

Disruption and maturity: The next phase of biologics

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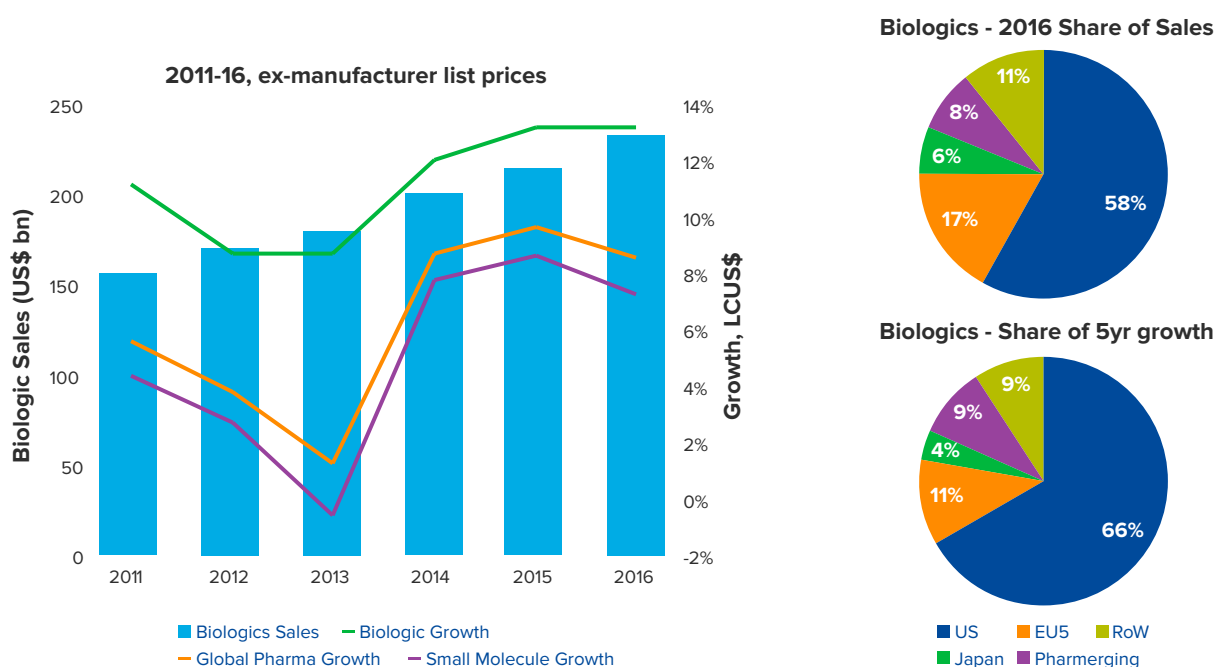
Introduction to the changes shaping the biologics market

Biologics are a growth market. Their revenue has increased by 70% in the last five years to reach \$232 billion.¹ The market's growth has continued to outstrip that of small molecules despite several small molecule blockbuster launches in areas such as hepatitis and oncology. This is shifting the makeup of the total pharmaceutical market, increasing the share that biologic products hold from 16% in 2006 to 25%¹ and there are few signs that this trend will slow down.

70%

Biologics revenue has increased by 70% in the last 5 years to reach \$232 billion.¹

Figure 1: Global biologic sales and trends



Source: QuintilesIMS MIDAS MAT Q2 2016; Share of growth in LC\$. Brazil and Mexico non-retail included

Older Blockbuster biologics in the oncology and autoimmune spaces contribute the majority of this growth. The relative absence of off-patent competition in these incumbent therapy areas is partially responsible for higher-than-market growth. There have also been several strong launches which have supplemented and will eventually drive biologic spending, particularly in oncology. Long-term prospects for biologic growth is positive due to industry's investment into larger biologic pipelines.

There are threats to the sector's continued outperformance versus small molecules. One significant development is the use of biosimilars. Once major biologic products in the US face biosimilar competition, falling prices will dampen growth. In turn this will enable wider access to better value biologics for patients. In some markets, once biosimilars are made available, total molecule spending will first increase from volume growth before falling due to increasingly competitive pricing.

