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The Biotech Report
Biosimilars and Follow-on Biologics (FOBs)

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Report Outline

I. Introduction

On March 23, 2010, the new Biologics Price Competition and Innovation Act (BPCI Act) of 2009 was signed into law creating a statutory corridor for FDA approval of follow-on biologics (FOBs) as “biosimilar” to or “interchangeable” with “biologics” products.

Currently, biologics represent about one third of the total therapeutics in development, with the number expected to rise significantly. Some of the branded biologics ‘cost to treat’ is as high as $100,000 per year per patient.

Prior to the BPCI Act, innovators of biologics were concerned (basing their judgment on parallels with the small molecule approval process), that generic versions of their products may be able to secure abbreviated regulatory approval as the “bio-generic” will only be required to be “similar” or “highly similar”. Also, due to the nature of biologics it would have been easy to design around and avoid infringing their patent[1]. The innovators of biologics were convinced that a greater exclusivity for their products, much longer than small molecule drugs which get a 5- year ‘New Chemical Entity’ data-exclusivity post launch, was needed.

Other arguments that supported greater exclusivity for biologics were higher costs to develop these compared to the small molecules[1]. The cost of capital and production costs associated with uncertainties in manufacturing and failures at late-stage were all higher[1]. Similarly, average clinical development times for biologics have been found to exceed development times for small molecule drugs[1]. Until the BPCI Act was signed into law, a generic pathway and legislative structure existed for NDA products but not for biologics commercialized under a Biologics License Application (BLA).

Current Healthcare Reform Law defines a biosimilar as being approved under an “abbreviated application”. Based on this, the FDA’s primary challenge will be to ensure an adequate demonstration of safety and potency, while maintaining an abbreviated application.

II. The Hatch-Waxman Act Revisited

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the 'Hatch-Waxman Act' serves as the cornerstone for competition between branded and generic pharmaceutical companies. Hatch-Waxman deployed the abbreviated new drug application (ANDA) that requires generic manufacturers to demonstrate that their product is "bioequivalent" to the branded drug.

The Hatch-Waxman law was drafted with the goal of striking a balance between two important principles of free market society, "Innovation" and "Competition".

Innovation[2]:

- Defines the conditions for patent extensions beyond the then 17 years (currently 20 years).
  - 100% approval time + 50% testing time
  - Up to max extension of 5 years
  - Patent cannot be extended beyond 14 years following approval of the product
- Exclusivity[2]
  - NDA data kept proprietary by the FDA
  - 5 Years' data exclusivity for New Chemical Entity (NCE) that runs concurrently with the patent term (if not expired already).
  - 3 Years' data exclusivity for improvements to the approved brand products via clinical trials

Competition[2]:

- ANDA Process - Only "bioequivalence" required
- Allows testing before the brand patent expires
- 180-day exclusivity for first successful ANDA filer
- Paragraph IV certification reduces the 5-year NCE data exclusivity to 4-years

Thus, beyond the normal 20 year patent term, there are multiple pathways for preventing generics to step-in. A few other mechanisms include[3]:

1) Seven-year Orphan Drug Exclusivity: Those intended to treat rare diseases or conditions with less than 200,000 patients.
2) Six-month Pediatric Exclusivity: Pediatric exclusivity for an additional six months is acquired after submitting study requirements to the FDA upon its request (or innovator's own initiative).
3) Paragraph IV certification contests: Innovator drug applicants must identify in their NDA any patent(s) that covers the drug, which are then listed in the FDA's Orange Book. ANDA applicants must submit a certification for each patent listed in the Orange Book for their drug. These certifications correspond to one of the four statutory paragraphs:

I. The drug has not been patented
II. The patent has expired
III. The date on which the patent will expire, and that the generic will not go on the market until that date passes
IV. The patent is not infringed or is invalid

Paragraph IV certification mandates that the innovator be notified that the orange book patent has been challenged. The patent owner has 45-days to decide whether to sue the ANDA applicant for infringement, otherwise the FDA will approve the ANDA.

If the patent owner (innovator) files suit, the FDA will stay approval of the ANDA for 30 months from the date of the notice. This 30-month stay (or market exclusivity for the innovator) remains in effect till a court reaches a decision or otherwise alters the stay period[3].

4) Citizen Petition: A Citizen Petition is a request made to the FDA regarding a specific aspect of a pending application, such as, questioning the quality of a competitor's product and resulting in a "hold" on the ANDA until decided[3].

