overcome the objections of lack of novelty and inventive step, arguing that since the claimed HER2 antibody comprises additional amino acids in the sequence, it is not the same antibody composition as disclosed in any of the cited prior art documents. The applicant argued against the Section 3(e) objections on the basis that the cited prior art documents lack (i) a disclosure of an antibody with additional amino acids as claimed, and (ii) the presence of working examples to show the efficacy of the claimed composition in the specification, that is, desired biological activity of the claimed antibody comprising this variant. In the hearing submissions the applicant mentioned that since the claimed variant of the antibody is not known, its biological activity was unpredictable and experimental data from the application shows that the claimed antibody inhibits proliferation of human breast cancer, the objection under Section 3(d) should be waived off. It is interesting to note that, in addition to data from the examples of the specification, the applicant also highlighted that the claimed antibody had received regulatory approval for use in treating metastatic breast cancer.

The patent office found the submissions made by the applicant persuasive, and the patent was granted.

A patent was granted to an application, 135/DELNP/2011, with a single domain antibody which binds to human CD28 monovalently (antibody binds to only one antigen). The applicant was able to establish the claimed domain antibody was novel, possessed the inventive step and is not disclosed in the cited prior art documents. With regard to the objection under section 3(d) the applicant submitted that the claimed antibodies are not a "known substance" and the key differences were in terms of single variable domain antibody with specific amino acid sequences of three CDRs, possessing a high affinity for binding to CD28 and not causing CD28 activation.

The applicant was able to overcome the objection of new form of known substance under Section 3(d) by:

- narrowing the claims pertaining to antibody or antigen fragments
- defining and including the details of the specific sequence IDs covered in the CDR region of claimed variants of a known antibody and
- by explaining the structural aspects of the difference in claimed antibody in comparison to antibody disclosed in the prior art.

In certain cases, the data on efficacy of a claimed antibody relates to the affinity of the antibody binding, inactivation or activation of selected receptors involved in an immune response, and a demonstration of anti-proliferation activity of the claimed antibody. Applicants have successfully been able to traverse the objections under Section 3(d) by submitting that since the claimed antibody variants satisfy the novelty and inventive step requirements, the claims do not fall under the scope of Section 3(d).

The application [2293/KOLNP/2008], on the pharmaceutical composition comprising histone deacetylase inhibitor (PXD-101) in combination with an antibody was granted a patent. The claimed components of the pharmaceutical composition PXD-101 with an antibody selected from Rituxan, Avastin and Velcade were known and cited in the prior art document. Objections were raised for lack of novelty, inventive step and under section 3. However, the applicant was able to overcome the objections under Section 3(d) by admitting that though the individual compounds of the claims are known, the claimed invention is for utilising a specific combination of PXD-101 with a second therapeutic agent. Additionally, the combination demonstrated improved anti-proliferative activity in myeloma cases (unlike when the compounds were individually administered). The applicant argued that since the combination exhibits a synergistic effect resulting in inhibition of tumour growth and decrease in the number of viable cancer cells the claimed composition is patentable.

An application [1576/DELNP/2007] covering antibody-drug conjugate comprising – a cysteine engineered antibody selected from huMAb4D5-8 (trastuzumab), an anti-EphB2R antibody and an anti-MUC16 antibody along with a drug component (selected from maytansinoid, an auristatin, a dolastatin and a calicheamicin) was granted a patent. Though all the claimed components were disclosed in the prior art, the patentee submitted that they are novel and inventive, since the native amino acid sequence is replaced with an engineered sequence (that is, cysteine present in the heavy and light chain of the antibody). The applicant deleted claims attracting a Section 3(d) objection to overcome the new use or new form of the known compound.

The objection of a new form of a known substance of a known antibody can be overcome by establishing the efficacy of the claimed antibody and by further characterising the sequence of the antibody and detailing any changes made in the sequence of the claimed antibody at the antigenic binding region. Objections are waived off in cases of new use of a known substance for antibodies covering combinations or conjugates or use of antibody for a new indication wherever the applicant is able to submit efficacy data.

Objections under 3(d) can be overcome in cases where there is a combination of known antibodies, if the applicant is able to establish the difference between the claimed combinations of known antibodies by demonstrating efficacy pertaining to the effect of the claimed combination. It is imperative to highlight here that even if the use of the antibody for a specific disease or condition is already known and is in use, if the applicant demonstrates efficacy through increased safety profile of the claimed combination of antibodies, the applicant is able to overcome the new form of a known substance objection.

A patent for the application [1356/CHENP/2012] was granted to a chimeric molecule against malaria comprising an immunoglobulin, an antigen non-specific Th1 or Th2 CD4 domain linked to humanised immunoglobulin via a linker. The claims were objected to for lack of inventive step and under Section 3(d). The claimed chimeric molecule was considered as a new form or a complex of a known substance in absence of efficacy data by the patent office. However, the applicant submitted that since the chimeric molecule comprises more than one component and such a combination is a new substance and not a new form of a known substance. They cited the Intellectual Property Appellate Board (IPAB) decision *Ajantha v/s Allergan*³⁶ to argue that a combination in the explanation of Section 3(d) refers only to a combination of a substance with one or more of its derivatives, but not another substance. Since the present antibody conjugate claimed is found to be novel, inventive and is a new substance, the Section 3(d) objection should be waived off.

There are certain cases where applications have been able to overcome the new use objection against known combinations under section 3(d). One such instance is if the applicant is able to demonstrate improved efficacy with in vivo data included in the specification of a combination of known antibodies claimed as a pharmaceutical composition. In a granted patent [1990/KOLNP/2011] the claims covered hu38SB19, an anti-CD38 antibody and vincristine as a pharmaceutical combination. The claims were objected to on the grounds of lack of novelty, inventive step and under Section 3. The patentee submitted the cited prior art documents that disclosed the claimed antibody and vincristine as conjugate, whereas the claimed pharmaceutical combination hu38SB19 antibody and vincristine components existed as separate physical components. Further the patentee submitted efficacy data demonstrating that the administration of the claimed components in combination at an optimal dose exhibited synergism to decrease tumour growth.

A patent [1576/DELNP/2007] was granted to an antibody drug conjugate comprising a cysteine engineered antibody selected from huMAb4D5-8 (trastuzumab), an anti-EphB2R antibody and an antiMUC16 antibody along with a drug moiety selected from - maytansinoid, an auristatin, a dolastatin and calicheamicin. In their examination report the patent office noted that all the claimed components are disclosed in the prior art. The patentee's submission was that since the native amino acid sequence is replaced with an engineered sequence - that is, cysteine - present in the heavy and light chain of the antibody, they are novel and possess an inventive step. The objection under Section 3(e) that claims are mere admixture resulting only in the aggregation of the properties was overcome by the patentee by amending the claims to cover a composition of an antibody-drug conjugate.

³⁶ ORA/21/2011/PT/KOL

In general, no synergistic data was provided to overcome the objection under Section 3(e) for granted patents. In most cases the claims are either deleted or accepted by the patent office (if the claimed composition is found to satisfy the inventive step). From our analyses we could not identify any case where a Section 3(e) objection was overcome against composition claims by submitting the synergistic data.

Objections under Section 3(i) are usually overcome through deletion of claims.

Since antibodies occur in nature patent applications covering antibodies are also objected to under Section 3(c).

Objections were raised under Section 3(c) in a patent [1287/CHENP/2009] granted for a monoclonal antibody molecule CR6261 against an influenza virus (comprising the H1 and H5 subtype of H1N1). The applicant overcame the objection by submitting that the claimed human monoclonal antibody is derived from or based on human germline immunoglobulin sequences or is derived from synthetic sequences. As this involves substantial human intervention through chemical or biochemical nucleic acid modifications, Section 3(c) does not apply.

In the patent [2302/CHENP/2009] claims covering human antibodies, the applicant submitted that the claimed human antibodies with substitutions of certain amino acids do not correspond to the sequence of antibodies encoded by the human genome. Since it involves human intervention with elaborate and sophisticated technical processes, the objection under Section 3(c) was waived off.

In general, to overcome the objection under Section 3(c) against antibodies, the applicant either deletes the claims or submits it afresh (since the production of antibodies is by recombinant technology via immunisation of transgenic mice). The entire process involves a substantial level of human intervention and therefore objections raised under Section 3(c) could be waived off.

In most cases, applicants adopt a two-step strategy:

- Firstly, to overcome the objections under Section 3, they amend the claims by limiting the scope of the coverage of invention or delete the claims which attract Section 3 provisions.
- Secondly, to submit that if the claims are found to possess novelty and an inventive step, the need for submitting any efficacy data under section 3(d) and synergistic data under section 3(e) is not required.

A summary of the analysis of the claims of the rejected and granted dataset shows that claims for known antibodies and their preparation - including fragments, variants, and known antigens, new use of known antibodies and undefined epitope specifically in absence of any efficacy data - are usually rejected by the patent office. Whereas if the applicant is able to submit the efficacy data for the claimed antibodies, the application proceeds to grant the patent. The patent office usually raises an objection under Section 3(d) noting that in the absence of working examples to demonstrate the efficacy such claims fall under the ambit of Section 3(d). Claims pertaining to *in-vitro* methods, but which could be construed to encompass *in vivo* methods – such as immunisation techniques to

obtain antibodies, diagnostic aspects, prophylactic treatment, administration of antibody and claims pertaining to a specific dosage - fall under Section 3(i). Claims covering antibodies in a composition or a formulation in absence of demonstrable synergistic effect or lack of any surprising effect of the claimed components in a composition or combination are rejected under section 3(e).

Comparison of Patents where Claims were Objected to vis-à-vis not Objected to Under Section 3(d).

In our analysis of granted patents and rejected applications, we also tried to identify any inconsistencies in the application of Section 3 provisions. We searched for applications having broad similarities in the claimed subject-matter and the surrounding fact pattern in terms of the prior art background. However, we could not identify such examples for antibodies because when the claims underwent amendments and proceeded to be granted, the scope of the coverage of the invention changed. Additionally, the objections raised were also waived off during the investigation process. Therefore, instead of identifying inconsistencies we did a comparison of granted and rejected patents for antibodies, to understand the application of Section 3 provisions while examining the applications for antibodies.

The examples discussed above illustrate contexts where objections are raised under the legal provisions concerning statutory exceptions to patentability. However, such objections are not always invoked uniformly.

In the granted patent data, objections under Section 3(d) were not raised for 118 out of 330 patent applications in the first examination report. We have outlined a few examples below.

A patent [1287/CHENP/2009] was granted for a monoclonal antibody molecule CR6261 against an influenza virus, comprising haemagglutinin (HA) of the H1 and H5 subtype of H1N1. An objection raised under Section 3(d) (a new form of a known substance). The prior art disclosed that the claimed antibody was capable of recognising and binding to an epitope in the HA2 subunit of the influenza haemagglutinin protein (HA). Additionally, information pertaining to the unknown technical effect or efficacy is produced by the claimed antibody over the disclosure made in the prior art. The applicant overcame this argument by mentioning that the amended claims cover the human antibodies and not murine antibodies C179 as disclosed in the prior art. Further, the claimed antibody possessed an unknown technical effect. The application was then accepted by the patent office without further scrutiny.

A similar patent [1202/KOLNP/2010] - covering a monoclonal antibody specific to haemagglutinin from influenza virus H5 subtype - was granted. Though, FER raised an objection for lack of novelty and inventive step by citing the prior art documents (which disclosed that the claimed components detected the H5 subtype avian influenza virus in a biological specimen). The patent office objected to the claims only under Section 3(i). It is unclear why the objection under Section 3(d) was not raised.

An application [2339/CHENP/2009] that was granted a patent covered an antibody or antigen binding fragment which binds to h1L-4R (human interleukin -4 receptor) with six CDRs of the HCVR (heavy

chain variable region) and LCVR (light chain variable region) of SEQ ID Nos: 579/59 or 581/59. The prior art documents disclosed human monoclonal antibodies that bind to h1L-4R comprising VH and VL sequences similar to the claimed antibody and use of antibody in the treatment of arthritis. The patent office objected to the application for lack of inventive step and under section 3(d) for absence of submission of data on significantly improved therapeutic efficacy of claimed antibody. Under Section 3(d) it noted that the claims are a new form of a known substance, or it is a new use of a known antibody as there is no difference in the amino acid sequence when compared with the known antibody disclosed in the prior art.

The applicant was able to overcome the objection under the inventive step by claiming that since the antibody possessed unique and unexpected properties like enhanced affinity it effectively inhibits the activity of the IL-4, thereby exhibiting unexpected technical advantage. The applicant argued that since these features render the claimed subject matter inventive over known antibodies and as novelty of the claims is acknowledged, Section 3(d) objection does not apply to the present set of claims. The submission made to overcome the objection of lack of inventive step was cited as data to prove technical advantage of claims over the VAB16F31 antibody which also possesses the same set of CDRs. The patent office accepted the submission without assessing whether the claims had overcome the objection of new form of a known substance and new use of a known substance raised under Section 3(d).

In a similar case [1121/DELNP/2007] with claims related to IL-4 (Interleukin -4) antibodies, a patent was granted covering an anti-IL4 specific human monoclonal antibody. However, in this case a Section 3(d) objection was not raised. The objections against the claims included lack of novelty and an inventive step and fall within the scope of Sections 3(j) and 3(i). The applicant submitted that since the claimed invention is a fully human IL-4 antibody with high affinity it fulfils the inventive step requirement and was then granted a patent.

To conclude, antibody technology has evolved over many years with most of the technology established and well known. Given the unique provision of Section 3(d) of the Indian Patent Act, the patent office should strive to provide a detailed explanation when raising objections under this section. A clear distinction of what is a new form of a known substance or discovery of a known substance when considering applications covering antibody inventions should be clearly indicated in the examination report.

It is pertinent to note that two key issues plague the examination process of antibody applications:

- Firstly, in most cases, the applicant's submission is reproduced verbatim in the Section 15 order or a line of acceptance of submissions made by the applicant post-hearing is noted for proceeding with a grant of patent.
- Secondly, the lack of detailed reasoning in either rejecting or granting the patent application in the Section 15 order has created an ambiguity in understanding on what grounds a patent application is rejected and when granted how the applicant overcomes the objections.

Further, while considering the submissions made by the applicant to overcome the Section 3 objections, the kind of data considered by the patent office while assessing these applications is also not included in the order.

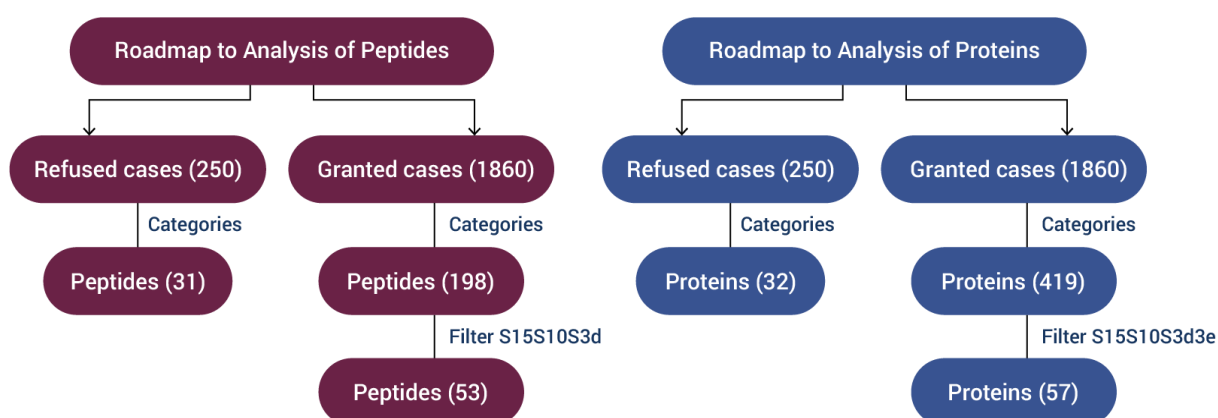
Proteins and Peptides

The peptide/protein drugs are regulated as conventional chemical drugs or biologics. However, the fine line between peptides and proteins has not been made clear. But FDA guidelines on biosimilars clearly categorised peptides are those:

- (i) which are alpha amino acids polymers chemically synthesised and less than 100 amino acid residues, and
- (ii) which are up to 40 amino acids, irrespective of chemical or recombinant ways of synthesis.