Maturation of the biologic market

Small molecules have had a 110 year history of scientific advancement, regulatory and industry evolution. In contrast the modern biologic industry is relatively nascent. The earliest marketed example was 35 years ago with the approval of the first recombinant therapeutic protein, human insulin.

Biologics have a huge potential. Yet, much of this potential is still largely untapped, in terms of therapeutic spread, medical efficacy, and population access. This potential will gradually be realised as biologic technologies are translated into treatments, occasionally transformational ones.

Within the next five to ten years the biologic market will go through a period of rapid maturation and transformation from the current model:

- **Biologics entering non-traditional biologic disease areas.** Biologics are entering therapy areas where they have not been present historically, such as asthma, dyslipidaemia, and allergy. They will expand treatment options for patients in these indications, many of which are underserved. Collectively these are important areas for future biologic growth, but will also present challenges of market creation
- **Disruptive drugs and technologies.** The number of novel biologic molecules approved by the EMA and FDA has surged in the past three years. In 2016 50% of FDA new chemical entity approvals were for biologics. This period of high biologic innovation output will bring drugs that will compete with and expand the current biologic market. New technologies also have the potential to be game changing, both in efficacy and technological platform
- **Biologic asset revaluation.** The biologic model, both in pre-commercialisation and commercialisation is now well understood and proven effective. Confidence in the growing role biologics are playing in the pharmaceutical market is impacting acquisition trends
- **Biosimilars bring value.** We are entering a transformative period where the largest biologics will soon face biosimilar competition in all major markets. Opinions and guidelines formed during this initial phase will have lasting impact beyond 2020
- **Competition and market environment.** While previously many new biologics were first-in-class, now many biologics are entering the market competing with the same mechanisms of action, increasing the ferocity of competition. As payers find they have increasing choice in many areas, such as autoimmune, competitive dynamics for biologics increasingly resemble those of mature small molecule areas and payers place pressure on price and discounts

These five market trends will transform the biologic space in the next five years. Players with interest in biologics face both challenge and opportunity in this new era; what is clear is that the biologic market will be more complex.

Player archetypes in a maturing market

These biologic maturation events will have differing impact depending each player's strategic position.

Established biologic players

The largest biologic players are not just large within the biologic space, but the scale of their biologic success has made them global pharmaceutical leaders. Examples are Roche, Sanofi, and Amgen. These players face pressure to remain leaders in their areas of focus:

- **Revenue erosion.** The greatest challenge is the threat of biosimilars eroding revenues. Follow-on biologics such as PEGylated filgrastim and modern insulins have been successful in capturing and protecting franchise revenue in the past. However, recent follow-on launches such as those in the insulin space have not performed as well, leaving many large biologics vulnerable to biosimilar erosion. The current payer environment is not as open to innovation on the franchise. Follow-on innovation remains important for improving patient outcomes, but to achieve adoption they must also be designed with the payer's perspective. Roche's subcutaneous formulation of Herceptin in European markets is an example of when follow-on can succeed. The new formulation reduces treatment time from 30-90 minutes to 5, saving time for the patient and beds/staff for the clinic. It has taken 28% of HER2 franchise sales and the share is growing. Along with the other HER2 follow-on Roche products, only 43% of the franchise in Europe is currently vulnerable to biosimilar competition¹
- **Greater competition.** Biologic classes such as growth factors, insulins and anti-TNFs have several comparable products available and are therefore highly competitive areas. It took many years for these competitive environments to develop and for many indications particularly within oncology, the market remains relatively uncompetitive. However, this lack of competition is not an intrinsic property of the biologic market; it is a consequence of their relative novelty. A larger pipeline of biologics has meant that many players are developing treatments in the same indication, sometimes with the same mechanism of action. Previously validated pathways also reduce clinical trial risk, facilitating "fast follower" strategies. The result is that the window of opportunity for a first-to-market biologic will be shorter, with less differentiation. The more competitive future biologic market will impact the return on investment for manufacturers. This can already be seen in many of the recent biologic launches such as immuno-oncologics, respiratory biologics and PCSK-9 inhibitors
- **Maintaining leadership.** In times of high innovation output, established players are frequently challenged by new competitors entering their field. These companies can often be more dynamic, making and acting on decisions quickly. Bristol-Myers Squibb (BMS) is an example of a company which broke into a leadership position through partnering early and investing heavily. BMS moved up from rank 11 in oncology to rank 3 between 2011 and 2016¹, establishing itself as a long-term leader in immuno-oncology and a partner of choice for biotechs. Similarly, Alexion was founded as a small biotech in 1992, but has now become a top 30 biologic player thanks to its focus on rare diseases.