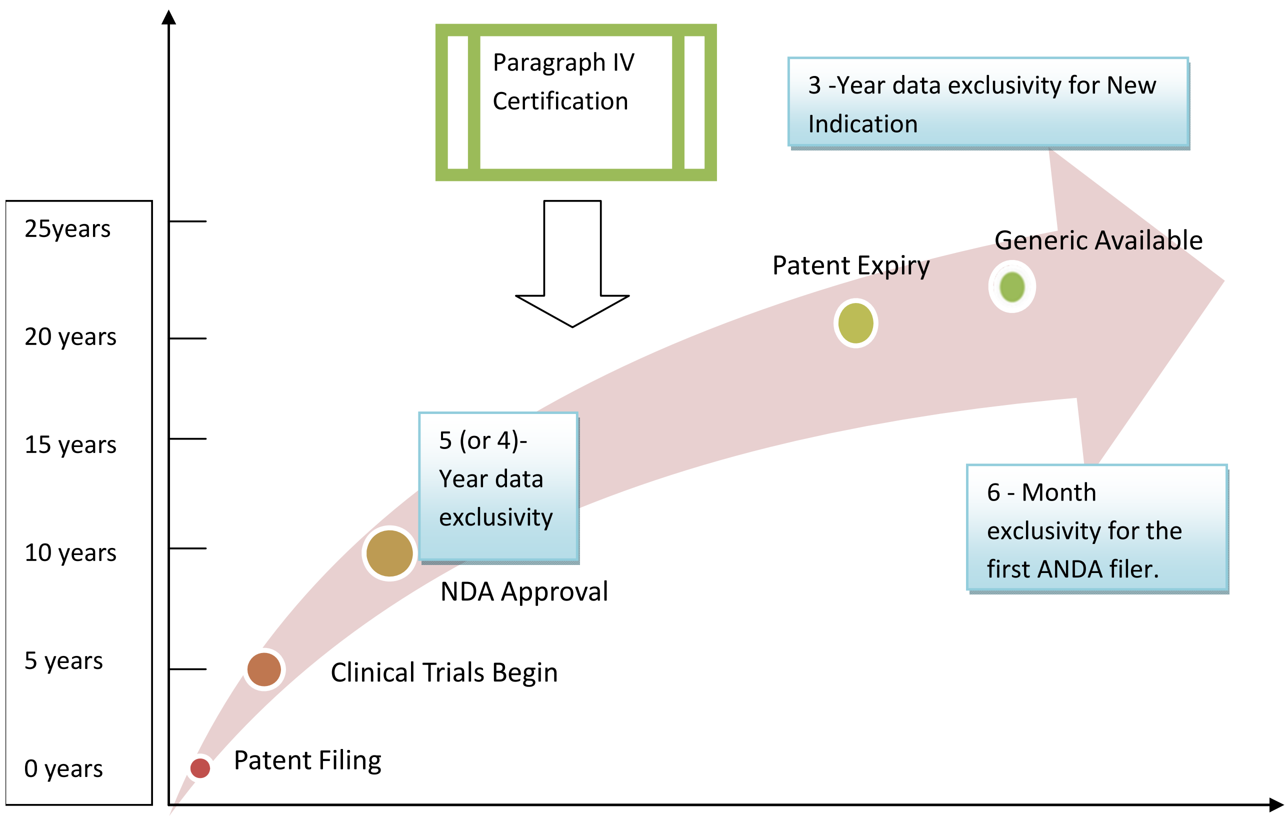

Figure 1. Typical Small Molecule Drug Development Process and Timing of Generic Entry

III. The Biologics Market

A biologic is defined as any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings[4].

It is vital to note that insulin, glucagon and human growth hormone, are grandfathered into the same category as small molecule drugs and are regulated as drugs under the Federal Food, Drug and Cosmetic (FDC) Act and not biological products under the Public Health Services (PHS) Act[4].

Biologics are macromolecular in nature, and usually have a molecular weight greater than 500kd. Being very large molecules, determining their physiochemical characteristics, such as tertiary structure, location, and extent and type of glycosylation, is far more complex and these molecules tend to be less well defined[4].

Compared to synthetic drugs, biologics tend to be rather labile, and are usually very heat and shear sensitive[4].

Main Categories of Biologics[5]

Recombinant proteins (world market of over $47bn in 2009): this segment includes various product categories, from EPO (anaemia), to G-CSF (neutropenia), to insulins, growth hormones, coagulation factors, alpha interferons (anti-viral therapies) and beta interferons (MS therapies). These products are now well characterized and offer a relatively simple molecular structure[5].