Peptides are between small molecules and large proteins, due to their structure and properties. However, the building blocks for proteins or peptides are amino acids, which is a basic unit in their polymeric chain. The backbone of a peptide or a protein unit is connected by amide bonds - which is a repeating amide bond (-C(O)-NH-) covalently linking amino acids in the main chain. Amino acids can be one among 21 naturally occurring amino acids or unnatural amino acids (other than naturally available amino acids). These amino acid side chains can also be modified by attaching to other chemical groups through a flexible linker unit to obtain side chain conjugates, for enabling additional properties desirable for a protein or peptide. These side conjugates can be attached either with or without a linker unit, which are repeating units for providing necessary spacing needed between two chemical groups. Similarly, the addition of amino acids refers to extending the main chain units either on the N (left end) or C terminus (right end) of the primary sequence shown as A' and B' for N terminal extension, or C' in the case of C terminal extension. Substitution refers to replacing one amino acid unit with another.

Steps involved in the analysis of peptides



Our initial sorting of categories led to 31 refused cases of peptides for comparison with 198 granted peptides cases. We anchored our pharmaceutical granted patents study around Sections 3(d) and 3(e). We believed that using these as filters would provide a dataset that is quantifiable and comparable. To have a manageable dataset for comparison, 53 granted cases were selected by

applying filters S15+S10+S3d. Similarly, 32 refused cases of protein compared with 419 granted protein cases. 57 granted cases were selected by applying filters S15+S10+S3d+S3e. We looked at how objections were raised.

Understanding the Context and Pattern of Objections

We captured different scenarios under which the patent office raised Section 3(d) and 3(e) objections:

- Substitution of amino acid in a peptide chain with an amino acid carrying side chain attachment (4542/KOLNP/2011) was flagged under Section 3(d) under - new form of known substance.
- Similarly, substitution of more than one amino acid with up to five amino acids with side chain attachment, as in the case of 189/CHENP/2011, was also flagged as a new form of known substance. The latter case provided similar substitutions, including position, which was cited in the prior art.
- In another case (500/DELNP/2010), simple substitution of amino acid in the parent chain of a peptide invoked an objection under Section 3(d) for a new form of known substance.
- In another example (3403/CHENP/2010), substitution of an amino acid with an unnatural amino acid (anything outside the naturally known 21 amino acids from nature) tagged with a side chain attachment in a protein chain was flagged under Section 3(d). Prior art cited identical substitution with an analogous side chain attachment group drawing Section 3(d) for a new form of known substance.
- Addition (extension) of amino acids to either N or C terminus
- In the case (2126/DELNP/2007; 1881/DELNP/2007) compositions comprising combinations of known substances were objected to under Section 3(d) for new use of known substances along with Section 3(e) citing them as admixtures.
- In the case of proteins, formulations comprising combinations were objected to as new use of a known substance (3268/DELNP/2007). The following compositions - comprising known substance under section 3(d) as "mere new use of a known substance" (3891/DELNP/2005) without any mention of Section 3(e), or just as "known substance" under Section 3(d) (7520/DELNP/2006) along with Section 3(e) for a composition claim covering an active ingredient and carriers – were all objected to. In all these cases, the compositions involved combinations of one or more pharmaceutical substances and each of them was covered in the prior art.

Applicant v/s the Patent Office - how the Objections were Overcome

All the transactions - from reply to the FER, until a decision is issued under Section 15 - would effectively decide the case either in favour or against the applicant. Here is the compilation of arguments - both successful and unsuccessful - made by the applicants to get over the objections.

There were many cases (4542/KOLNP/2011, 189/CHENP/2011, 500/DELNP/2010, 3403/CHENP/2010, and others in the previous section) where the initial arguments to counter Section 3(d) were to show that the substance was novel, followed by reference to examples and figures showing superior properties of the substance compared to a cited reference substance.

The patent office withheld the objection in these cases, not satisfied with the reasoning provided in the reply to the FER, to schedule further hearing. Eventually, the applicants decided to abandon the application.

For compositions claims, in the case of 1603/CHENP/2010 (concerning a peptide), the applicant argued that the composition, which was a combination of active ingredients with a carrier, as “novel, inventive and a synergistic composition” and countered that “composition is a new substance as such and never be considered as a new form of known substance” and suggested that it may not fall under the purview of Section 3(d). The applicant referred to different data tables and noted the composition as a synergistic mixture for Section 3(e). This application was granted eventually. In the case of 7520/DELNP/2006, when section 3(d) was raised for a composition claim comprising a single active ingredient along with a carrier, the applicant argued Section 3(d) could only be raised for “a mere discovery” or for “a known substance with a known efficacy”. The applicant further argued that though the compound was known, their effect was not explored in a specific diseased state (chronic obstructive pulmonary disease patients), emphasising that the composition claims cannot fall under the ambit of Section 3(d). Surprisingly no Section 3(e) argument was made by the applicant despite the objection. This application was eventually refused, noting that it was “related to mere use of admittedly known ingredient FGF 2 in making pharmaceutical composition with already known ingredients”.

In a carefully scrutinised case, 3268/DELNP/2007, covering peptide formulation comprising a combination of active ingredients, the patent office objected to them as “known components” under Section 3(d). The applicant showed efficacy data of a formulation involving this compound, but the data was hard for us to decipher without legends. The patent office cited “there is change in solubility of insulin in the present formulation, which provides stability. Efficacy data should be provided for any change in efficacy of insulin in the composition” and the applicant decided to withdraw this case.

Here are some more claims involving proteins:

- the cases involving composition (4143/CHENP/2008, 1641/DELNP/2009) comprising one or more compounds and a carrier, had to show synergistic activity. The application was issued for the case (4143/CHENP/2008) where data was shown over the individual components.
- Different sets of objections were raised by the patent office in another case (1641/DELNP/2009) in the FER “discovery of a new property of already disclosed composition” (increased vivo half-life) under Section(3d). The applicant overcame this by using the inventive step argument. The hearing notice withheld 3d under a different argument “mere use of known substance”, and the applicant argued that the composition was not anticipated by prior art and does not fall under 3d. This application was issued by the patent office based on the above arguments.

In some cases, for example, in 337/CHENP/2010, whenever the patent office had raised objections under section 3(d) for a new form of known substance, the applicants would argue that the compound is novel and inventive, especially in cases involving peptides. These cases (337/CHENP/2010, 1877/DELNP/2003) had amino acids added to one end of the terminus in a native sequence. The applicants pointed that as a difference compared to the prior art with amino acids substitution at various positions of the native sequence. This raised the question - does the addition (extension) of amino acids to a native sequence constitute a new compound or a new form of known compound? The applicants argued that the addition of amino acids to the terminus was novel and inventive and cannot be compared to prior art with substituted amino acids at different positions from the prior art. Also, the applicants had asked the patent office to list the known compound, and in the absence of the known compound they had compared their data with the native sequence to overcome the objection under Section(3d). The question remains, on why the patent office failed to list the known compound, the absence of which had prompted the applicant to use the native sequence to get over Section(3d) argument. It is worth mentioning that in 1877/DELNP/2003, the applicant had argued that Section 3d's 'new form of known substance' would be more apt for derivatives of a chemical structure than a biological entity. The clause states that - biological entity cannot be compared with chemical entity, derivatives of biological entity cannot be considered as a new form. The case (2757/DEL/2008) involved a protein chain carrying either N or C terminus extension of the native chain. But when the patent office insisted on efficacy data, the applicant compared efficacy with the wild type (native sequence), instead of comparing with the known compound.

In another interesting case under Section(3d) - for a new form of known substance, covering side chain conjugates of a peptide (1313/DELNP/2006) - the applicant had pointed out the difference in the spacer unit of the linker attached to the side chain of a peptide to prove it as a new compound. The applicant then compared efficacy data with the native peptide instead of comparing the closest prior art with the spacer unit linked analog of a peptide. There is another case (563/DELNP/2006), involving side chain conjugate of insulin derivatives which could present itself as a blueprint in overcoming the Section3(d) argument. Here again, the applicant pointed out the difference in the spacer unit of the linker attached to the side chain - suggesting a new chemical entity compared to the prior art - to overcome the new form of known substance argument under Section3(d). This example clearly charts out the comparison on efficacy, despite showing the compound was novel with different analogs but not with the closest known prior art.

In the case (4118/DELNP/2008) when an objection under a new form of known substance was raised, the applicant pointed out the structural difference in the backbone structure to the prior art compound. This clearly shows the chemical structure as completely different compared to the prior art. Interestingly, the applicant in this case had requested the PO to list the known compound and in the absence of specific details of the known compound, the applicant had cited it was hard to get over the objection. The Controller didn't pursue the objection, accepted it as a new compound and granted this case.

Analysis of Granted v/s Refused

One would understand the contrasting picture only if refused and granted cases are compared under similar circumstances. Even though the number of comparable cases is limited, here are some key points for consideration.

To counter Section 3(d), the applicant for a granted case 1411/DELNP/2012 (relating to IGF-1 protein), argued that the substitution of an amino acid in the native sequence was novel. Interestingly, the prior art had leucine amino acid substitution at the same position. Asparagine amino acid was originally present in the place of Methionine on the native sequence. This patent was issued when superior efficacy (in vitro data) was shown over the native protein, despite the prior art clearly showing an analog of IGF-1 (Leucine substituted). This case carried different and extensive examples comparing in vitro efficacy with different substitution at various places but failed to compare with the closest mutant in IGF-1, that is, leucine. Compare this with a refused case, 3403/CHENP/2010, which carried amino acid substitution in the main chain of insulin. The patent office raised objections for claiming a new form of known substance and refused this case for not providing efficacy data. The only difference between the refused (3403/CHENP/2010) and granted case (1411/DELNP/2012), other than the protein chain sequence, is the efficacy data. But the point to be noted is efficacy was not shown or compared with the closest analog in the prior art cited by the patent office.

Among composition-based cases, in 4143/CHENP/2008 - comprising (a) one or more compounds selected from nitazoxanide and tizoxanide, and (b) an interferon -, there was a reference to figures with data to overcome objections from Section 3(e). For this case, there were no Section 3(d) objections raised, unlike in the cases mentioned earlier (7520/DELNP/2006, 1603/CHENP/2010). Interestingly, in a refused case covering a composition involving a combination of active ingredients (3891/DELNP/2005), it was challenged under Section 3(d) as "mere use of known sequences", without a Section 3(e) objection for a composition claim. The applicant tried to overcome the Section 3(d) objection citing novelty associated with the composition, but it was eventually rejected under 'new use of known substance'.

Curious Cases with no Section 3(d)

Having analysed a handful of cases with more questions than answers on Section 3(d), we wondered if any discrepancy exists for the cases without Section 3(d). It is worth recollecting that without 3(d), the applicant can bypass the need for showing data for improvement in efficacy. An oxyntomodulin peptide (1268/MUMNP/2012) with substitutions of natural and unnatural amino acids in the main chain ducked under the radar of Section 3(d). In another case (11/MUMNP/2010) the substitution of N terminal amino acid with other amino acids slipped under Section 3(d). Eventually both these cases were granted. This was in contrast to another granted case, 1318/KOLNP/2009, with amino acid substitution in the main chain of Ghrelin, which was flagged under Section 3(d) for unnatural amino acid substitution. In the case of a granted case (2512/MUMNP/2010) involving a side chain conjugated Insulin, the only difference with the prior art compound is the spacer unit difference in the linker used in the side chain from the cited reference in the FER, yet Section 3(d) was overlooked. Notably, in vivo potency and pharmacokinetic profiles were compared with insulin detemir and not with the efficacy of any of the closest analogs cited in the FER. It must be pointed out that without Section 3(d) it was not expected that the applicant would compare efficacy with any known analogs. In another case of a granted patent (154/MUMNP/2011), no objection under 3(d) was raised for extension of insulin B chain by adding amino acids to the terminus, in contrast to another granted case with extended amino acids terminus (2757/DEL/2008).

Analysis of the Patenting of Proteins and Peptides

Considering that Section 3(d) arguments outnumber Section 3(e) in our analysis and factoring in the number of applications - nearly 1000 filed in Biotechnology for the year 2018-2019 - clear guidelines on Section 3(d) for Biologics would pave way for good patents issued by the PO.

- The guidelines must focus on listing the known compound and efficacy for the known compound whenever Section 3(d) is raised. With no clarity on the current guidelines, the applicant can get away by comparing efficacy with the native compound without showing any improvement with the latest known derivative of the compound.
- The FER must clearly mention the known compound in Biologics. Any small modification could impart major structural changes in the macromolecule and thereby affect its properties. What constitutes a known compound - is it substitutions with natural or unnatural amino acids, addition (extension) of main chain, side chain attachment to peptides/proteins?

Vaccines

Vaccines represent one of the major classes of biologics. The WHO describes vaccines as agents that reduce risk of getting a disease by working with the body's natural defences to build protection.³⁷ Unlike other biologics that are useful for treating disease, vaccines are primarily concerned with prophylaxis, that is, disease prevention (although some therapeutic vaccines also exist). Since vaccines limit the spread of infection by building immunity to infectious agents in a population, they fulfil an essential role in global public health.

Needless to say, in the last three years, the Covid pandemic reinforced the centrality of vaccines as a pillar of the pharmaceutical system on which we all depend.

Since vaccines function by training the immune system to recognise infectious agents, the active ingredient in vaccine preparations may be whole microorganisms (such as bacteria, viruses or parasites), or isolated components (antigens) thereof. These are broadly referred to as 'whole' and 'subunit' vaccines respectively. These broad classes may be further divided into subcategories³⁸ as follows:

1)

- Live attenuated vaccines - these consist of a live microorganism which is manipulated to weaken its pathogenicity. Examples include the BCG vaccine for Tuberculosis and the oral Polio vaccine.
- Inactivated/killed vaccines - the microorganism is inactivated by physical processes (such as heat) or using chemicals. Examples include the Rabies vaccine, and most flu vaccines.

2)

- Protein-based vaccines – these consist of isolated proteins from microorganisms that act as antigens, peptide fragments or shorter antigenic stretches (also called epitopes) of antigenic proteins, or DNA/RNA that encodes for such proteins and peptides. For example, the HepB vaccine for Hepatitis B.
- Polysaccharide vaccines – some microorganisms have their surfaces decorated with polysaccharides or sugar molecules, which can also be used to raise immunity. Examples include vaccines against meningococcal bacteria.
- Conjugate vaccines – some antigens are not sufficiently immunogenic on their own and may be linked / conjugated to other molecules (usually proteins) to improve their immunogenicity. For example, the HiB vaccine for protection from Haemophilus influenzae bacteria.
- mRNA vaccines – or messenger RNA vaccines – are the newest development in the field of vaccine technology. During the Covid pandemic, the world saw the first two vaccines brought to market using this technology, from BioNtech/Pfizer and Moderna. These vaccines offer as-yet unmatched flexibility and agility in both development and production, due to the largely

³⁷ <https://www.who.int/health-topics/vaccines-and-immunization>

³⁸ <https://vaccine-safety-training.org/home.html>

synthetic, or biochemical manner of process, as opposed to traditional vaccine technologies, which involve biological processes³⁹.

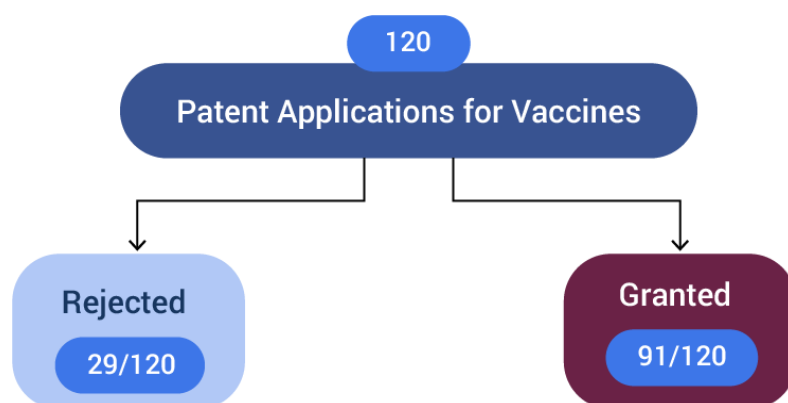
These classes represent the most common types of active ingredients in vaccines, but other categories also exist, for example, toxoids (inactivated toxins) and therapeutic vaccines.

In addition to the active ingredient, vaccine preparations usually include other components such as adjuvants, stabilisers and preservatives. Adjuvants help boost an immune response to the antigenic component of the vaccines, while stabilisers and preservatives ensure a vaccine retains efficacy after storage and transportation.

Vaccines Patents

A patent for a vaccine may seek to protect the active antigenic ingredient, processes or methods for generating it, formulations of vaccine preparations that include adjuvants/stabilisers/preservatives, or methods of using vaccines specifying dosage, timing and/or modes of administration. In addition, patents may also be sought for combinations of antigenic ingredients to immunise against multiple disease-causing microbes/strains of the same microbe (for example, the MMR vaccine that protects against the measles, mumps and rubella viruses).