Large established players need to stay on the cutting edge of biologic R&D or risk losing leadership within their space. Business development will remain an important source of this innovation, but the challenge will be to keep it cost-effective given the greater future competition on the market

Niche biologic innovators

Small biotechnology companies are the lifeblood of the biologic industry. The positive market environment for biologic products has placed these companies in a position of strength with respect to access to capital. This has given some the ability to push through development while retaining autonomy. However, the gains from deals have never been greater. Licensing leading products whilst keeping earlier pipeline and the scientific talent is a popular compromise.

Our understanding of the science behind biological technologies is improving, and investor confidence has increased. However, the fact remains that many novel technologies pursued by biotechs will be high risk areas of research.

Players looking to enter the biologic space

These are companies which predominantly invested in small molecule research and did not previously consider biologics as key to their strategies. Large pharmaceutical companies such as AstraZeneca and GlaxoSmithKline have not historically embraced the biologic wave. Many mid-sized innovative companies also fall under this category since they have specific disease area focus, often in therapy areas with little biologic use.

Biologic therapies are becoming relevant in a greater number of disease areas. These companies will be looking to extend disease area leadership by following opportunities for investment in biologic products and biotech capabilities. For example, AstraZeneca, one of the leading companies in the respiratory space with its small molecule Symbicort franchise, is now poised to enter the respiratory biologics space with benralizumab.

The challenge for these prospective biologic players will be to secure deals for the most promising pipeline candidates. They will be competing with other big pharma for increasingly sought after and expensive assets, with a disadvantage in aspects such as experience, biologics manufacturing infrastructure, and capital in the case of mid-sized companies. However these mid-sized companies do have a greater capability for focus, particularly in niche therapeutic areas and technologies.

Biosimilar players

Biosimilar players are presented with an opportunity to take sales from 15 of the top 20 biologics in the majority of developed countries by 2020, a market value greater than \$80Bn². Investment barriers have meant that these players will face fewer competitors relative to the small molecule generic market. However, the competition that is present have formidable resources to draw from. Leading players have been gaining experience taking biosimilars through regulatory approval. Their legal teams/partners have been setting precedents while clearing patents to prevent at-risk launch. This experience will be invaluable when preparing launches for the many biosimilar targets that will be present moving forwards. Some players such as Novartis/Sandoz, Merck & Co and Amgen will be playing in both the originator and the biosimilar space. These hybrid players are able to leverage their expertise in biologic development and manufacturing to generate synergies. They also have the financial capacity to invest heavily in the space. However, they will face a certain degree of conflict of interest.



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Biosimilar players also have the ability to bring bio-betters to market. Today's off-patent originator molecules were engineered over 15 years ago. Since then, scientific advancements have enabled biosimilar developers to improve the molecule significantly. Novel screening methods have aided the detection and replacement of immunogenic sections of protein; iterative binding assays have improved specificity and binding strength; better understanding of structure/solution stability and stress tests have improved the temperature stability and shelf-life. However, these improvements on biosimilars are limited by the regulatory requirement to keep the molecule similar to the originator, this is to enable simple switching and to avoid dosage confusion. The challenge is that there is currently no dedicated FDA or EMA regulatory guidance for bio-betters. Approval through a novel medicines pathway would require the developer to invest in clinical trials at scale similar to creating a new product. If the improvements on the molecule are not transformative- and payers don't see a profound value, the return will not be high enough to justify investment. In the longer term, the development of an abbreviated bio-better pathway remains a possibility. As the biosimilar market becomes more competitive, players looking for product differentiation may explore this bio-better route.