Monoclonal antibodies ($35bn market in 2009): These products mainly indicated to treat cancer and autoimmune diseases (RA, MS), are much more complex in their molecular structure, are much bigger than an EPO and are more difficult to reproduce. Because they are more recent, they still boast extensive patent protection[5].

Vaccines ($21bn market): These are biological products par excellence, manufactured from genetic material (eggs, cell lines) with limited stability and subject to contamination risk. They tend to be complex and expensive to produce, giving generics manufacturers extra technological and industrial hurdles to overcome[5].

Enzymes ($2bn market in 2009). This is a very specific category but also includes proteins, which are authorized under the BLA procedure. It therefore comes under the definition of biologics[5].

Source:	EvaluatePharma®						
Report:	Top 10 US Biotech Drugs Based on 2009 US Sales[6]						
Rank	Technology	Product	Generic Name	Company	2009 (Millions)	First Introduction	Patent Expiry
1	Recombinant product	Enbrel	etanercept	Amgen	$ 3,283	11/3/1998	2012
2	Monoclonal antibody	Remicade	infliximab	J & J	$ 3,088	8/24/1998	2018
3	Monoclonal antibody	Avastin	bevacizumab	Roche	$ 3,061	2/26/2004	2019
4	Monoclonal antibody	Rituxan	rituximab	Roche	$ 2,784	11/27/1997	2018
5	Recombinant product	Lantus	insulin glargine	Sanofi-Aventis	$ 2,661	6/30/2000	2015
6	Recombinant product	Epogen	epoetin alfa	Amgen	$ 2,569	6/30/1989	Expired
7	Recombinant product	Neulasta	pegfilgrastim	Amgen	$ 2,527	4/15/2002	2015
8	Monoclonal antibody	Humira	adalimumab	Abbott	$ 2,519	1/6/2003	2016
9	Monoclonal antibody	Herceptin	trastuzumab	Roche	$ 1,446	10/1/1998	2019
10	Recombinant product	Avonex	interferon beta-1a	Biogen Idec	$ 1,406	5/16/1996	2026

IV. What are follow-on biologics (FOBs)?

Follow-on biologics (also referred as biosimilars) are generic equivalents of biologics. The term "bio-generics" is avoided completely due to the significant differences in the relationship between small molecule entities and their generics.

To be approved as a generic, a small molecule drug must have the same active ingredient, strength, dosage form, and route of administration as the reference drug, and it must also be "bioequivalent." Generic drugs have an active ingredient that is same structurally to their innovator counterpart and that they act the same way in the body. The bioequivalence of the generic drug is demonstrated through relatively simple analyses such as blood level testing, without the need for cumbersome and fiscally intensive human clinical trials. In approving a generic drug under 505(j) of the FDCA, FDA determines that the generic is "therapeutically equivalent" to the innovator drug, and is interchangeable with it[7].

On the other hand, process controls for biologics are established separately for each unique manufacturing process/product, and are not applicable to a manufacturing process/product created by another manufacturer. These processes are generally closely guarded by the original manufacturer. Therefore, it would be difficult or impossible for a second manufacturer to make the "same" biologic without intimate knowledge of and experience with the innovator's process[7].

Many biologics are protected by process patents only, owing to the limitations of patenting natural products. Patents on biologics are often narrow enough for a FOB to gain regulatory approval without infringing on the innovator's patent[1].

Equally, the living systems used to produce biologics can be sensitive to very minor changes in the manufacturing process. Small process differences can significantly affect the nature of the finished biologic and, most importantly, the way it functions in the body[7]. To ensure that a manufacturing process remains consistent, biologics manufacturers must tightly control the source and nature of starting materials, and consistently employ stringent QC protocols that assure predictable manufacturing outcomes[7].

Additionally, when a follow-on manufacturer establishes a new manufacturing process, beginning with new starting materials, it will produce a product that is different from and not therapeutically equivalent with that of the innovator. Complexity of biologics renders the only way to establish with certainty whether there are differences that affect the safety and effectiveness of the follow-on product is to conduct clinical trials[7]. However, a clinical trial is both cost and time intensive process plus riddled with uncertainties.

It is argued that the protein structure (in biologics for example) cannot be solved by a single method and needs multiple, orthogonal analytical techniques. Showing bio-similarity with the innovator's macromolecule is complicated by the diversity of protein structure, including higher-order folding and associations plus post-translational modifications[8] (PTMs).