Examination outcomes for vaccine patent applications

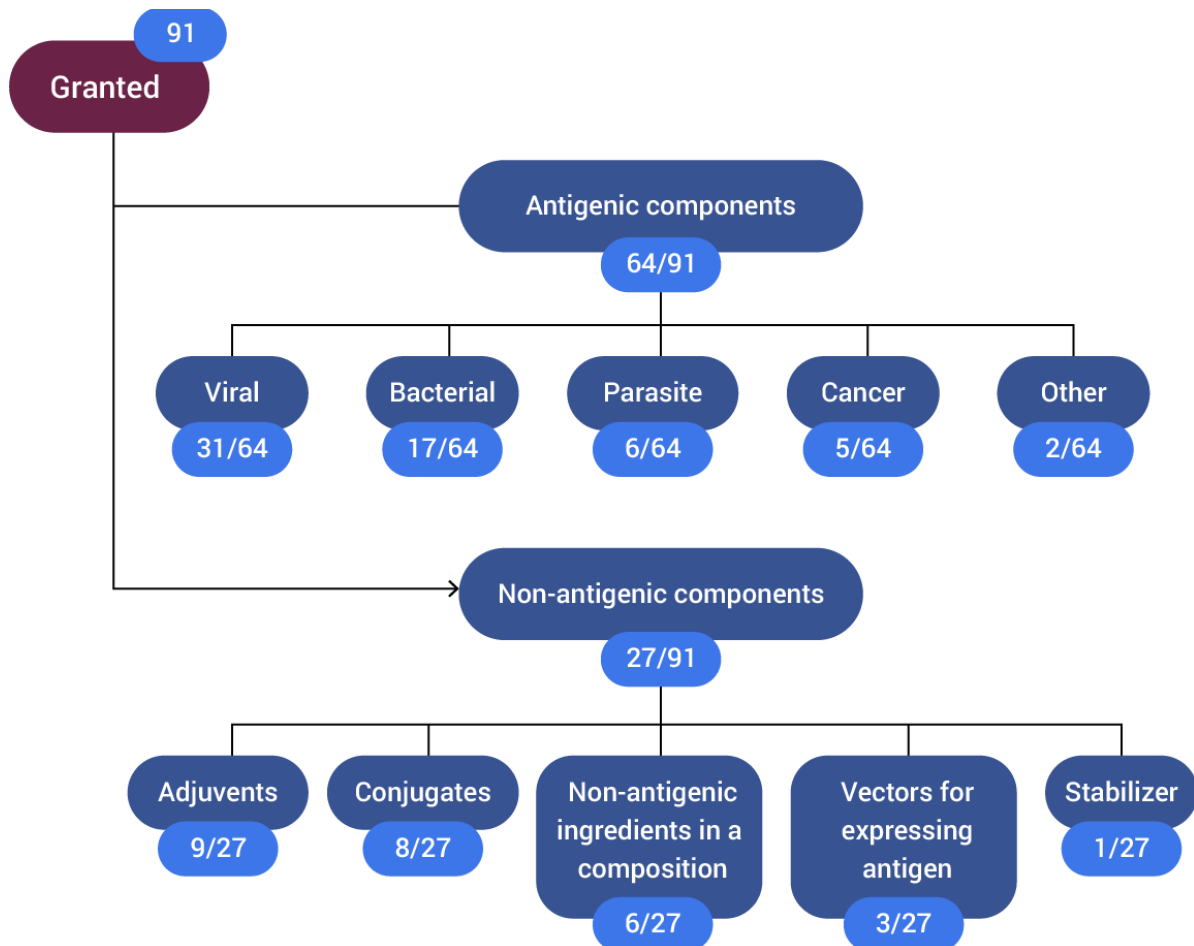


Our dataset identified 120 applications for vaccines, of which 91 proceeded and were granted, while 29 were refused.

³⁹ Achal Prabhala & Alain Alsalhani, Pharmaceutical manufacturers across Asia, Africa and Latin America with the technical requirements and quality standards to manufacture mRNA vaccines, AccessIBSA & MSF Access Campaign, December 2021, <https://msfaccess.org/pharmaceutical-firms-across-asia-africa-and-latin-america-potential-manufacture-mrna-vaccines>

Subject Matter of Granted Patents

Subject-matter of granted patents

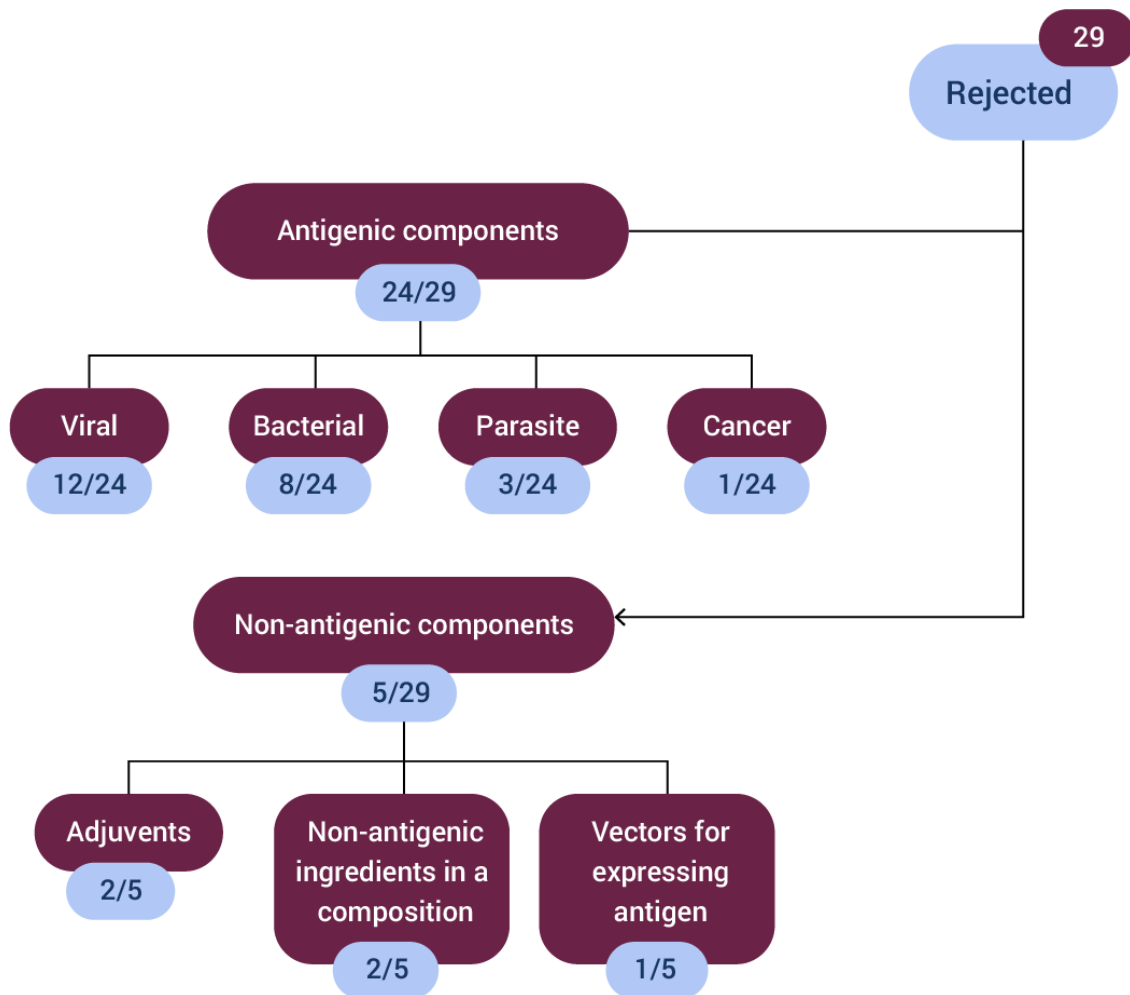


Our dataset identified 91 granted patents related to vaccines (as illustrated just before). About two-thirds (64/91) of these patents seek protection for the active antigenic component of the vaccine, with a focus on specific infectious agent(s)/disease(s). Around half of such patents relate to viral vaccines (31/64), followed by bacterial vaccines (17/64), parasite vaccines (6/64), therapeutic cancer vaccines (5/64), vaccines for allergic disease (3/64) and other diseases (2/64).

Next, less than a third (27/91) of the granted patents seek to protect non-antigenic components of the vaccine. These include patents to adjuvants (9/27), conjugates that may be covalently linked to an antigen (8/27), non-antigenic constituents of a vaccine composition (6/27), vectors that enable antigen expression/production (3/27) or stabilisers (1/27).

Subject Matter of Rejected Applications

Subject matter of rejected applications



Likewise, we identified 29 applications concerning vaccines from the dataset of rejected applications, the vast majority of which concerned the antigenic component of the vaccine (24/29). Again, viral vaccines account for half of such applications (12/24), followed by bacterial vaccines (8/24), parasite vaccines (3/24) and an application for cancer vaccine (1/24).

Finally, the remainder of the rejected applications (5/29) are related to non-antigenic components. These include applications where the claims concern adjuvants (2/5), non-antigenic constituents of a composition (2/5) and vectors for antigen expression (1/5).

Almost 75% of all patent applications that we identified relate to the antigenic components of a vaccine (88/120 overall; 64/91 from grants and 24/29 from rejected applications). The remaining applications are generally more concerned with other components of a vaccine and are not restricted

to any disease in particular (32/120 overall; 27/91 from grants and 5/29 from rejected applications). Thus, the majority of the applications seek patent protection for vaccines that are specific to certain diseases. Such applications are often most relevant in a commercial context, acting as possible barriers to market entry by competitor products.

Types of Claims in Applications for Vaccine Antigenic Components

The scope of protection offered by such applications depends on the type of claims in an application. For example, claims could be directed to a process/method of preparing a vaccine or product claims that protect the core antigenic component(s) in isolation or formulated along with other ingredients in a vaccine composition. Process patents are generally regarded as narrower in scope in comparison to product patents, as competitors can avoid infringing on such claims if they are able to work around the particular method/process as claimed. Even among product patents, claims to an isolated antigenic component are the broadest in scope relative to claims concerning combinations of such components, or claims concerning compositions where other non-antigenic components are also specified.

Applications for vaccine antigenic components – distribution according to claim type

TYPE	PROPORTION (NUMBERS)		
	OVERALL	GRANTS	REJECTS
Whole organism/subunit	47% (41/88)	50% (32/64)	37% (9/24)
Composition	26% (23/88)	28% (18/64)	21% (5/24)
Combination	23% (20/88)	16% (10/64)	42% (10/24)
Process	4% (4/88)	6% (4/64)	

Almost half of all applications (both rejects and grants) concerning antigenic components are fairly broad in scope, since their principal independent claim is directed to the isolated antigenic component, either as a sub-unit or a whole organism. The remainder are concerned with - (i) compositions (26%) or (ii) combinations of antigenic components (23%). Narrower claims to processes/methods for preparing a vaccine only account for a small fraction of all patent applications (4%). However, these proportions are notably different across the granted and rejected applications. Applications for vaccine combinations account for the majority of rejected applications, while claims of broader scope concerning core antigenic components are the majority in the granted dataset.

Statutory Exceptions and Examination of Applications

Compositions and combinations (3(d) and/or 3(e))

As discussed above, patents for compositions and combinations of antigenic components together constitute about 44% of all grants for patents concerning antigenic components. If the antigenic component(s) in these compositions/combinations was previously known, these patents ought to have attracted (and successfully overcome) objections under Section 3 of the Indian Patents Act, particularly under Sections 3(d) and 3(e). As explained previously, Section 3(d) denies patent protection where the claims concern only new forms of known substances, including combinations, with no improvement in properties related to efficacy. Similarly, claims concerning substances that are only an admixture of known components resulting in aggregation of their properties are held unpatentable under Section 3(e). Therefore, for any combinations/compositions with known component(s) – for instance where a concomitant novelty objection is raised – an objection under Section 3(d) and/or Section 3(e) likely applies. Indeed, 3(d)/3(e) objections were raised during prosecution for the vast majority (24 of 28) of granted patents concerning a composition/combination. However, there were a few instances (4 of 28) where no 3(d)/3(e) objections were raised. In one such case (5530/DELNP/2006), the examination report alleged that a vaccine composition lacked novelty, arguing that the antigenic component of the composition was known in the prior art. Unexpectedly, no objection under 3(d) or 3(e) was raised despite the antigenic component being a previously known substance formulated as a composition, with no further components specified.

Objections to claims concerning combinations of known antigens were raised under either of 3(d) or 3(e). For example, in the case 5040/DELNP/2008 the claims concerned a vaccine composition comprising a combination of two known porcine viruses, while in 2299/DELNP/2007, the claims related to a composition combining multiple known antigens from a Hepatitis C virus. In both cases, these claims faced objections under Section 3(d). However, similar claims faced objections under Section 3(e) for other cases. For example, in 1893/CHE/2011, the claims were directed to a vaccine combination of a rotavirus and a poliovirus.

Claims concerning compositions predominantly faced objections under Section 3(e), where the antigenic and non-antigenic components of the composition/formulation were each previously known. For example, in 2398/CHENP/2011, the claims were directed to a composition comprising an influenza viral protein and a galactosylceramide derivative as an adjuvant. Since these components were previously known to be used in immunogenic compositions, their use in combination was considered to be a mere admixture of these agents objectionable under 3(e).

New Forms/uses of Known Substances (3(d))

It is not just compositions and combinations that are found objectionable under statutory exceptions to patentability. 3(d) also excludes new forms of known substances including “derivatives” of a known substance where no improvement in properties regarding therapeutic efficacy can be seen. This may

extend to sub-unit type vaccines, particularly if the antigens are considered to be a new form of a previously known antigen. For example, in 3450/DELNP/2009, the claims concerned a bacterial (streptococcal) vaccine comprising a recombinant protein that included two known epitopes (antigenic fragments) from a bacterial protein in sequence to result in a “chimeric vaccine”. Since the epitopes were previously known, a 3(d) objection was raised, arguing that the chimeric version of admittedly known epitopes was a “new form” of a previously known substance. An objection under 3(d) may also apply when the sub-unit vaccine only relates to a “new use” of a known substance. For example, in 1813/KOLNP/2010, the claims concerned a cancer vaccine comprising an antigenic protein derived from a tumour cell. Since the tumour cell protein was previously known, a 3(d) objection was raised alleging use of the protein in a vaccine composition amounted to a mere new use, that is, as an antigen.

Naturally Occurring Substances (3(c)) and Methods of Treatment (3(i))

An exception under Section 3(c) is relevant for vaccine patents, since it prohibits patenting of any living thing that may be found to exist in nature. In 4262/DELNP/2008, the claims as filed concerned an isolated canine influenza virus as a vaccine. Since the claim included no further limitations to distinguish the claimed virus from its naturally existing counterpart, a 3(c) objection was raised.

Finally, claims directed to vaccination methods, usually specifying modes or dosages of administration are uniformly objected to under Section 3(i).

How are Objections Overcome?

Based on our analyses, overcoming an objection under Section 3 often requires both an amendment of the claims to distance the claimed subject-matter from the prior art, and evidence from the application supporting an improvement in therapeutic efficacy and/or synergy. A clear divide appears to exist between grants and rejected applications regarding available data in the application. Applications that overcame objections almost always presented evidence from the examples of the application supporting a technical effect, and most rejected applications failed to provide such evidence.

Scrutiny of Submitted Evidence

However, this is not to say that just about any evidence submitted is sufficient to overcome Section 3 objections. A few examples from rejected applications, where data was submitted but was not found to be satisfactory, are also discussed below.

In the case 1893/CHE/2011, the claims attracted an objection under Section 3(e), since the claims concerned a combination of known virus strains (a rotavirus and a poliovirus). The application was rejected since the patent office noted that the evidence provided by the applicant only demonstrated a uniform efficacy and immunogenicity against both antigens claimed in the combination, which was regarded to be an aggregation of known properties. Interestingly, the patent office disregarded

additional evidence regarding stability of the formulation that the applicant had also provided, on the basis that this evidence “do not prove or reveal the synergistic effect of the claimed combination as required under clause (e) of Section 3 of Patents Act, 1970”.

116/KOL/2007 is another example of a rejected application where the patent office regarded evidence submitted by the applicant as unsatisfactory for overcoming a Section 3(e) objection. Here, the claims concerned a composition comprising a combination of multiple known bacterial strains (including *Haemophilus influenzae* and *Streptococcus pneumoniae*) and an objection under Section 3(e) was raised. Although the applicant argued for synergy based on data from human clinical trials present in the application, this was found to be unsatisfactory as the final decision states that “no synergistic effect has been shown in specification for the claimed composition”.