Outlook: landscape of the biologic market

Biologics are concentrated. Currently the top 10 biologic therapies account for 36% of all biologic spending. This is far above the top 10 small molecules, which collectively hold only 20% of the original brand small molecule market.¹ The same concentration also applies in terms of therapeutic landscape. The three largest biologic therapy areas (autoimmune, diabetes, oncology) are worth \$110Bn,² over half of all biologic revenue. They are represented in 9 of the top 10 biologics, and are increasingly relevant due to their contribution of 70% of biologic growth since 2010.

The large therapy areas have dominated the biologic market as a result of a high number of strong launches into high-unmet-need indications, and the lack of biologic entrance into other large disease areas. However, a change in the market is imminent. These areas are increasingly competitive and the introduction of biosimilars will add further downward pricing pressure. This, in combination with new biologics launching into other therapy areas will result in a more diverse biologic market; and the pipeline has got several promising and high impact candidates.

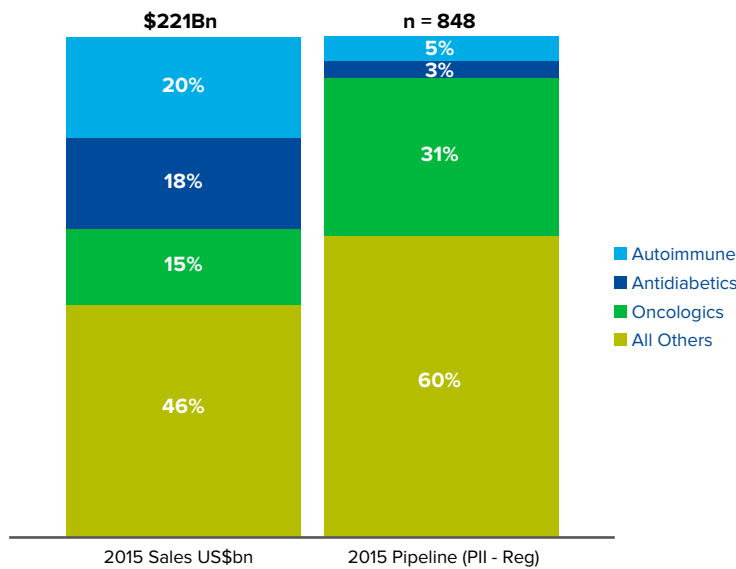
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Figure 2: Biologic sales and PII+ pipeline by Therapy Area - 2015



Source: : IMS Health MIDAS MAT Q4 2015

Autoimmune and diabetes biologic pipelines contain considerably fewer candidates than oncology, even though these spaces hold higher revenue share. Despite a new generation of autoimmune biologics and the diabetes combination treatments in the pipeline, if the uptake of biosimilars in the US is strong, growth will fall. This will materialise in the form of increased competition and discounting within indications.

Biosimilars will open up space for spending in other areas. One of the most profound changes in pipeline makeup has been the rise in oncological treatments, up from 25% of the biologic pipeline in 2010 to 34% in 2015.³ The oncology pipeline also contains some of the most valuable assets in development. Examples include waves of immuno-oncology treatments and antibody-drug conjugates. We forecast that the immuno-oncology segment of the biologic market will be worth over \$22Bn by 2020, and up to \$31Bn by 2025.⁴

Over half of the biologic pipeline is in therapy areas with few or no biologic treatments on market. Their large presence in the pipeline is a sign of biologics broadening their therapeutic focus, bringing new areas for growth.