Acylation/deacylation, amidation, methylation, phosphorylation, sulfation, oxidation, and PEGylation are some of the PTMs that occur after a protein's translation from RNA and play a crucial role in protein function. The best-known PTM is glycosylation, the addition of sugar residues to amino acids bearing amino or hydroxyl groups. Sugar moieties can be short (a few hundred Daltons), or longer and more branched (up to several thousand Daltons). FOB manufacturers are aware that, although sugars are omnipresent in biological systems, they are not easy to analyze or reproduce[8].

FOB manufacturers will need to reproduce the glycosylation of the innovator's product to show interchangeability with, as glycosylation has a large influence on a protein's functional characteristics[9]. Furthermore, design of the production process and conditions during fermentation can alter the outcome, posing a major challenge to manufacturers of FOBs[9].

The Immunogenicity Problem[10]

The primary safety concern for biosimilar agents is their potential immunogenicity. The use of biologics to replace endogenous proteins, which may be present at insufficient concentrations, carries the serious risk of stimulating the immune system to develop anti-product antibodies that may attack the endogenous protein. Although these proteins are designed to closely match human proteins, they have the potential to induce an immune response, especially when administered as multiple doses over prolonged periods. The level of immunogenicity can be markedly different for products considered to be very similar. There is dearth of a single technique that can definitively predict the immunogenicity of a particular protein[10].

There may be no clinical consequence for developing an immune response to a biologic. The patient may develop binding antibodies that do not significantly affect the activity of the biologic or endogenous protein. On the other hand, anti-product antibodies can bind to, and attenuate the activity of, a biologic, and general effects include allergy, anaphylaxis or 'serum sickness'. Major clinical impact can occur if the endogenous protein with essential biological activity is also neutralized[10].

An event cannot be ruled out where a biosimilar causes the immune system to induce antibodies even though the original biologic was non-immunogenic.

V. The BPCI Act of 2009[11]

According to the BPCI Act of 2009, the FOB applications are sub-divided into two classes: A) Biosimilars and B) Interchangeables

A biosimilar product is highly similar to the reference product (with differences only in inactive ingredients) and there are no differences in terms of safety, purity and potency with the original (reference product).

An Interchangeable product is a biosimilar that can also be substituted with the original without intervention from the prescriber. Interchangeables are given one year market exclusivity, where only another interchangeable is not approved (but a biosimilar can be approved).

Under the BPCI Act, a sponsor may seek approval of a "biosimilar" product under new section 351(k) of the PHS Act. A biological product may be demonstrated to be "biosimilar" if data show that the product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency[11].

In order to meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider[11].

New Biologics License Application (BLA) approvals now have a market exclusivity of 12 years and a data exclusivity of 4 years, even in the absence of a valid patent. BLA sponsors agree that 12 years of exclusivity are essential because it was easier to design around patents for biologic drugs than around those for small-molecule drugs and also the costs for developing a biologic are significantly higher than a small-molecule drug.

Manufacturers of FOBs will now probably prefer to file a new BLA than subject to the 12-year delay as any higher cost would be offset by the greater profit opportunity available to early market entrants.

Patent Infringement Resolution[12]

Unlike Hatch-Waxman, the BPCI Act does not require a central repository of patent and exclusivity information like FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for small molecule drugs. Similar to Hatch-Waxman, however, the BPCI Act does contemplate an initial exchange of information between innovator and FOB product companies prior to potential patent litigation. The BPCI Act has a complex procedure, starting with the FDA's acceptance of a BPCI applicant's application for review[12].

- A FOB applicant must send notice of its application to the sponsor of the approved reference product within 20 days of FDA's notification that the application has been accepted for review[12].
- Within 60 days of receiving the applicant's notice and application, the reference product sponsor must provide a list of all patents for which a claim of patent infringement could be brought by the sponsor[12].
- Within 60 days of receiving the sponsor's patent list, the FOB applicant may respond with its own list of patents, but it must provide a detailed statement (similar to a "notice letter" in the generic pharmaceutical context) explaining why, on a claim-by-claim basis, each listed patent is invalid, unenforceable, or not infringed by the proposed biosimilar. The FOB applicant can also respond by submitting a statement that it does not intend to begin commercial marketing of the biosimilar before the date of patent expiry[12].
- Following receipt of the FOB applicant's statement, the reference product sponsor has another 60 days to provide its own detailed statement regarding the infringement of the

proposed biosimilar, as well as a response to the applicant's allegations of validity and unenforceability[12].