Thus, it is encouraging to see that not just any evidence is deemed satisfactory and that the evidence submitted is subjected to close scrutiny by the patent office.

Post-filing Evidence and what is Admissible

In terms of evidence, the IPO suggests that improvement in properties with regard to efficacy should be stated “clearly and categorically in the description... ..at the time of filing the application...or subsequently by way of an amendment of specification under section 59.”⁴⁰ This suggests that evidence to overcome 3(d) must be present in the application as originally filed or by way of a subsequent amendment of the application to include such evidence. However, our analysis shows that evidence available after the filing date (or “post-filing” evidence) was also considered in the absence of any amendment of the application. For example, in overcoming 3(d) objections raised during the prosecution of 3495/KOLNP/2008, the applicant relied on post-filing evidence to argue for an improvement in therapeutic efficacy. Allowing post-filing evidence appears questionable, particularly in light of the section from the IPO’s manual quoted above. If applicants are allowed to rely entirely on post-filing evidence to overcome a 3(d) objection, this could amount to an unfair advantage for some applicants over others. For example, applicants who file an application without any experimental evidence so that they may secure an early filing date could effectively gain an advantage over later applications which are actually supported by evidence for improved therapeutic efficacy.

It is worth noting, however, that in the case 3495/KOLNP/2008 the application included some preliminary evidence from data in the examples of the application as originally filed to argue for therapeutic efficacy. Conversely, in 5040/DELNP/2008 and 6656/DELNP/2006, the application lacked any evidence in the examples of the application as originally filed. The applicants attempted to overcome 3(d)/3(e) objections solely on the basis of post-filing evidence but were unsuccessful. Hence, it appears that post-filing evidence is admissible only when there is at least some evidence already available “at the time of filing”, but it would help if the IPO could provide further guidance in this regard.

⁴⁰ Section 09.03.05.04 in the Manual for Patent Office Practice and Procedure, published November 2019

Overcoming 3(e) without Demonstrating Synergy

Although demonstration of synergy is usually required to overcome a 3(e) objection, we found that this requirement is not absolute, particularly for vaccines. For example, the claims in the case 8081/DELNP/2007 concerned a 13-valent polysaccharide conjugate vaccine. The vaccine comprised polysaccharides from 13 different strains of *Streptococcus pneumoniae* that were conjugated to a carrier protein. This application was not identified by our methodology, but we included this in our analysis since this application provided an interesting example of a vaccine patent application where third parties (opponents) intervened by filing an opposition, prior to the grant of the application (in accordance with Section 25(1) of the IPA). Conjugates of polysaccharides from each of the 13 individual Streptococcal strains, as well as 7-valent and 9-valent combinations were previously known. So, the opponents alleged that the 13-valent combination was not patentable according to the exception under Section 3(e), in addition to opposing the application under grounds of novelty and inventive step.

The applicant was unable to provide data for synergy from the combination of 13 strains. Instead, the applicant argued that a uniform immune response against each individual antigen was unexpected, relying on the principle of “antigenic interference”. Antigenic interference refers to the competition between multiple antigens in raising an immune response in a subject, when these antigens are administered concurrently, or in close succession to a subject. This is a significant hurdle in the development of multivalent vaccines, where the administration of multiple antigens from different strains has the unintended consequence that an effective immune response is raised against only some, but not all, antigens in a combination. The applicant provided evidence to show that antigenic interference existed for multivalent pneumococcal vaccines. Prior efforts to generate 11-valent vaccines had failed because the vaccine failed to protect against infection by some strains in the combination. Thus, even in the absence of evidence for any synergy, the applicant was able to demonstrate that a mere aggregation of properties could not be expected to exist due to underlying antigenic interference. This appears to be contrary to the prescribed requirement for overcoming a 3(e) objection as suggested in the IPO’s manual, which states that “all the substances which are produced by mixing components or a process of producing such substances should satisfy the requirement of synergistic effect in order to be patentable.”⁴¹

However, applicants are not always able to circumvent the requirement to show synergy to overcome a 3(e) objection in the absence of concrete evidence for antigenic interference for the particular combination claimed. For example, 1893/CHE/2011 and 1999/DELNP/2007 are both applications concerning combinations of previously known antigens and 3(e) objections were raised during prosecution. In both cases, the applicants attempted to do away with the requirement for demonstration of synergy for the claimed combination by invoking antigenic interference. However, they failed to provide evidence that antigenic interference actually existed for the combination of antigens in question, and these applications were refused.

Addressing Objections Solely by Amendment

⁴¹ 09.03.05.05 in the Manual for Patent Office Practice and Procedure, published November 2019

It appears that Section 3 objections do not always require data to be overcome, and these objections may also be addressed by amending the claims. For example, in 1483/KOLNP/2009, the claims concerned a live vaccine composition where a live Salmonella bacterium was engineered to express avian influenza viral antigens. The examination suggested this combination of features was known, and a 3(d) objection was raised. In response, the applicant overcame the objection by amending the claims to specify additional features of the engineered bacterium that helped produce the viral protein antigen, as these features were not known in the prior art. Thus, the applicant relied only on limitations in the claim to distinguish the subject-matter from the prior art and successfully argued that the 3(d) objection no longer applied in view of the amendments.

Overcoming Objections under 3(c) and 3(i)

It would appear that objections under 3(c) can be addressed by amending the claims to include additional limitations indicating the claimed subject-matter is distinct from a naturally occurring living thing. For example, in 4262/DELNP/2008 (also mentioned above), the claims were amended to define the virus of the claims by additional mutations in a structural protein that would not be found in a naturally occurring canine influenza virus.

Since claims concerning methods of treatment of human subjects are not admissible, Section 3(i) objections are usually addressed by deleting such claims. In any case, these claims are often not the sole or principal independent claim in an application. Expectedly, we found no claims concerning such methods amongst the granted vaccines patents.

Inconsistencies in Examination

The examples discussed above illustrate contexts where objections are raised under the legal provisions concerning statutory exceptions to patentability. However, such objections are not always invoked uniformly. Our analyses identified examples of applications indicating inconsistencies in the way these provisions were used (as compared to the prosecution of pairs of applications having broad similarity in the claimed subject-matter and the surrounding fact pattern in terms of the prior art background). These include a comparison between a rejected application and a grant, as well as a comparison across granted patents. These scenarios are outlined in more detail below.

A Comparison of Vaccine Patents - Rejects v/s Grants

Inconsistent application of 3(d) - new form of a known substance (237/DELNP/2010 & 1813/KOLNP/2010)

In 237/DELNP/2010, the claims concerned a canine parvovirus vaccine comprising a variant of a known VP2 protein antigen. The variant differed from the VP2 protein, which was known to be immunogenic, by substitution of a single amino acid in the protein sequence for a different amino acid. This was considered to be a “novel variant” (that is, a new form) of a known substance and a 3(d) objection was appropriately raised. The applicant failed to provide evidence for immunogenicity and could not overcome the 3(d) objection, and the application was subsequently rejected.

On the other hand, a similar objection was not raised during prosecution for 1813/KOLNP/2010, where the claims concerned new variants of a known peptide antigen. In this case, the invention concerned a therapeutic cancer vaccine. The claims were directed to short peptide fragments that could act as immunogens. The examination report indicated that a *similar* peptide from the prior art was known to be a cancer vaccine, and the function of this peptide in cancer treatment was previously disclosed. The claimed peptides were each distinguished from this previously known peptide in that a single amino acid in the sequence was substituted by a different amino acid, that is, they are novel variants of a known substance.

Both cases discussed above concerned a claimed protein/peptide antigen that differed by a single amino acid substitution relative to a previously known protein/peptide antigen. However, 1813/KOLNP/2010 did not face objections under Section 3(d) for being a “new form” of a known substance. Instead, the FER raised a Section 3(d) objection suggesting that the claims were a “mere use or new use of [a] known gene product by different mutation” (the emphasis was added). The difference under which a 3(d) objection is raised (that is, new use, as opposed to new form of a known substance) is important, as it has distinct implications in terms of evidence required to overcome the objection.

As discussed previously, Section 3(d) stipulates that “a new form of a known substance which does not result in the enhancement of the known efficacy” is not patentable. The “new form” exception under 3(d) is a *conditional* exception – that is, only new forms that do not “result in the enhancement of the known efficacy” are not allowed. If an applicant is able to show that a new form has improved efficacy over that of a previously known substance, then the objection may be overcome. In contrast, the “new use” objection under Section 3(d) is *unconditional* – claims to a new use of a known substance are not admissible, regardless of any evidence for efficacy. Hence, it would be expected that the “new use” objection could not have been overcome for the case 1813/KOLNP/2010, other than by amending the claims. Surprisingly, the patent office appears to have accepted the applicant’s submitted evidence regarding the efficacy of the claimed peptides to function as immunogens to dismiss the 3(d) “new use” objection. The patent office did not provide any reasoning in their decision regarding their approach to treating the “new use” objection as a conditional exception.

Further, even if we are to assume for the sake of argument that the patent office had objected to the claims as a “new form”, the evidence that the applicant had submitted was still deficient, as it did not satisfy the condition of showing an “enhancement of the known efficacy”. The examination report in 1813/KOLNP/2010 indicates that a similar peptide lacking amino acid substitutions as specified in the claims – also referred to as the “wild-type” – was known to be immunogenic. Therefore, it appears that data for a “known efficacy” was available. The evidence submitted in response to the 3(d) objection relied on data from the examples in the case 1813/KOLNP/2010. These examples describe results showing the immunogenic activity of the claimed variant peptides in comparison with a wild-type peptide, specifically results from tests of cytolytic activity. The results compare cytolytic activity of variant peptides with the known wild-type peptide and note that there was “*equal* cytolytic activity” (emphasis added; data from Examples 11 and 12, which the applicant referred to in their response). Since cytolytic activity of the wild-type peptide and variants was equal, the data indicates that there was no enhancement of the known efficacy. However, this discrepancy appears to have gone unnoticed due to insufficient scrutiny of evidence.

A Comparison Across Grants

The example discussed above is based on a comparison between datasets of granted and rejected applications. In addition, we also proceeded to look for further inconsistencies within our dataset of granted applications. We focused on a subset of 19 applications (from the 60 granted applications) where no objections under Sections 3(d) or 3(e) had been raised. Again, comparing grants in a similar fashion as described in the preceding section, we were able to identify additional examples indicating inconsistent application of provisions under statutory exceptions to patentability.

The IPO considers an objection under 3(d) pertinent if a vaccine includes a protein/peptide antigen that is a modification of a previously known protein/peptide antigen. For example, in 237/DELNP/2010 (also discussed in the preceding section), a 3(d) objection was found applicable where the claims concerned an amino acid substitution at a single position in the sequence of a VP2 protein that was previously known. In 2743/DELNP/2009, the claims concern an avian influenza vaccine comprising a modification of the H5 protein of influenza virus. The modifications in this case involved a substitution in position 223 and an insertion of an additional amino acid at position 328 of the wild-type H5 protein. The examination report raised objections under novelty and the inventive step on the basis that the wild-type H5 protein was a known immunogen. However, the modified H5 protein of the claims was not considered a “new form” of a known substance since no objection under Section 3(d) was raised during prosecution. It is arguable that an objection under 3(d) was found inapplicable in this case because there were multiple modifications involved, that is, both substitution and addition of amino acids to the wild-type H5 protein sequence. However, it is impossible to ascertain if such considerations were considered, since the Patent Office does not usually provide reasoned explanations where no objection is raised.

We also identified inconsistent examination of claims concerning combinations of known substances, where an objection under Section 3(e) is likely applicable. For example, a 3(e) objection was raised for 1184/MUM/2009, where the claims concerned a bacterial vaccine comprising a combination of a meningococcal polysaccharide antigen and an adjuvant based on compounds extracted from a

Withania Somnifera plant. Since both antigen and adjuvant were individually known previously, the combination attracted a 3(e) objection as a mere admixture aggregating known properties. The applicant then submitted evidence for synergy of the combination to overcome the 3(e) objection. On the other hand, the case 9927/DELNP/2012 concerned a vaccine composition comprising a combination of an antigen, an immunostimulatory oligonucleotide as an adjuvant, and cholesterol. The examination report alleged a lack of novelty and inventive step on the basis of previous disclosures of vaccine compositions comprising the components in various combinations in the cited prior art. Despite prior knowledge of the immunogenic properties of components of the vaccine either singly or in limited combinations, no objection under 3(e) was raised. Consequently, there was no requirement for the applicant to provide evidence of synergy for the claimed combination, possibly lowering the evidentiary threshold required for patentability of this application.

Reflections on Vaccine Patents

The Application of Statutory Exceptions

- **Positively:** It is encouraging to see that exceptions under Section 3 are broadly applied to various categories of biologics, and that anti-evergreening provisions such as 3d/e/i have been useful in rejecting possible secondary patents in biologics.

It is also interesting to see Section 3(c) has been applied to limit the scope of some biologics patent applications for vaccines and antibodies so that protection is limited only to engineered/isolated forms, but not equivalents that may also be found to exist in nature. This provision is possibly of greater importance for biologics that have naturally existing counterparts, than pharmaceuticals that are mostly synthetic molecules not otherwise found in nature.

- **Issue:** However, possible that these provisions might still be underutilised.
 - Firstly, inconsistencies described in the previous sections highlight gaps and scenarios where objections ought to have been raised but were not. It is possible that there are many applications where an appropriate objection under section 3/d/e/i was applicable but wasn't raised. We have highlighted several inconsistencies in the application of statutory exceptions in the categories analysed, namely, peptides/proteins and vaccines. We find this is particularly an issue with identifying "new forms" of known biologics under Section 3(d), which predominate in the inconsistencies we have identified.
 - Also, objections under these grounds were raised in the range of 70-85 % in the categories we examined. In a previous report⁴² pharmaceutical patents, we noted that about 70% of patents related to secondary patents for previously known compounds. For biologics, the extent of secondary patenting is likely higher, at least based on available information on patent lifecycle management for top-selling biologics.⁴³

⁴² Dr. Feroz Ali, Dr. Sudarsan Rajagopal, Dr. Venkata S. Raman & Roshan John, *Pharmaceutical Patent Grants in India: How our safeguards against evergreening have failed, and why the system must be reformed*; <http://accessibsa.org/media/2018/04/Pharmaceutical-Patent-Grants-in-India.pdf>

⁴³ Previous reports suggest that the extent of secondary patenting may extend further in case of biologics. For example, a previous study identified over 247 patent applications for Abbvie's Humira, 219 applications for Roche's Avastin and 204

Accordingly, we would expect grounds under Sections 3d/3e/3i to be raised more frequently.

- **Recommendations:**

- Improve identification of new forms. The current biotech guidelines globally provide very few examples which do not even apply to most categories of biologics. Explanation of 3(d) already does this for pharmaceuticals, but an equivalent library of possible alternative forms for biologics need to be drawn up and to be included in the overall guidelines. As biologics are still somewhat nascent and constantly evolving, the guidelines will also need to be updated more frequently (at least once every 1-2 years).
- Proactively raise objections under Section 3. For several granted applications, we find that the claims were alleged to lack novelty, but no Section 3 objections were raised in the examination report. For example, in the vaccines category, this happened in 5 out of 89 applications. In these cases, the novelty objection was overcome by amending the claims, or by emphasising any differences between the claimed biologic and the prior art. While the argument/amendment may suffice for establishing novelty, it is arguable that such biologics may instead be considered as “new forms” of a substance known from the prior art cited for novelty. Including a concurrent 3(d) objection in the FER in such a scenario would also necessitate the applicant to explain why the biologic is a completely new entity, and not just a new form that falls within the scope of 3(d).

Data / evidence for Overcoming 3(d)/3(e)

- **Positively:** Some exceptions to patentability under Section 3(d) and 3(e) are conditional, in that the applicants can overcome these objections by submitting evidence for improvement in efficacy, or by demonstrating that a combination is more than a mere aggregation of properties.

A clear divide between the rejects and grants in terms of evidence submitted indicates that the patent office ensures that Section 3(d)/3(e) objections are overcome only when satisfactory evidence is presented.

- **Issues & recommendations:** There is greater clarity required on the admissibility of post-filing evidence for overcoming 3(d)/(e) objections. The examples we have discussed appear to run contrary to the guidance in the MoPP which suggests that such evidence must already be present at the time of filing of the application.