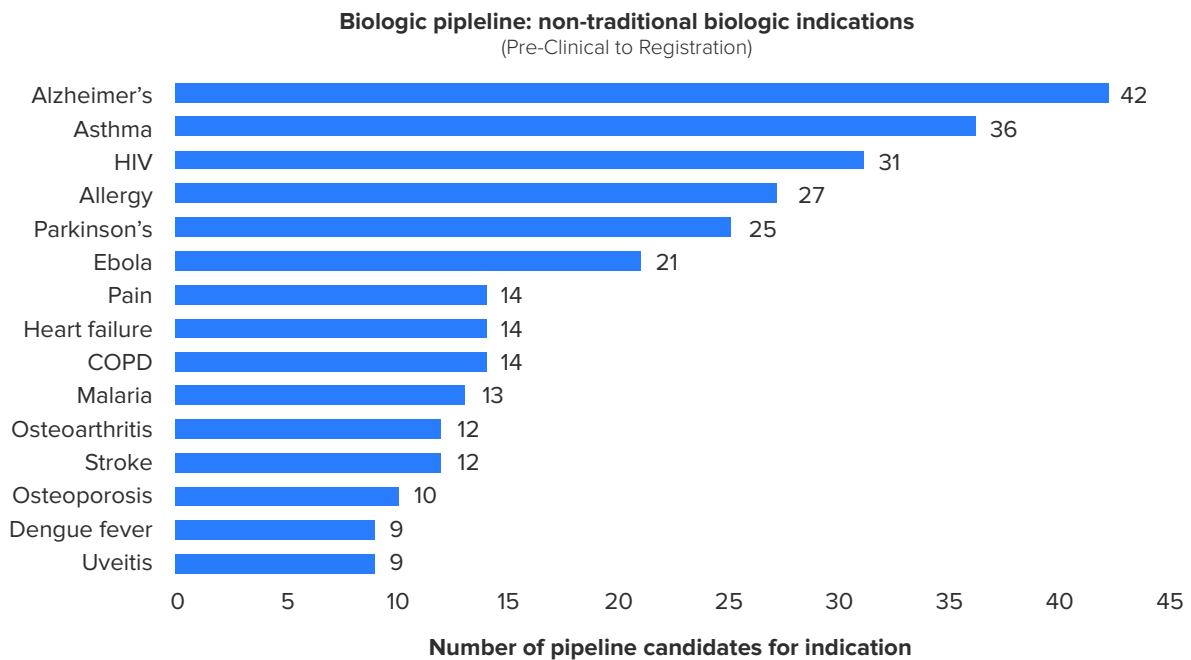
Biologics in non-traditional biologic disease areas

2015 was the year that two high profile classes of biologics had their first launches, the anti-PCSK9 mAbs⁵ for hypercholesterolemia (Repatha and Praluent), and an anti-IL-5 mAb for severe asthma (Nucala). These launches were particularly important because the indications they were approved for have seen either no biologics (hypercholesterolemia) or a single biologic (asthma-Xolair). Both diseases are highly prevalent and mainly treated by primary care physicians using widely available generics. Healthcare systems have not been accustomed to structuring administration of these patients with biologics, let alone paying for them.



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Figure 3: Likely disruption within these markets



Source: : IMS Health R&D Focus Q4 2015; Thought Leadership analysis

These launches are not isolated products. There is a substantial 25% of the current biologic pipeline that is targeting indications which broadly share similar characteristics: small molecule dominated, highly genericised, and a large patient population which could see benefit from treatment.

Biologic agents entering these indications will be transformative not only because of their disease modifying efficacy in clinical trials, but also because of the rapid change in disease market size and growth that would follow a successful launch. These biologics will typically be more expensive than other treatments for the indication. This is because they are non-generics targeting subpopulations, offering improvements on the standard of care. Payers will be concerned about rising costs at a time when spending in these therapy areas was starting to decline on a per capita treatment cost basis. These could have significant budgetary impact as a result of the high prevalence for many of the diseases. For example, in the US 40% of the population has elevated cholesterol levels. Therefore, even if a very small subsection of this population clinically benefits from treatment, the cost implications are huge. We have already seen health technology assessors impose restrictions on these therapies, contributing to their underperformance to date.