- If the parties agree about the patents-in-suit, then the reference product sponsor has 30 days after the agreement to bring the infringement action[12].

The reference product sponsor and the FOB applicant needs to work closely to seek out any licensing agreements and other amicable negotiations before adopting a more belligerent recourse.

A word on Biosimilars in Europe[5]

Europe has applied one key principle: to consider the biosimilars as new products. They are treated as new products and have to undergo comparative clinical trials to prove that there is no clinically significant difference between the copy and the original, in terms of efficacy and side effects. Established as non-substitutable, they are launched under different brand names from the original product. Guidelines have been laid down for all the major product categories, and biosimilar competition has begun to grow[5].

The EMEA guidelines make a distinction between biosimilars that are a protein, an immunological product (vaccines or allergens) or a blood-derived product (coagulation factors, antithrombin, immunoglobulin, etc.). For the blood-derived products, Abbreviated New Drug Applications which only include similarity trials will not be accepted. The biosimilars will have to have a 'new product' application, with all the upstream studies that that encompasses, whether they are pre-clinical (pharmacokinetic, pharmacodynamic, efficacy, safety), clinical (pharmacology/toxicology) or involve the safety of the production process[5].

VI. Conclusion

The passage of BPCI Act of 2009 has given the manufacturers of biologics new framework to support their innovations. On the other hand it has also tried to imitate the Hatch-Waxman Act vis-à-vis the generics, for the FOB applicants and addressed its loopholes to prevent gaming of the system. With regards to patent disputes, it encourages co-operation and dialogue between the innovator and FOB applicant to work together for six-months prior to filing suit.

Overall, the law's ultimate goal is to encourage innovation, maintain competition and make breakthrough therapies available to patients at affordable prices, all at the same time. The 12 year exclusivity given to BLA approvals will enable these companies to recuperate their investment and make profits. Equally, a FOB manufacture can look to filing an abbreviated BLA and carry the needed clinical trials (like in Europe) only to demonstrate interchangeability but without repeating or duplicating trials needed for a fresh BLA.