A consistent approach to raising objections for compositions and combinations is needed. Compositions and combinations form a major proportion of the applications across all categories, and attract objections under (i) 3(d), (ii) 3(e) or (iii) 3(d) and 3(e). This inconsistent approach could

applications for Biogen/Genentech's Rituxan. As the vast majority of these are likely secondary or follow-on patents seeking to extend the term of patent protection, the extent of secondary patenting is likely to be >70%. (Sources: 1. *Drug Pricing and Pharmaceutical Patenting Practices* February 11, 2020, <https://sgp.fas.org/crs/misc/R46221.pdf> 2. *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices*, <https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>

have other implications on evidence-based requirements since it is not clear whether the threshold to overcome objections under 3(d) and 3(e) are different. For example, 3(d) requires that an improvement in efficacy relates only to therapeutic efficacy, and not to other parameters (such as physicochemical properties, bioavailability, etc unless these are shown to impact on therapeutic efficacy). 3(e) requires evidence that the combination/composition is not a mere aggregation of properties, but there is no stipulation that this property must be related to therapeutic efficacy. Additionally, although the MoPP suggests that a demonstration of synergy can be used to overcome 3(e), this is not strictly required.⁴⁴ So, it is possible that some applications may face relaxed evidence-based requirements, depending on whether 3(d) or 3(e) is raised. The examination guidelines need to be updated to clearly indicate when each of these provisions is applicable for claims concerning compositions comprising previously known substances/combinations of previously known substances.

Closer scrutiny of submitted evidence is required for overcoming Section 3(d). In several instances, it appears that the evidence provided by applicants to overcome a Section 3(d) objection was questionable. Specifically, evidence submitted by applicants to show an improvement in efficacy made flawed comparisons to an alternative compound other than the one cited as the closest known compound from the prior art. Applicants were also able to circumvent the requirement to show an improved efficacy when the patent office failed to specify the compound alleged as previously known. To counter these practices, the patent office needs to re-evaluate its approach and establish clear guidelines specifying what evidence may be allowed, or what comparisons are deemed appropriate to show an improvement in efficacy. Additionally, it would also help if the patent office could substantiate an objection under Section 3(d) by clearly indicating in the exam report/hearing notice what the previously known substance is, so that applicants may respond with evidence that is pertinent to addressing the objection.

⁴⁴ As seen in the case of vaccines, where evidence of antigenic interference was acceptable to circumvent the synergy requirement.

Recommendations

1. The first step in addressing potential intellectual-property-related monopolies around biologics is to be able to identify what intellectual property exists, in the form of patents. Creating specific national classification codes for biologics - and their constituent technological parts - in India will allow for national patent examiners to be able to identify them. This exercise can be carried out retrospectively with the right classification codes in place. Publishing the results in India will have useful follow-on effects in terms of the ways other countries can then benefit from the work of the Indian Patent Office. Lastly, asking for a similar change in International Patent Classification codes at the World Intellectual Property Organisation will help drive a global identification exercise.
2. The second step in addressing intellectual-property-related monopolies on biologics is to create effective examination guidelines and/or regulations to govern their evaluation. The current system is unsustainable, because of the high degree of inconsistency in evaluating comparable patent applications. Currently, the Indian Patent Office currently operates with several policies, guidelines and regulations designed for specific categories of technology. This privilege should be extended to biologic pharmaceuticals. The aim of the guidelines/regulations formulated should be to ensure the clear, consistent, transparent and fair evaluation of biologic patent applications in the country. Furthermore, these guidelines/regulations should take advantage of the flexibility India has when implementing the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), as it has done with other categories of technology.
3. The third step required towards effectively addressing monopolies on biologics, especially in situations of crisis with the affordability or supply of a particular biologic, or in the case of a more general emergency, such as a pandemic, is the ability to withdraw monopoly protection, in order to open up manufacturing of them to a wider, competitive base at more affordable prices. Currently the Indian government - through Section 100 of the Indian Patents Act - has the ability to notify (in the official Indian Government Gazette) the "government use" of a set of identified patents, or the patent estate covering a specific biologic pharmaceutical, or a related technological platform, such as mRNA. While the theoretical existence of this ability in the law is useful, the Indian government needs to actively use it when needed. Since the introduction of the amended patent law in 2005, the Indian government has not used this provision even once, despite several crises which called for life-saving medicines to be made accessible. One of the reasons that the Indian government has not used Section 100 of its patent law more is that there are no checks and balances on government to compel them to consider it.
4. To address this issue, Section 100 could be amended, or supplemented with regulations, to establish a formal mechanism or process to monitor the impact of patents on access to medicines. The intellectual property landscape of biologics demands a mechanism by which civil society and industry can compel government to use Section 100 and invoke government

use of patents when urgent public health concerns require them to.

5. Section 84 of the Indian Patents Act currently allows for an “interested party” to file for a compulsory licence. There are two problems with the provisions herein. The first is that Section 84 requires the interested party to identify a specific set of patents to be compulsorily licensed, which, as our evidence shows in this report, is impossible when it comes to biologic pharmaceuticals, including vaccines. Section 84 therefore, needs to be amended, to allow for compulsory licensing cases on a product as a whole, or for specific platform technologies, without the requirement of having to identify all relevant patents, in the manner of Section 100 for government use. The second is that Section 84 operates with a restrictive definition of “interested party” which is limited to anyone with the ability to produce the technology. This effectively includes only the pharmaceutical industry (when it comes to pharmaceuticals). It excludes civil society groups, for instance, or patient groups advocating for treatment for a single disease. Section 84 needs to be amended to allow for a wider definition of “interested party” which includes any individual or organisation within the country that can demonstrate a clear connection to the patent/s in question.

2.

Monopolies on Biologics,
including Vaccines, due
to Trade Secrets and
Pharmaceutical Regulation

Chapter 2: Monopolies on Biologics, including Vaccines, due to Trade Secrets and Pharmaceutical Regulation

Summary

Compared to small molecules, vaccines and other biologics have a higher degree of entry barriers due to monopolies resulting from trade secrets and pharmaceutical regulation. These entry barriers lessen the number of competitors in the market and compromise the intensity of competition. As a result, biosimilars are fewer in number and in their ratio to originator biologics than is the case for small molecules, they take longer to come to market, and the price of biosimilars does not drop as much as it does when generic small molecules enter the market.

Generally, there are three types of entry barriers in biologics. These are: the high cost of setting up of manufacturing facilities, patent barriers, and regulatory barriers related to marketing approvals. Modular facilities have now substantially reduced the cost of manufacturing. Patent barriers have been dealt with in detail in the previous section of this report.

The third barrier, which is how trade secrets and regulatory barriers create monopolies is perhaps the least understood and the most intractable. In the case of small molecules, generic manufacturers do not have to repeat tests for safety and efficacy of the product, since these have been already established by the originator; they only need to show equivalence. Therefore, in jurisdictions where data exclusivity does not exist, that is, where the pharmaceutical regulatory agency is allowed to rely on originator data, a generic manufacturer only needs to show bio-availability and bio-equivalence, which are not time-consuming or expensive to carry out. By contrast, almost all countries require manufacturers of follow-on biologics to conduct clinical trials – either in full or part, such as comparative clinical trials, which are both time-consuming and expensive – in order to be approved.

This requirement of clinical trials is largely due to the regulatory assumption that the process is the product, and therefore that the non-originator has to follow the manufacturing process of the originator. When there are deviations from the manufacturing process of the originator, which is to say, in the case of any non-licensed biologic manufacture, the burden of proving safety and efficacy rests on the manufacturer and demands clinical studies. Biologic manufacturers have effectively used trade secrets as a tool to manage competition. Because of the perpetual time protection trade secrets offer, as against a limited 20-year patent term, they present an opportunity for biologics manufacturers to stonewall generic competition. Much of the technical and critical know-how that relates to the development of biologics is protected as a trade secret. This can include data originating from research, cell-lines, sequence IDs, vectors, constructs, media conditions, methods of isolation, storage conditions, manufacturing processes and clinical trial data, among others.

Biosimilars, which are non-licensed biologic products made by a manufacturer other than the originator, require animal studies as well as comparative clinical trials, that is, trials that use both the originator product and the biosimilar.

However, new developments have led to a reconsideration of the biosimilar approval process. In 2021, the Medicines and Healthcare products Regulatory Agency in the UK changed its guidelines for the approval of biosimilars in the country by dropping the need for comparative clinical trials. In 2022, the WHO similarly amended its own guidelines for the approval and regulation of biosimilars, by doing away with the compulsory need for comparative clinical trials.

In the case of vaccines, however, which are a distinct category of biologics, there is no regulatory pathway whatsoever for non-originators, or generic or follow-on manufacturers. While there are tremendous benefits to be gained from having a faster, cheaper process for biosimilar approval, the covid pandemic laid bare the need to have similar reform instituted in the process of “generic” vaccine approval.

Within vaccines, there is a further problem, which is an inability – so far – to take advantage of the most significant milestone of the pandemic, which is the approval of mRNA-based vaccine technology for use in humans. We now have vaccine technology that eliminates the cell-based biological component, and therefore means that a range of equivalence pathways potentially open up. Regardless, whether with traditional biological vaccines, or newer vaccine technologies such as vector-based or protein-based vaccines, or with the newest technology, mRNA vaccines, there are potential pathways to creating generic alternatives that need to be explored. This is a crucial step in fortifying ourselves against this pandemic, and those to come.

Introduction

Until recently, most of the big drug approvals were for small molecules, for example, Lipitor (Atorvastatin), Advair (Fluticasone/salmeterol), Aspirin (Acetylsalicylic acid), Zoloft (Sertraline) and Zocor (Simvastatin) among others. These small molecules had a simple structure and were relatively cheap to manufacture. The advent of genetic engineering opened avenues for biologic production and since then biologics have become an integral part of medical treatment. By the end of 2022, the number of biologic approvals narrowly outpaced that of small molecules, a landmark in biologics' steady rise since the end of the twentieth century.⁴⁵ Biologics are produced from living organisms and differ from small molecules due to their structure, size, complexity and development process and costs. Biologics include bio-therapeutics such as monoclonal antibodies, growth factors, vaccines, blood products and plasma.

Since biologics are produced through methods different from those employed for small molecules, the regulatory framework for the marketing approval of the non-originator versions of biotherapeutics (non-originator or generic version of biotherapeutics are referred to as biosimilars) is different from the generic approval of small molecules. In case of small molecules, the cost of generic manufacturing is low since the regulatory framework is efficiently streamlined and requires simple bioavailability and bioequivalence studies between the generics and the originator product. In most jurisdictions where there is no data exclusivity, the regulatory authority depends on the safety and efficacy data of the originator to approve the generic version of the small molecules. Further, the simplicity of bioequivalence studies ensures that the product is launched in a relatively short time. On the contrary, in the case of biologics, national regulatory bodies across all jurisdictions require clinical trials for approval of biosimilars in the absence of a licence from the originator. Biosimilars are inherently expensive to manufacture because of their structure and complexity which is further buttressed by the onerous regulatory requirements of costly clinical studies, a factor which is absent in the case of small molecule generics. These regulatory barriers coupled with the uncertain intellectual property milieu have virtually stifled the adoption of biosimilars across the globe and severely limited their access and affordability.

This chapter examines the regulatory barriers for the production of biosimilars and vaccines. The report argues that the entry barrier emanating from the regulatory framework is primarily due to trade secret protection.

The first part of this chapter examines the entry barriers related to biosimilars, providing a brief description of biosimilars and the existing Indian regulatory framework. It then discusses the latest developments related to biosimilar marketing approval guidelines. Finally, the report provides certain law and policy measures to complement the regulatory reform to lower the entry barriers for biosimilars.

The second part of the chapter looks at the marketing approval framework of vaccines in the context of non-originator/follow on vaccines. The chapter, as a whole, argues the need for reforming vaccine

⁴⁵ Senior M. Fresh from the biotech pipeline: fewer approvals, but biologics gain share. *Nat Biotechnol.* 2023 Feb;41(2):174-182. doi: 10.1038/s41587-022-01630-6. PMID: 36624153; PMCID: PMC9838261.

regulatory framework to minimise the rigour of trade secret protection and facilitate the approval of a regulatory pathway for non-originator /follow on vaccines.

Biosimilars

In the past two decades there have been major advancements in the development of therapeutic proteins, popularly known as biotherapeutics - both in the market as well as in the development pipeline. Biotherapeutics are an important class of medicines since they serve patients suffering not only from chronic diseases like cancer, but also for those in need of novel therapies, and around which new innovations are being driven such as autoimmune disorders and rare diseases. Chronic diseases present an immense burden on the economy both via direct costs in the form of medical expenditures and indirect costs in the form of unemployment or loss of productivity.⁴⁶ Apart from the disease burden, chronic diseases are also responsible for a major share of mortality burden in all places outside sub-Saharan Africa.⁴⁷ The global biologics market was valued at USD 382.85 billion in 2022⁴⁸ and is expected to reach a value of USD 749.62 billion by 2028, thus registering a CAGR of 10.80% during the forecast period.⁴⁹ Biotherapeutics accounted for 8 of the 10-top selling branded drugs in terms of revenues in 2020.⁵⁰ Biotherapeutics' targeted approach and substantial reduction of side effects, in areas such as oncology, have made them one of the most promising therapeutics. Biotherapeutics have therefore become the treatment of choice by physicians and patients and are generating significant revenues and enjoying larger market share and thus their importance in both clinical and economic terms continue to grow.⁵¹

In the case of biotherapeutics the expiry of patents has led to the production of a class of compounds which are similar to those in the original products. These have different terms, including "similar biotherapeutic product", "similar biological medicinal products", "biosimilar products", and "biosimilars". In the small molecule segment, patent expiries have historically resulted in very steep price erosion after the entry of generic versions. As soon as the patent and data exclusivity periods expire, generic versions of the drug are introduced in the market at a price which is less than even half of the originator's price. After the launch of a generic version of a small molecule compound, the price of an innovator reduces by 40% on average, while the price of a generic is more than 50% lower than the originator and, in some cases, may go down to even 70-90%. On the other hand, the price of a biosimilar is linked with its originator compound. Though an exact estimate may not be known, it is perceived that the biosimilars have been priced 10-30% lower as compared to the originator molecules.⁵² This can be attributed to the low generic competition in this segment purported by prohibitive costs, primarily due to high cost of research and development, and the rigid entry barriers relating to their manufacturing, intellectual property, and marketing approvals.

⁴⁶ World Health Organization, "Economic Burden of Disease," Health Economics, <https://www.who.int/choice/economicburden/en/>

⁴⁷ <https://www.who.int/management/programme/ncd/Chronic-disease-an-economic-perspective.pdf?ua=1>

⁴⁸ <https://www.globenewswire.com/news-release/2022/08/09/2494541/0/en/The-Global-Biologics-market-is-projected-to-grow-at-a-CAGR-of-8-82-By-2032-Visiongain-Reports-Ltd.html>

⁴⁹ <https://www.reportsanddata.com/report-detail/biologics-market>

⁵⁰ <https://www.fiercepharma.com/special-report/top-20-drugs-by-2020-sales>

⁵¹ Belloni, A., D. Morgan and V. Paris (2016), *Pharmaceutical Expenditure And Policies: Past Trends And Future Challenges*, OECD Health Working Papers, No. 87, OECD Publishing, Paris, <https://doi.org/10.1787/5jm0q1f4cdq7-en>.

⁵² Simoens, S., Jacobs, I., Popovian, R. et al, *Assessing the Value of Biosimilars: A Review of the Role of Budget Impact Analysis*, *PharmacoEconomics* 35, 1047–1062 (2017). <https://doi.org/10.1007/s40273-017-0529-x>

Entry Barriers

High Cost of Establishing Manufacturing Facilities

The development of a biosimilar requires substantial investment in setting up the manufacturing infrastructure, expertise and technology to create the product. With the entry of multiple players and new interchangeability requirements across various jurisdictions, optimising the cost of biosimilar manufacturing is critical for ensuring its success. The introduction of modular production facilities represents a paradigm shift in the manufacturing of biosimilars. These production facilities are extremely cost efficient and allow a greater return on investment for biosimilar manufacturers. It has been estimated that the cost saving from such facilities is approximately three to four times that of the standard fed-batch manufacturing facilities. Furthermore, the time taken to set up such modular facilities is approximately one third of the time required for the establishment of a traditional factory. These facilities offer the advantage of a smaller footprint due to the significant reduction of cleaning and sterilisation procedures, leading to a reduction in upfront costs as well as operational costs on an ongoing basis. The modular facilities are thus not only cost effective but also represent advantages in terms of reduced time-to-production, ensured global regulatory compliance, increased flexibility and environment sustainability. Setting up such modular facilities will provide an easier route for a large number of small biosimilar manufacturers to enter the market and help to bring affordable biosimilars to the market.⁵³

The Monopoly Systems around Biologics

Biologic manufacturing involves high investments and research, and hence manufacturers recover their costs through a multi-pronged approach to protect their inventions. They tend to create a balanced and virtually impregnable IP portfolio consisting of both patents and trade secrets. For biologic products the entire patent portfolios are either protected by primary patents or by secondary patents, that further extend the term of patent monopoly.⁵⁴ For example AbbVie, which markets one of the bestselling biologic drugs, Humira, has been able to keep the competition away successfully through its patent portfolio. A study revealed that AbbVie had filed 247 patent applications on various aspects of Humira, translating into 132 patents.⁵⁵ It has been alleged that almost 75 patents were filed a few years before the patent expiration when biosimilar competition was set to begin, thus extending the patent protection until the year 2034.⁵⁶ AbbVie is not the only such case. Almost all biologics manufacturers seem to have followed similar strategies and used the existing patent system to discourage competition and keep the prices high. What is of grave concern is that patents

⁵³<https://www.prnewswire.com/news-releases/worldwide-modular-manufacturing-facilities-in-pharmaceutical-and-biotechnology-industry-to-2035-increasing-preference-and-demand-for-personalized-therapies-drives-growth-301748289.html>

⁵⁴ Heled Yaniv, *The Case for Disclosure of Biologics Manufacturing Information*, *The Journal of Law, Medicine & Ethics*. 2019;47(4_suppl):54-78. doi:10.1177/1073110519898043

⁵⁵ *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting Is Extending Monopolies and Driving Up Drug Prices*, I-MAK 6-8 (Aug. 2018), <https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>

⁵⁶ *Failure to Launch: Patent Abuse Blocks Access to Biosimilars for America's Patients*, Biosimilars Council 8 (June 2019), <https://www.biosimilarscouncil.org/wp-content/uploads/2019/06/Biosimilars-Council-White-Paper-Failure-to-Launch-June-2019.pdf> [hereinafter *Failure to Launch*] (estimating that it would cost \$3 million per patent to challenge the patent thicket surrounding Humira).

which were supposed to be engines of growth in scientific advancement with a limited time monopoly of 20 years have now moved towards being engines of financial growth with a much-extended time period. The practice of filing secondary patents has essentially increased the protection period to almost double, thereby effectively thwarting competition and keeping cheaper biosimilars at bay.⁵⁷

If systemic gaming through the patent system was not sufficient, as outlined in the first part of this report, biologic manufacturers have effectively used trade secrets as another tool to manage competition. Because of its perpetual time protection (as against a limited time period of 20 years for patents), trade secrets present an opportunity for biologics manufacturers to virtually stonewall generic competition. Most of the technical and critical know-how is protected as trade secrets. The extent of information protected by trade secrets includes - data originating from research, cell-lines, sequence ID, vectors, constructs, media conditions, method of isolation, storage conditions, manufacturing processes and clinical trial data among others.⁵⁸ As a result, there is no way a biosimilar manufacturer can have access to any trade or technical know-how. Information in the form of cell lines and so on is crucial for reducing development costs and accelerating approval.

These protective measures are further augmented by the exclusive and extended protections available under market and data exclusivity periods. Data exclusivity prevents follow-on manufacturers from relying on the originators' test data submitted for marketing approval while seeking such approval for its own product. In the US, approved biologics are granted a 12-year period of exclusivity under the BPCIA.⁵⁹ This includes four years of data exclusivity for biologic drugs, while the remaining eight years are for market exclusivity. Based on the anti-trust law, these exclusivity periods seek to prevent investments of drug innovators from follow-on manufactures. Such long exclusivity periods keep the biologics off-limits for those who need them. The loss from such long exclusivity periods can be gauged not only in terms of the monetary viewpoint, but also from that of innovation. Data exclusivities impede innovation which relies on prior knowledge.⁶⁰ A major difference between the Indian and the US regulatory regimen is the lack of regulatory market exclusivity. Unlike the US and Europe, where biologics have an exclusivity period, in India biosimilar sales are only restricted by patent exclusivity. However, proposals under free trade agreements (FTAs) like the Trans Pacific Partnership Agreement (TPP), or the EU-India FTA, or the UK-India FTA - where pharmaceutical companies have been lobbying for extended data exclusivity periods - are indicative of the wave of arguments for longer protection times to data exclusivities.

These barriers to biologic drugs due to either patent grants, trade secrets and market exclusivity, and/or data exclusivity, far exceed their monopoly periods.⁶¹ Cumulatively, these factors have practically stalled the launch of generic versions of even the patent expired bestselling biologics into the markets. These factors have lowered the return on investment associated with biosimilar medicines, disincentivizing companies from investing in the development of future biosimilars. All these factors interact with each other and must be evaluated in conjunction. Though technological

⁵⁷ Overpatented n (11)

⁵⁸ <https://www.lexology.com/library/detail.aspx?g=09ecc65e-8daf-43d2-b131-48db583fb57d>

⁵⁹ See 42 U.S.C. §262, *Biologics Price Competition and Innovation Act of 2009*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf>.

⁶⁰ https://www.ip-watch.org/2015/07/27/decision-time-on-biologics-exclusivity-eight-years-is-no-compromise/#_ftn21

⁶¹ Dzintars Gotham, *Cell line access to revolutionise the biosimilars market*, F1000Research 2018, 7:537, <https://doi.org/10.12688/f1000research.14808.1>

development can overcome the barriers posed by trade secrets, the regulatory framework disincentives such efforts. As a result, current regulatory requirements for the marketing approval of biosimilars functions as an entry barrier and limits competition.

Regulatory Barriers

Biologic drugs are large, complex molecules whose exact composition and manufacturing process is protected as a trade secret. According to WHO, the demonstration of bioequivalence of the generic medicine to a reference product is usually appropriate and sufficient proof that therapeutic equivalence between the two exists.⁶² However, the approach established for generic medicines is not suitable for the development, evaluation and licensing of a biosimilar. This is because biotherapeutics are complex proteins and more complicated to manufacture than small molecules and in most cases cannot be reproduced exactly. One of the biggest challenges for biosimilar manufacturers is to have comparable protein quality attributes to the originator molecule. Biologics are produced from living organisms, hence unless the biosimilar manufacturer utilises the same 'cell-lines' - which play a vital role in determining the final comparability of the product and have a similar manufacturing process - they are unlikely to obtain a similar compound. The regulatory approval for biosimilars therefore requires a totality of evidence comparable with the originator product also known as the reference biologic product (RBP).

A biosimilar manufacturer will normally not have access to confidential details of the originator's manufacturing process; thus, the process will differ from that of the originator. Unlike small molecules, because of their inherent nature, protein-based molecules cannot exhibit a 100% structural similarity. It is worth noting that this applies equally to both originator and biosimilar molecules. In order to achieve a high-quality product which is as similar as possible to the originator's, the biosimilar manufacturer will have to undertake a highly cost-intensive reverse-engineering process. Thus, they will need to assemble all available knowledge of the RBP, that is, the type of host cell, the cell-lines, the formulation, multitude of processes and container closure system used for marketing the RBP among others. Most national regulatory guidelines prescribe a stepwise development of biosimilars starting with a comparative characterisation of the molecule to prove the structural similarity with the originator molecule, which is then followed by pre-clinical and clinical studies including a full-fledged Phase 3 Comparative Clinical Trials (CCTs) – a highly costly and time-consuming requirement. The challenges of cost-intensity of the process coupled with the regulatory barriers have virtually eliminated the competition and created a quasi-monopoly for the originator even in the absence of patent protection.⁶³ These onerous regulatory requirements make the production of biologics time and research intensive and therefore exorbitantly expensive, and not many patients have therefore been able to access this class of drugs. Consequently, challenges in affordability remain even after the expiry of patents.

One of the most important documents that was believed to be a harbinger for the introduction of biosimilars in the markets was the WHO's 2009 SBP Guidelines.⁶⁴ This document provided scientific

⁶² https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf

⁶³ Diependaele L, Cockbain J, Sterckx S, *Similar or the Same? Why Biosimilars are not the Solution*, The Journal of Law, Medicine & Ethics. 2018;46(3):776-790. doi:10.1177/1073110518804241

⁶⁴ https://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

principles, including the stepwise approach which should be applied for demonstration of similarity between the biosimilars and its RBP. Based on the growing scientific and technological advancement, in April 2022, the Expert Committee on Biologic Standardization (ECBS) came forward with a revised Biosimilar Guidelines replacing the earlier 2009 SBP Guidelines.⁶⁵ The most important change in the revised guidelines was the waiver of the mandatory comparative efficacy trial for the marketing approval of biosimilars. Unlike small-molecule generic which simply need to demonstrate a bioequivalence to the brand/originator drug, a biosimilar must prove that it is “highly similar” to the originator product (also called as a reference product) that is, there should be “no clinically meaningful differences” between the biosimilar and the originator product. For satisfying this condition, the biosimilar manufacturer is required to conduct additional comparative efficacy trials. These trials expend a lot of time and financial resources from a manufacturer’s perspective, thus preventing the biosimilar manufacturers from launching their drugs at an affordable price. The waiver of comparative efficacy trials is expected to considerably lower the cost of biosimilar manufacturing which may lead to a steep decline in the biosimilar market price. Additionally, the WHO guidelines have also adopted a limited, exception-based approach towards animal studies focusing on “minimising the use of animals in testing”. A few months prior to the revised WHO guidelines, the UK Medicines and Health Products Regulatory Agency (UK MHRA) also released new guidelines on the licensing of biosimilar products, where it stated that “ although each biosimilar development needs to be evaluated on a case by case basis, it is considered that, in most cases, a comparative efficacy trial may not be necessary if sound scientific rationale supports this approach”.⁶⁶ The UK guidelines also clearly waived off animal studies stating that “no in vivo studies from animals are requested as these are not relevant for showing comparability between a biosimilar candidate and its RPA.” A similar framework on animal studies is also reflected in other jurisdictions including the Health Canadian (Canadian Regulatory body) which states that in vivo toxicology studies (animal studies) are generally not needed.⁶⁷ In a major development US President Joe Biden has signed the [FDA Modernization Act 2.0](#), which allows the country’s Food and Drug Administration to do away with animal testing for the purposes of drug and biological product applications.⁶⁸

The removal of comparative efficacy trials and animal studies reflects a global shift in the approach of the scientific bodies and would significantly alter the market dynamics in the biotherapeutic space. The WHO guidelines have been virtually adopted by many developing countries to formulate their own regulatory pathways for biosimilars. In compliance with the previous WHO guidelines, many developing countries, including India, have made it mandatory to conduct clinical trials for obtaining the relevant marketing approval for biosimilars. With a shift in the stance of WHO and other regulatory bodies like the UK MHRA, US FDA and Canada, it is time for national regulatory bodies to revisit their guidelines to increase the affordability and accessibility of biosimilars.

⁶⁵ <https://www.who.int/publications/m/item/guidelines-on-evaluation-of-biosimilars>

⁶⁶ Guidance on the licensing of biosimilar products; UK MHRA, Published May 06, 2021 available at <https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products>

⁶⁷ https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf

⁶⁸ https://www.einnews.com/pr_news/608779826/no-more-animal-testing-president-biden-signs-the-bill-meeting-professor-niazi-s-recommendations

Biosimilar Regulation in India

In India, the regulatory framework for biosimilars - Guidelines on Similar Biologics - was published in 2012 and later revised in 2016.⁶⁹ These guidelines describe the requirements that a biosimilar applicant needs to demonstrate with respect to quality, safety and efficacy. A biosimilar manufacturer in India is required to carry out an elaborate analytical, non-clinical and clinical studies comparing, head-to-head, the biosimilar with the RBP. The demonstration of 'biosimilarity' must be based on a complete analytical characterisation, comparability assessment and clinical pharmacology studies to compare the PK and PD parameters between the biosimilar and the RBP, and clinical trials to confirm that there are no clinically meaningful differences between the two. The development of robust and comprehensive initial comparability studies will help in demonstrating similarity of the biosimilar with that of the RBP. This is then followed by a CCT to establish the clinical safety and efficacy of the product. Generally, a reduction in data requirements is possible for preclinical and /or clinical components of the development programme by demonstrating the comparability of products and the consistency in the production process (which may vary depending on the characteristics of the RBP). The guidelines are highly subjective and further state that the confirmatory clinical safety and efficacy study can be waived if all the conditions mentioned below are met:

1. Structural and functional comparability of a similar biologic and a reference biologic can be characterised to a high degree of confidence by physico-chemicals and in-vitro techniques
2. The similar biologic is comparable to a reference biologic in all pre-clinical evaluations conducted
3. The PK / PD study has demonstrated comparability and has preferably been done in an in-patient setting with safety (including immunogenicity for adequate period justified by the applicant) and efficacy measurements
4. A comprehensive post-marketing risk management plan has been presented that will gather additional safety data with a specific emphasis on gathering immunogenicity data
5. The confirmatory clinical safety and efficacy study cannot be waived if there is no reliable and validated PD marker.

Apart from CCT, Indian Guidelines also require animal studies during the various stages of biosimilar development, especially pre-clinical studies. The Indian Guidelines partly mirror the previous WHO, U.S. and European guidelines with their emphasis on detailed structural and functional characterisation of the proposed biosimilar in comparison to the RBP. Without defining exactly what constitutes necessary proof for a PK/PD study to demonstrate comparability, it is hard to say whether many biosimilars will qualify for approval without full-fledged safety and efficacy trials.

Given all the IP and the regulatory framework currently encompassing the biosimilar area, it can be clearly supposed that the current ecosystem for biosimilar development is highly non-competitive.⁷⁰ The prices of biosimilars likely will remain high, thus stalling their availability for use in public health. Certain changes need to be incorporated to make biologics truly affordable and accessible for the

⁶⁹ http://dbtindia.gov.in/sites/default/files/uploadfiles/Guidelines_on_Similar_Biologics%2C2016.pdf

⁷⁰ Heled n (10)

Indian market. This report makes a specific case for changes that would require the regulatory authorities to share information in the form of cell-lines, originator dossier information with prospective, qualified manufactures and a case for removing Phase 3 CCTs.

Overcoming Trade Secret Barriers through Regulatory Reform

Evaluating the progress of scientific knowledge, technical advancement, accumulation of experience in the field and fast-expanding national regulatory needs and capacities, there have been vociferous demands for modulating the current regulatory and patent frameworks and to use the flexibilities ingrained within the legislative frameworks to make it more equitable and responsive to social concerns - especially for developing countries to access affordable medicines. Looking at the importance of biologics in the current treatment regimens, if the current needs in the investments are reduced, it will open avenues for substantial reduction in price and consequently increase their affordability. Sharing of cell lines with prospective manufacturers, establishment of set PK/PD markers and removing the requirement of Phase 3 CCTs would be a step towards addressing these challenges in the development process. Regulatory authorities play a central role in creating and sustaining patient access to biologic medicines. The core function of a regulatory body is to evaluate and approve safe and effective medicines. They should put a framework in place which effectively weeds out extraneous, unnecessary, and potentially unethical demands that severely limit their availability and impacts their sustainability. Regulators should respond to advances in the scientific development of biologics and streamline the regulatory requirements to foster a sustainable growth environment. Some of the important steps could include:

- Removal of Phase 3 clinical trials
- Sharing of cell lines
- Sharing the dossier information with prospective and qualified manufacturers.

Removal of Phase 3 Clinical Trials

Scientists across the globe had questioned the rationale behind the comparative clinical trials (CCT) for the approval of biosimilars.⁷¹ There is overwhelming data demanding the removal of Phase 3 CCTs for biosimilar manufacturing. According to them, using the latest analytical techniques, the characterisation exercise can establish a very close similarity with the originator's molecule. The advancement in analytical techniques have progressed to a state where biosimilar manufacturers should be able to prove similarity in the same way that original biologic manufacturer proves "comparability" in analysing the variability in their own process changes post-approval.⁷² It has been observed that if two biologics are analytically alike, they would be functionally alike. The advancement in sensitivity and specificity of the analytical techniques has enabled the biosimilar developer to

⁷¹ <https://www.healthpolicy-watch.org/revise-biosimilar-guidelines-scientists-demand-who-says-not-now/>

⁷² McCamish M, Woollett G, *Worldwide experience with biosimilar development*. MAbs. 2011 Mar-Apr;3(2):209-17 in Price II and Rai, supra not 24

capture the molecular structure of the originator drug very accurately, and this structural similarity of the biosimilar is thus reflected in its therapeutic efficacy.⁷³

Based on these advancements in analytical and functional testing over the years, - the ECBS had considered a request to review the WHO 2009 Guidelines on biosimilars at the 73rd meeting of the WHO Expert Committee on Biological Standardization (ECBS) held in December 2020. This request was in keeping with the spirit of the Resolution WHA 67.21, which was adopted by the 67th meeting of the World Health Assembly in 2014. The review was completed and the ECBS had adopted the WHO Similar Biologics Products (SBPs) guidelines for updating and revision. After a span of eight years since the consultation process began, the WHO revised guidelines presented considerations to the “amount and type of clinical data required”. The revised guidelines state that *“A comparative efficacy trial may not be necessary if sufficient evidence of bio-similarity can be inferred from other parts of the comparability exercise.”*⁷⁴ As mentioned previously, the new UK guidelines have also waived of comparative clinical efficacy trials.⁷⁵ Both these documents mark a very progressive milestone in the evolution of evidence-based requirements for biosimilar approval by waiving off the need for a comparative clinical efficacy trial and instead centring the biosimilar approval on a set of comprehensive comparability exercises.