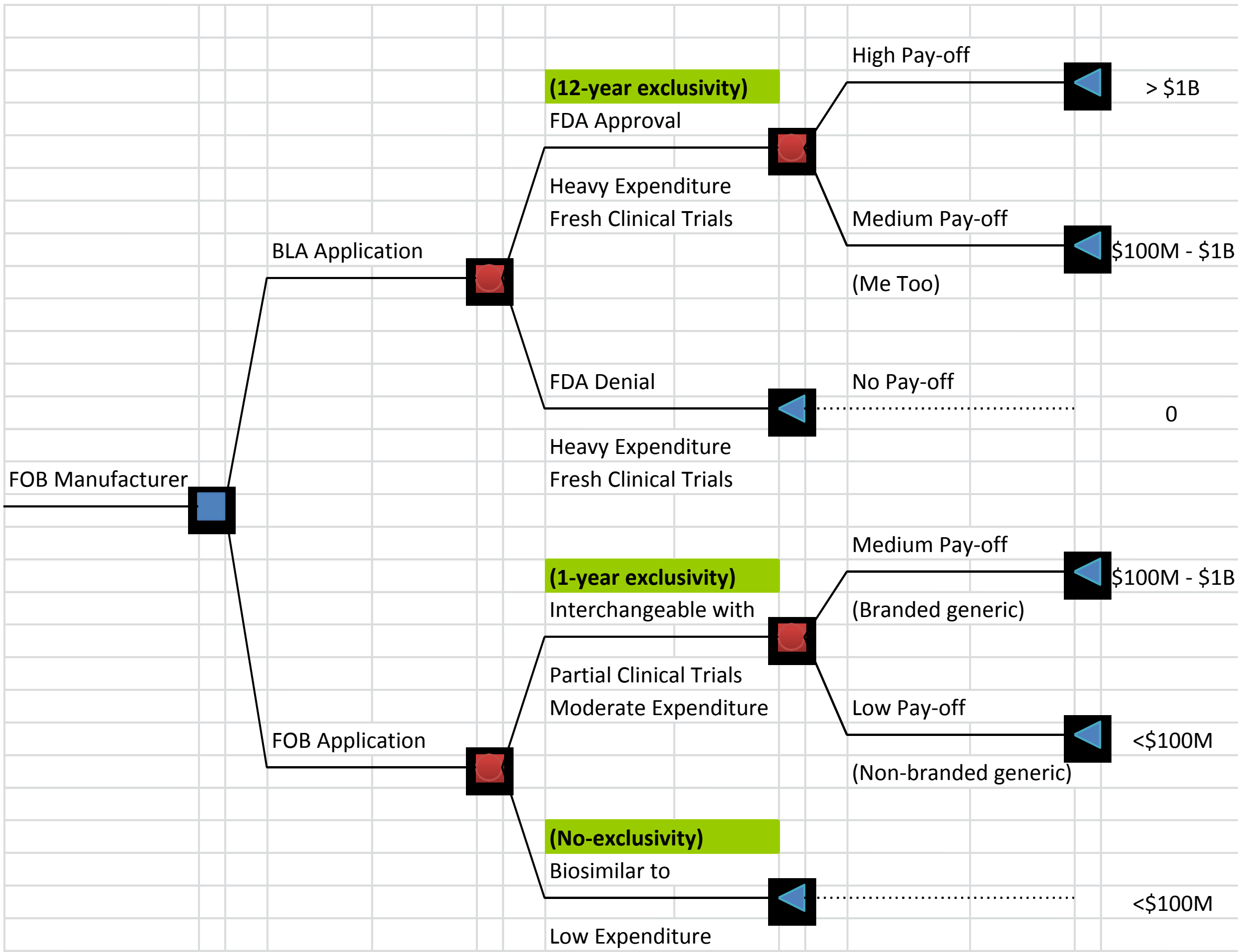

Chart 2. A Rough Decision Tree for a FOB Manufacturer.

For a FOB manufacturer, with the passage of BPCI Act, two options unfold:

<u>File a BLA application:</u>
Conduct fiscally intensive clinical trials and go towards a BLA application process with a probability of FDA denial but a higher pay-off whether approved, driven by the 12-year market exclusivity.

<u>File a FOB application:</u>
Refer to the data of the innovator and go towards a generic manufacturer's route.

In this case, conducting partial clinical trials that demonstrate the patient outcome equality with reference product may result in a FDA nod towards "interchangeable with" product and achieve one year exclusivity. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider[11]. Pay-off for an "interchangeable with" though not as high as a fresh biologic drug will still be higher than "biosimilar to" product.

Biosimilars or FOBs are significantly different than generic versions of small molecule drugs. They are both a risk intensive and fiscally intensive endeavor and will not offer a low-cost alternative presented by the small molecule generic drugs, however a minor price advantage cannot be overruled.

As with the Hatch-Waxman Act, newer challenges will rise with the passage of time, precedence will be set for multiple complex scenarios and loopholes closed.

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Vaibhav M. Varkhedkar (Victor) is a Vice President at the New York office of ORC international, charged with development of the firm's oncology practice. Victor has more than 15 years of experience in the healthcare industry. He is a co-author of eleven publications in healthcare and scientific journals and has gained peer-recognition as a co-inventor on 14 U.S. patents and more than 20 international patents. Victor has served as the primary researcher on numerous high-profile studies for large pharmaceutical companies such as Pfizer and Johnson & Johnson, as well as several leading biotech companies.

In Oncology, Victor has led research studies on advanced breast cancer, hepatocellular carcinoma, renal cell carcinoma, gastrointestinal stromal tumor, colorectal cancer, non-small cell lung cancer and hematologic malignancies.

Victor received his M.B.A. from the Fuqua School of Business at Duke University, where he also acquired a certificate in health-sector management. He holds a M.S. degree in Medicinal Chemistry from the college of pharmacy at the University of Rhode Island during which he also completed coursework for the doctoral degree and a Pharmacy degree (B.Pharm.) from KMK college of Pharmacy, University of Mumbai, India.

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Dr. Christine Dalzell is responsible for the management of the New York Custom Market Research division of ORC International. Dr. Dalzell has more than 15 years of experience in primary research the past 10 of which have been focused exclusively in the pharmaceutical and healthcare arena with particular focus CV, CNS and Psychiatric diseases. In addition to her therapeutic category expertise, Dr. Dalzell has extensive experience in statistical modeling and data analysis, including Cluster Analysis/Segmentation, Logic Modeling, Multiple Regression, Path Analysis, Structural Equation Modeling and Trade-off models such as Conjoint, Discrete Choice and MaxDiff.

In addition to her work with ORC International, Dr. Dalzell has been a research consultant for the New York Harbor Healthcare System. Among other projects, she has worked on a project intended to assess the impact and contributions of Nurse Practitioners in the area of compensation and pension examinations for veterans.

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