However, the WHO guidelines have proposed some additional conditions to carry out the comparability exercise, which provide the justification for the CCT waiver. One of the most important requirements to initiate the comparability exercise is the characterisation of the molecule. According to the WHO, *“Characterization and evaluation of the quality attributes of the RBP should be the first step to guide the development of the SBP”*. Thus, the initiation of the establishment of the bio-similarity starts from the selection of RBP. The guidelines define a Reference Biotherapeutic Product as *“a biological product used as the comparator in a direct head- to-head comparability exercise with a biosimilar in order to demonstrate similarity in terms of quality, safety and efficacy. Only an originator product licensed on the basis of a full registration dossier and marketed for a suitable period of time with proven quality, safety and efficacy can serve as an RP.”* Thus, one of the conditions for the selection of RBP is the presence in the market for a *“a suitable period of time with a proven quality, safety and efficacy”*. This suitable period of time provides a *de facto* monopoly to the originator product even in the absence of patent protection because no biosimilars can be developed without the presence of an RBP until a suitable period of time has lapsed since its presence in the market. The term “suitable period of time” has not been defined in the guidelines. For instance, a biosimilar version of the monoclonal antibody combination for COVID-19 approved last year cannot be developed citing the fact that the originator product has not completed a suitable period of time in the market. In effect, a biosimilar for a newly introduced biotherapeutic is impossible.

WHO is the main influential agency, and its guidelines form the basis of implementation of biosimilar regulatory guidelines for many developing countries. The revised guidelines have waived the requirement of conducting phase comparative efficacy trials for biosimilar approvals and made animal studies a rarity. Against these guidelines, national and regional regulatory authorities should

⁷³ Webster, Christopher J et al, *An Efficient Development Paradigm for Biosimilars.* BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy vol. 33,6 (2019): 603-611. doi:10.1007/s40259-019-00371-4

⁷⁴ <https://www.who.int/publications/m/item/guidelines-on-evaluation-of-biosimilars>

⁷⁵ <https://www.gov.uk/government/consultations/mhra-draft-guidance-on-the-licensing-of-biosimilar-products/consultation-document-mhra-guidance-on-the-licensing-of-biosimilar-products>

consider immediate implementation of the revised guidelines to approve safe and efficacious biosimilars. As mentioned above, the US and UK have formally removed animal studies as a requirement for the biosimilar marketing approval regulation. With WHO easing the regulatory barriers for the approvals of the biosimilars, the Indian regulatory body should also revisit the regulatory requirements for biosimilar medicines in line with scientific advances and accumulated regulatory and clinical experience, such that it can facilitate biosimilar approval and lay the foundation for a competitive biosimilar market with a focus on accessibility to patients.

Furthermore, Indian guidelines clearly state that the clinical trials cannot be waived off in the absence of a reliable PD marker. Identification of such biomarkers is a lengthy and resource-intensive process. The situation is made worse by lack of global regulatory consensus on the detailed requirements for appropriate biomarkers. Given the scientific and technological advancements and the long standing regulatory and clinical experience with biologic medicines, including biosimilars, the presence of suitable biomarkers should no longer be treated as the pivotal factor in waiving comparative clinical efficacy studies.⁷⁶ The current Indian regulatory guidelines are based on a considerable degree of precautionary assumptions that do not hold true after years of experience in the biosimilar area. Such assumptions hold little value in 2023, in light of substantive and verifiable scientific evidence that is available to refute the assumption. Requirements for comparative efficacy studies should be replaced by requirements for detailed analytical studies and physicochemical and functional characterization and pivotal PK studies as set forth in the UK MHRA and WHO Guidelines. The demonstration of similarity in quality with a sound PK or PD study (in case PD biomarkers are available) is sufficient to assure the safety and efficacy. India has been very steadfast in leading the world in the approval of biosimilars. Without access to crucial manufacturing information, biosimilars will continue to lack the competitive edge necessary to bring down market prices.

Sharing Cell Lines

As discussed previously, biologics are particularly complex molecules which are extremely difficult to manufacture. Given the complexity of the manufacturing process, it would be difficult even for an originator to replicate their own product. Hence the replication of a product for a manufacturer with a considerable 'knowledge gap'⁷⁷ would be an extremely challenging task. The seminal point for all biosimilar manufacturers is the use of a cell line. Different cell lines have inherent differences which may lead to varied structural alterations, which may further alter the nature of the final product. If a biosimilar manufacturer has to develop a new cell line efficient for producing a biologic product with the same desired functional region, it is highly unlikely that the copy will be equivalent to the original biologic. Therefore, one of the most effective ways of addressing the issue is to ensure that the manufacturing process resembles the RBP closely. This can be achieved by sharing the original cell line associated with the RBP. To achieve this, the originator's cell lines can be submitted to the regulatory authority which can then be subsequently shared with the qualified biosimilar manufacturers, before the expiry of the patent on the product.⁷⁸ More specifically it has also been

⁷⁶<https://www.igbamedicines.org/doc/IGBA%20Biosimilars%20Clinical%20Trial%20Tailoring%20policy%20paper%20Sept2020%20revision02.pdf>

⁷⁷ Declerck P, Farouk-Rezk M, Rudd PM, *Biosimilarity Versus Manufacturing Change: Two Distinct Concept*, Pharm Res. 2016 Feb;33(2):261-8. doi: 10.1007/s11095-015-1790-3. Epub 2015 Sep 17. PMID: 26381277.

⁷⁸ See Gotham n (17); Heled n (10)

recommended that the originator deposits the cell line at the time of regulatory approval, so that the biosimilar manufacturers may be able to access it a few years in advance.⁷⁹ A higher level of similarity in the cell line levels will result in greater similarity between the two products and will ultimately lead to reduction in the amount of clinical assessment of the biosimilar product. Sharing of cell lines will not in any way diminish the value of other aspects of the manufacturing process, as the biosimilar manufacturer will still have to reverse engineer the entire manufacturing process, including certain critical attributes, up to the final formulation for commercial use. It will only buttress the confidence of the regulatory assessment and increase certainty levels that will help in reducing further clinical assessment studies. This could prove to be a competitive edge and incentive for the manufacturer, by reducing a part of the developmental cost and shortening the time period of bringing a biosimilar product to market.⁸⁰ The constituting principle in generic manufacturing should be followed in case of biosimilar manufacture, that is, after the expiry of the exclusivity period. The biosimilar manufacturer can have access to all the necessary information for the purpose of producing a biosimilar product.

Sample deposition is not a new concept in the Indian legal system. It is well known in Indian patent law that depositing the biological samples is mandatory for enabling the completion of specifications for completing an application according to the Indian Patent Act. Further, a deposit could be required so that the invention can be practised by any person - which is available from International Depositary Authority (IDA) - instead of duplicating the effort. The deposition satisfies the issues of enablement and sufficiency of disclosure as prescribed under Sections 10(4) (a) and (b) in addition to representing the best method of performing the invention.⁸¹ The intent in case of patent law has also been to make it available to third parties for the purpose of practising the invention. The same premise holds good for regulatory law. A question that begets consideration is that if the cell line has already been deposited at the patent level, then what is the need for duplicating the process at the regulatory level? Firstly, it has been pointed out that the patent office may lack the expertise to effectively monitor the disclosure and determine whether the appropriate cell line has been deposited. Secondly, the patent disclosures are generally filed at a very nascent stage, much before the clinical trials may have actually taken place. Consequently, while the originator may have deposited a sample of a cell line capable of producing the desired functionality, it may not be the cell line that is subsequently used when the product is marketed, and hence may not be appropriate for the purpose of reducing variations or proving similarity (which is the ultimate aim of producing a competitive biosimilar).⁸² Thus, while it is the very job of the regulatory authorities to ensure that a safe and effective product is allowed, ensuring rigour at this stage will only enable higher levels of certainty. Therefore, the regulatory agencies should insist on mandatory deposit of cell lines of RBP as part of the marketing approval. Such a deposit can also scale up the production of particular biotherapeutics to meet public health needs, especially in emergency situations like pandemics.

⁷⁹ Diependaele L n (19)

⁸⁰ *ibid*

⁸¹ <https://ipindia.gov.in/writereaddata/Portal/ev/sections/ps10.html>

⁸² W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 Iowa Law Review 1023-1063 (2016)

Sharing Regulatory Information

The regulatory authorities can proactively share the information in the dossiers to minimise duplication of efforts and lower the resources necessary to manufacture biologics. Sharing information will ensure that the comparability of the biosimilars in terms of safety, efficacy and purity closely resemble that of the originator, which in turn will contribute to patient safety by helping to eliminate the predicament of unnecessary clinical testing on humans. It will also be a highly efficient way of introducing competitive biosimilars in the market, while maintaining the virtuosity of the regulatory framework. However, obligations under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement stand in the way. Article 39.3 of the Agreement prohibits disclosure of data related to pharmaceutical products without taking measures against unfair commercial use. Though there is an exception to this rule to “protect the public”, there is no shared understanding of the scope of this exception. There is also lack of clarity with regard to the term “unfair commercial use,” which can be interpreted to include non-originator products. These legal obstacles under Article 39.3 can be fixed by waiving the obligation under TRIPS. Furthermore, there is legal uncertainty regarding the scope of Article 39.3 to biologics because it covers only new chemical entities. Generally, the term ‘new chemical entities’ refers to small molecules produced through chemical synthesis. The fact that there is a separate provision for data exclusivity for biologics included in US Free Trade Agreements like the TPP, strengthens the argument that Article 39.3 does not cover biologics. Most importantly, unlike patents there is no public interest exception to disclose trade secrets. Most of the IP laws provide limitations and exceptions to rights and privileges of IP owners. Trade secret law therefore lacks this clear-cut articulation of the limitations and exceptions of IP laws.⁸³ In common law systems, courts often decide on a case-to-case basis, that is, with no legal predictability. Therefore, it becomes pivotal to build public health safeguards as part of the implementation of Article 39.3. The Doha Declaration on the TRIPS Agreement and Public Health states: “The Agreement can and should be interpreted and implemented in a manner supportive of WTO members’ right to protect public health and, in particular, to promote access to medicines for all.” This means that there is flexibility to introduce public health safeguards or provide exceptions to the obligations to protect the tests and other data against unfair commercial use. Developing country WTO member states should introduce exceptions to the obligations to protect tests and other data in public interest. The disclosure of regulatory information can be considered under the following circumstances:

- In case biotherapeutics in question are not available at an affordable price
- In cases where the production or supply of biotherapeutics in question is not sufficient to meet the public need
- To expedite the production under a compulsory or government use licence
- In case of public health emergency, epidemics or public non-commercial use.

Looking at the strain these diseases have caused on public health systems, it becomes imperative for regulators across the globe to partner with biosimilar manufacturers and develop alternate pathways or share information available with them.

⁸³ <https://ir.lawnet.fordham.edu/cgi/viewcontent.cgi?article=5061&context=flr>

Non-Originator Vaccines

Vaccines are the cornerstone for the management of infectious disease outbreaks and are the surest means to defuse a pandemic and epidemic risk.⁸⁴ Over the years, vaccines have provided a highly cost-effective means of improvement in public health. Scientific breakthroughs and technological advancement in vaccine development have transformed the health of the developing world as much as they have been instrumental in eliminating the burden of life-threatening infectious diseases among children in developed countries.⁸⁵ It is well-known that to deter vaccine competition, the original manufacturers resort to pre-emptive measures to disincentive follow-on manufacturers by keeping manufacturing cost high and thus reducing profitability. One such tool with vaccine manufacturers is the dyad of intellectual property protection - which consists of numerous filed patents protecting the invention - along with trade secrets protecting the production process). Although intellectual property barriers may not be the only limiting factor for scaling and diversification of vaccines, they are definitely a big contributor to the existing inefficiencies and skewed access of vaccines. Patents increase uncertainty and costs by delaying the entry of competitors in the market which is the formidable driving force in improving accessibility. The patent portfolio thickets created by vaccine manufacturers act as a deterrent to advance vaccine development, production and supply.

Unlike small molecules, vaccines are large and complex biological products and are made from biological materials rich in immunogenicity, such as proteins. Because of the proteinaceous nature of vaccines, variations in the process may result in post-translational modifications, which may adversely impact the immunogenicity of the vaccine. Hence, the approach of vaccine regulation is that an identical product may not be possible if an alternate manufacturing process is used.⁸⁶ Trade secret protection for vaccines protects the manufacturers production process and know-how including critical information like cell lines, biological and sequence database, and manufacturing process. The protection also extends to clinical trial data till perpetuity, as trade secrets do not have a finite expiry period. This perpetual monopoly prevents the replication of production processes, thus precluding duplicity in vaccines. Proponents undermining the impediments of intellectual property on vaccine manufacturing have implied the existence of other flexibilities in the TRIPS Agreement at both national and international levels to facilitate access where intellectual property is a barrier. However, it is useful to note that while these ingrained flexibilities like compulsory licences and allowing for parallel imports are sufficient to deter patent monopolies, they are insufficient to circumvent perpetual intellectual property barriers like trade secrets. Compulsory licensing of patents does not provide the licensee with access to manufacturing know-how; thus, it is unlikely to be generally effective for vaccines, unless the know-how is readily available. Incongruously, these barriers are deeply intertwined with scalability and therefore warrant that the inability to scale up vaccine production remains.

⁸⁴ Excler, J.L., Saville, M., Berkley, S. et al, *Vaccine development for emerging infectious diseases*, Nat Med 27, 591–600 (2021). <https://doi.org/10.1038/s41591-021-01301-0>

⁸⁵ <https://www.cgdev.org/sites/default/files/archive/doc/books/vaccine/MakingMarkets-complete.pdf>

⁸⁶ Crager SE, *Improving Global Access to New Vaccines: Intellectual Property, Technology Transfer, and Regulatory Pathways*, Am J Public Health 2018;108(Suppl 6):S414-S420. doi:10.2105/AJPH.2014.302236r

As outlined above, since the product is the process and therefore cannot be fully and precisely characterised in the same manner and to the same extent as small-molecule drugs, vaccine manufacturing is technically complex. Making a vaccine involves numerous steps, recreating and reverse engineering, and the process cannot be done without access to the manufacturing information. Non-originator/Follow-on vaccine manufacturers can accelerate the development only if they have sufficient knowledge of the manufacturing process as followed by the originator. Since the developers of follow-on vaccines do not have access to the original manufacturing information, they have to attempt to recreate the entire manufacturing process and also establish complete clinical comparability by testing it on animals and, ultimately, human subjects. Unlike generic medicines, where only bioequivalence (BE) and bioavailability (BA) studies need to be carried out, vaccine manufacturers need to establish a complete safety and efficacy profile before obtaining the marketing approval from the regulatory agency. Safety, efficacy and quality are the umbrella parameters for the exercise. The standard vaccine regulatory guideline mandates testing a new vaccine first on cells and then in animals, to see if it produces an immune response resulting in the production of antibodies. In Phase 1 trials, the vaccine is given to a small number of healthy volunteers to test safety and dosage as well as to confirm that it stimulates the immune system. In Phase 2, the trial is expanded to hundreds of volunteers which further test the vaccine's safety and ability to stimulate the immune system, while in Phase 3 trials, thousands of volunteers receive the vaccine. In addition to these, clinical trial oversight, marketing authorisation, vigilance, laboratory access, licensing of premises, market surveillance and control, and regulatory inspections also form a part of the approval process. Since the follow-on manufacturer has to repeat the complete process of the originator's manufacturing and clinical studies including efficacy trials, there is no concept of a generic vaccine. All these necessary steps thus make the process extremely complicated, uncertain and highly resource intensive. Consequently, developing a follow-on vaccine not only takes a number of years but also entails significant risks because of the scientific and clinical uncertainties and a risky legal and regulatory framework.

Though patents play a seminal role in vaccine development, removing only the patent barriers will not help in defusing the problem. Under the current regulatory framework, without information on the technical know-how or access to manufacturing information, it is very difficult and sometimes even impossible to establish a follow-on vaccine similar to the original vaccine within a short time frame. While India has a robust capacity to manufacture vaccines, many of the challenges confronting widespread vaccine availability stem from the inability to scale up and build local production capacity and ensure an adequate supply. Many of the barriers in scaling up flow from the lack of technical know-how. Therefore, the primary focus should be to carry out regulatory reform to fasten the production of non-originator vaccines by removing the impediment of trade secrets - often referred to as technical know-how - and trying to find alternatives to duplicating the safety and efficacy trials, especially Phase 3 trials. Regulatory reform in this direction will have substantial benefits, in terms of swift and rapid scaling up of manufacturing processes. At the World Trade Organization (WTO), the South African delegation reminded participants that "developing countries have advanced scientific and technical capacities...and that the shortage of production and supply [of vaccines] is caused by the rights holders themselves who enter into restrictive agreements that serve their own narrow monopolistic purposes putting profits before life."⁸⁷ To address the barrier emanating from trade

⁸⁷ <https://www.thenation.com/article/world/coronavirus-vaccine-justice/>

secrets it is important to take legal measures to create exceptions along with reforming vaccine regulation to create a regulatory pathway for the non-originator /follow on vaccines.

Streamlining Regulatory Requirements

For launching a generic drug in the market, all generic manufacturers follow the abbreviated approval pathways established by the regulatory agency. Over the last decade, recognising the increasing importance of biologics, many countries have come up with abbreviated regulatory frameworks for biologics. The EU was the first to establish a framework⁸⁸ followed by the US through the Biologics Price Innovation Competition Act.⁸⁹ The WHO has also established a set of guidelines for 'Similar Biologic Products', parts of which are currently under revision.⁹⁰ As opposed to biosimilars, the debate on establishing an abbreviated pathway for vaccines is still in its nascent stages. This primarily stems from the fundamental differences between vaccines and biotherapeutics, which requires specific regulatory considerations. While for biotherapeutics, active substances are usually proteins which can be well-defined, in most vaccines, the composition of active substances cannot be well-defined in terms of molecular composition which imposes difficulties in demonstrating the new preparations as similar to the original products.⁹¹ Another major safety concern in case of vaccines and biosimilars is the immunogenic response. While immunogenicity is an undesirable property in case of biosimilars, it is highly desirable in case of vaccines. Vaccines, unlike biotherapeutics, are administered to healthy individuals and therefore the stringency of safety requirements is tantamount. Hence the trade-off between relieving symptoms and adverse effects cannot be applied for vaccines.⁹²

A key issue is the amount of clinical trial data needed. Currently, the biosimilar approval pathway requires comparative Phase 3 clinical trials, but reforms are underway for making the clinical trials an exception and allowing the biosimilar manufacturers to prove similarity in the same way that original biologic manufacturer proves "comparability" in analysing the variability in their own process changes post-approval. According to the WHO guidelines, efficacy trials are required for vaccines under the following circumstances:

1. There is no established ICP (Immunological Correlate of Protection) that could be used to predict the efficacy of the new candidate vaccine.
2. There is no existing licensed vaccine with documented efficacy against a specific infectious disease to allow for bridging to a new candidate vaccine.
3. The use of immune responses to bridge the documented efficacy of a licensed vaccine to a new candidate vaccine is not considered to be possible. For example, because there is no known relationship between specific immune response parameters and efficacy or because the new candidate vaccine does not elicit immune responses to the same antigen(s) as the licensed vaccine.

⁸⁸ The EU guidelines for biosimilars. Available at: <http://www.gabionline.net/Guidelines/EU-guidelines-for-biosimilars>. Accessed May 10, 2014.

⁸⁹ <https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances>

⁹⁰ https://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

⁹¹ Corbel MJ, Cortes Castillo Mde L. *Vaccines and biosimilarity: a solution or a problem?* Expert Rev Vaccines. 2009 Oct;8(10):1439-49. doi: 10.1586/erv.09.97. PMID: 19803764.

⁹² *Ibid*

4. There are sound scientific reasons to expect that the efficacy of a vaccine cannot be assumed to be similar between the population(s) included in the prior efficacy trial(s) and one or more other populations.
5. It cannot be assumed that the vaccine efficacy demonstrated against disease due to specific strains of a pathogen (for example, serotypes or subtypes) would apply to other strains.⁹³

According to the WHO guidelines, efficacy trials are not required only in the following situation: *"Vaccine efficacy trials are not necessary if it is established that clinical immunological data can be used to predict protection against disease. For example, if there is an established ICP against a specific disease (for example, antitoxin levels against diphtheria and tetanus toxins, or antibody against hepatitis B surface antigen) the candidate vaccine should be shown to elicit satisfactory responses based on the relevant correlate(s)".*⁹⁴ Similar to the WHO guidelines, the EMA Draft Guideline on Clinical Evaluation of New Vaccines says that a new vaccine can be authorised without an efficacy trial in two circumstances:

- (i) where there is a well-established immune correlate of protection (ICP); or
- (ii) where 'immuno-bridging' takes place.⁹⁵

An Immunological Correlate of Protection (ICP) has emerged as the key to developing a vaccine among follow-on vaccine developers. ICP is a biological indicator that indirectly measures the vaccine's effectiveness against infectious disease. Through ICP, researchers can evaluate the efficacy of a new vaccine compared to another vaccine with proven effectiveness. Being able to rely on an ICP would simplify and accelerate vaccine development by allowing developers, instead of proving efficacy through lengthy Phase 3 efficacy trials, to demonstrate that their product achieves an accepted immune response in patients from which efficacy can be inferred. ICP studies not only help in bringing down the number of persons enrolled in Phase 3 trials, but they also help in reducing the cost of the compound. With abbreviated pathways in place for biosimilars, the Indian regulatory authority should also look at alternatives to efficacy trials like ICP for vaccines. Another important way of regulatory reform is to develop regulatory pathways to approve vaccines through limited clinical trials. This can be carried out by approving vaccines by extending the concept of biosimilars to vaccines. The "acceptance of the principle and its application to follow-on products may greatly facilitate the licensing process and lead to a range of cheaper biological medicines".⁹⁶

A hold-up in the use of ICPs for shortening the timeframe for developing follow-on vaccines is that they can only be determined from vaccine efficacy trials with long-term follow-up of post-marketing studies. ICP must first be established and accepted which may take considerable time and may not be feasible. Furthermore, only a limited number of infectious diseases have a widely accepted ICP. According to the WHO guidelines certain diseases like influenza, polio and Hepatitis B have well established ICPs. Consequently, regulatory authorities may not permit the waiver of efficacy trials even after the satisfaction of the above-posed conditions. This means that the follow-on vaccine

⁹³ https://www.who.int/biologicals/publications/clinical_guidelines_ecbs_2001.pdf

⁹⁴ https://cdn.who.int/media/docs/default-source/prequal/vaccines/who-trs-1004-web-annex-9.pdf?sfvrsn=9c8f4704_2&download=true

⁹⁵ Section 51. EMA Draft Guideline on Clinical Evaluation of New Vaccines (April 2018)

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-evaluation-vaccines-revision-1_en.pdf

⁹⁶ Corbel n (47)

developer must repeat most of the clinical studies of the originator including efficacy trials on many occasions. Thus, from the regulatory perspective there is no generic vaccine.⁹⁷ The introduction of a follow-on vaccine is thus an exercise that involves resources and time.⁹⁸ A follow-on vaccine developer can obtain waivers from the repetition of safety and efficacy studies if it could follow the same manufacturing process or technology of the originator. The only way for a follow-on vaccine developer to obtain the required information from the originator, for obtaining a waiver from the regulatory requirements, is via a technology transfer agreement. Technology transfer and know-how dissemination have been recognised as critical gaps in allowing rapid penetration of vaccines. Innovative technology transfer mechanisms should be employed to increase accessibility. Technology transfer agreements can help in addressing both short and long-term needs. In the short term it will help in addressing any existential crises, while in the long term it will equip the country in building infrastructure and technical know-how for vaccine production.⁹⁹ Sometimes, such transfer agreements can bring with them onerous requirements in terms of resources and cost. Governments should therefore develop creative approaches to encourage, consolidate, and institutionalise technology transfer. By evaluating economies of scale, governments can attach access conditions to their resources, demanding, for example, that companies charge affordable prices for their products and ensure that production be sufficient for equitable distribution.¹⁰⁰

Another way of expanding vaccine penetration in the market is by utilising the mound of regulatory information that the originators submit while applying for a regulatory approval. The manufacturing information is an integral part of the information supplied to the regulatory authorities; however, the regulatory bodies are also precluded from sharing such information with the follow-on manufacturers. For instance, WHO's Emergency Use Listing (EUL) states: *"As WHO is responsible for the EUL assessment process, the ownership of the reports arising from or relating to the EUL assessment process lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any commercially sensitive confidential information of the manufacturer. Confidential information in this context means:*

- *confidential intellectual property, know-how, and trade secrets (including, e.g., formulas, processes or information contained or embodied in a product, unpublished aspects of trademarks, patents, etc.); and*
- *commercial confidences (e.g., structures and development plans of a company)."*¹⁰¹

The information includes a description of characterisation, method of the manufacturer, specifications of drug substance and so on. The description of the method of manufacture includes a detailed description of the animal sources (including fertilised avian eggs), virus sources, cellular sources, purification and downstream, and synthetic drug substances. Thus, the dossier can provide critical information to replicate the product without the cooperation of the originator.¹⁰² However,

⁹⁷ Nguyen Aurelia, Schwalbe Nina, *Apples and oranges? Can second generation vaccines become as low cost as generic medicines?*, Vaccine, Volume 37, Issue 22, 2019

⁹⁸ Weinberg SH, Butchart AT, Davis MM, *Size of clinical trials and Introductory prices of prophylactic vaccine series*, Hum Vaccin Immunother. 2012;8(8):1066-1070. doi:10.4161/hv.20506

⁹⁹ <https://medicinespatentpool.org/news-publications-post/who-covid-19-tech-transfer-hub/>

¹⁰⁰ Ken Shadlen, *To Speed New COVID Vaccines, Look to Patenting*, available at <https://issues.org/covid-vaccines-development-distribution-patenting-shadlen/>

¹⁰¹ https://extranet.who.int/pqweb/sites/default/files/documents/EUL-FINAL-13_12_2020.pdf

¹⁰² *Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product*, available at <https://www.fda.gov/media/73614/download>

regulatory authorities keep the dossier as a trade secret and often lack the mechanism to disclose such information during a public health crisis such as the COVID-19 pandemic. Hence, access to dossiers of preferred products could be improved by standardising and streamlining the regulatory pathways for registering and approving vaccines. The regulatory authority should emphasise the submission of robust vaccine dossiers. The critical know-how included as a part of such dossiers should be made available to follow-on manufacturers in the following circumstances:

1. In case of public health emergencies
2. In case of issuance of a compulsory or government use licences
3. In case of non-affordability of vaccines owing to high price
4. In case of an unmet need.

There have been ideas to determine the relevance of bio similarity to vaccines.¹⁰³ Because of the nature of the mRNA vaccines, efforts to apply the bio-similarity concept to these recombinant vaccines has gained considerable traction. Though the COVID-19 pandemic saw the abbreviated regulatory approval of several vaccines, the regulatory guidelines are still in the nascent stage. In the guidance¹⁰⁴ issued by the FDA on the development of drugs and biological products for the treatment or prevention of COVID-19, it is stated that: "COVID-19 vaccine development may be accelerated based on knowledge gained from similar products manufactured with the same well-characterised platform technology, to the extent legally and scientifically permissible. Similarly, with appropriate justification, some aspects of manufacture and control may be based on the vaccine platform, and in some instances, reduce the need for product-specific data." This statement on accelerating the development based on similar products lucidly points to the application of the concept of bio similarity to vaccines. However, there is a need for clear regulatory guidelines defining the contours of application of bio similarity to vaccines which will help in enabling the development of biosimilar vaccines.

Inter alia it should also be noted that the current vaccine regulations were developed in the context of biologics and hence like biologics, any deviations from the manufacturing process of the originator are assumed to have implications on the safety and efficacy of vaccines. This assumption forms the basis of the vaccine regulatory framework. This assumption is now unseated by the arrival of the mRNA vaccine, which, due to the absence of cell-based biological components, can be considered as a chemical vaccine,¹⁰⁵ and hence bypasses any risk calculations associated with biologics. From a regulatory perspective, the non-originator production of mRNA vaccine may not require the same level of regulatory safeguards. With the right framework, going forward, non-originator mRNA vaccines may perhaps be approved with less onerous regulatory requirements. If effort is made to develop it, this manner of a distinct, abbreviated regulatory framework for mRNA vaccines can facilitate more competition in the market without compromising on safety and efficacy.

¹⁰³ Corbel MJ, Cortes Castillo Mde L, *Vaccines and biosimilarity: a solution or a problem?*, Expert Rev Vaccines. 2009 Oct;8(10):1439-49. doi: 10.1586/erv.09.97. PMID: 19803764. Available at <https://pubmed.ncbi.nlm.nih.gov/19803764/> last accessed Jun 17, 2023

¹⁰⁴ COVID-19: Developing drugs and biological products for the treatment or prevention of COVID-19 Guidance for Industry, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Feb 2021, available at <https://www.fda.gov/media/137926/download>

¹⁰⁵ Prabhala, A., Alsalhani, A. Developing countries can make the mRNA vaccines they need. *Nat Hum Behav* 6, 167 (2022). <https://doi.org/10.1038/s41562-022-01304-y>, available at: <https://www.nature.com/articles/s41562-022-01304-y>

Recommendations

To mitigate the monopoly impact of trade secrets and regulation barriers on biologics, we recommend the following:

- 1) Urgently revamp the regulatory guidelines on the approval of biosimilars in India, to promote access and competition in non-vaccine biologics. Indian procedures for biosimilar approval need to be brought in line with the UK procedures of 2021, and the WHO recommendations of 2022. In doing so, we would obviate the compulsory need for both animal studies as well as comparative efficacy trials, thus substantially reducing the cost of and time-delay in the entry of biosimilars in the market. These regulatory reforms would, further, utilise pharmaco-kinetic and pharmaco-dynamic studies (PK & PD studies in human beings) in lieu of the current, cumbersome regulatory procedures in place and substantially promote public health by facilitating a wider range of competitively produced biosimilars in India.
- 2) A significant regulatory barrier is the unavailability of cell lines to begin biosimilar development. However, India would be well within its authority to demand that all manufacturers of biologics, including vaccines, who seek regulatory approval in the country, deposit their cell lines, and other related material such as vectors, as a pre-condition for regulatory and marketing approval. While substantial work might still need to be done on original cell lines, the deposit of them would fast-track the development and production of biosimilars, especially as may be required under situations of concern around access or affordability, such as a local or international health emergency.
- 3) Another regulatory barrier in biologics is the unavailability of clinical trial test data and information related to the development and manufacturing of the product. This data is submitted to the Indian drug regulator during the marketing approval process but kept confidential. However, India is not bound to keep such data confidential, especially during situations of concern. In this case, we recommend implementing the flexibilities under Article 39.3 of the TRIPs agreement to enable the sharing of this information with prospective and qualified manufacturers to facilitate production to safeguard public health.
- 4) In the case of one important category of biologics - vaccines, India needs to consider remedies to allow the entry of non-originator/follow-on/generic/similar vaccines. There is currently no pathway to having a generic vaccine, and this is a problem that needs rectification, without compromising safety and efficacy.

There are several steps that need to be taken in this regard.

First, as the world's largest producer of vaccines, India could initiate expert consultations at the national and international level to examine the possibility of developing a regulatory pathway for non-originator production of vaccines, based on the advancement in vaccine science and technology.

Second, the consultations could take advantage of specific instances of vaccine technology that are already known to offer potential regulatory pathways that do not require a manufacturer going through the entire clinical trial process again – and thus adding in substantial time and expense to the process. These specific instances include:

- The possibility of an accelerated/generic pathway for all traditional (biological) vaccines using fully attenuated or partially attenuated pathogens; this regulatory process has been largely left unexamined for a long time.
- The possibility of extending the biosimilar regulatory pathway to all vaccine technologies for which characterisation is possible; these vaccine technologies would include vector-based vaccines, and protein-based vaccines.
- The possibility of taking advantage of the non-biological nature of mRNA vaccines and therapeutics and exploring the possibility of developing pathways that resemble generic small-molecule pathways more closely, for example, through chemical structure comparisons, and other simpler, bounded tests, which do not require extensive and repetitive clinical studies.

Monopolies on Biologics, including Vaccines:

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AND PHARMACEUTICAL REGULATION

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