However, it is important to consider that biologics entering non-traditional biologic disease areas may take longer to optimally position within the patient pathway. This is because primary care physicians and patients are not accustomed to prescribing and using biologics so could take longer to utilise the innovation. Historic examples of slow initial uptake for drugs in this category can be seen in Xolair and Prolia, however both of these drugs have now surpassed \$1billion sales.

25%

25% of the current biologic pipeline is targeting indications which have seen little or no biologic use

Technology and Science innovation in the long-term?

The potential of innovative technologies

Currently mAbs hold the lion's share of the biologic market sales, and remain the largest technology class within the biologic pipeline. However, the mAb dominance we see today could be outperformed by novel biologic technologies currently in the pipeline. In the next ten years therapies using non-established technologies will have launched into the market. Although only a handful of launches will occur before 2020, these first few will show us the potential of these therapeutic strategies to change the way we treat disease in the long term. There are four technology classes with significant pipeline scale which will be entering a pivotal stage during their first few launches by 2020.

- **Antibody drug conjugates:** A drug (e.g. a cytotoxin) is coupled to an antibody that specifically targets a specific biological marker (e.g. cell surface tumour antigen). The function of the antibody is to act as a vector, enabling targeted delivery of the toxic drug to the antibody target. When compared with standard drug treatment, it allows orders-of-magnitude lower dosage, reducing the undesirable systemic side effects caused by the toxic drug. This means that a drug or certain high drug dosages that may have previously been too toxic for use in treatment can be utilised safely

There are currently two antibody drug conjugates (ADCs) on the market, Kadcyca marketed by Roche/Genentech, and Adcetris marketed by Seattle Genetics/Takeda. There are an additional 17 antibody drug conjugates from Phase II through registration looking to enter the market in the near future³. Depending on clinical success and market acceptance, we may see ADCs becoming a more popular pipeline choice

- **Antisense/RNAi:** These are two similar naturally occurring biological processes in which RNA molecules modulate the level of gene expression. They have been manipulated for therapeutic benefit in order to prevent the expression of disease causing proteins with great specificity. They are relatively new technologies, RNAi was only utilised as a scientific technique in 1998, but they are showing great promise in a range of therapy areas from oncology to hyperlipidemia. Improvements in delivery systems have been key to enabling the use of these unstable RNA treatments. Two pioneering antisense RNA treatments were approved by the FDA in 2016, Spinraza and Exondys51. Spinraza is the only available treatment for spinal muscular atrophy, an orphan disease with a low life expectancy. Analyst consensus revenue for Spinraza is over \$1bn by 2021,⁶ substantial considering the novel technology. With 44 antisense/RNAi candidates in Phase II and later,³ this could be an important segment for biologic growth

- **Gene Therapy:** Gene therapies are treatments in which genetic material is incorporated into the cells of a patient with an intended therapeutic benefit. Much of the gene therapy pipeline candidates function by attempting to correct or replace a genetic defect which underlines the root cause of the disease. The only examples of approved gene therapies are Glybera- used to treat Lipoprotein Lipase Deficiency, and Strimvelis- treating ADA-Severe Combined Immuno Deficiency. The potential for gene therapies is that they aim to be curative

There are also gene therapies going beyond genetic correction and towards non-corrective, more sophisticated mechanisms of action. Examples are pipeline candidates aiming to stimulate nerve cell growth in patients with Parkinson's disease, and stimulate blood vessel growth for heart disease

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- **Cell Therapy:** Cell therapies are treatments in which intact, living, human cells are injected into a patient for therapeutic benefit. 60% of the cell therapies in development are autologous (fully personalised treatments where the cells themselves originate from the patient), the rest are allogeneic (off the shelf). In 2010 the FDA approved the first ever autologous cell therapy vaccine, Provenge. Although this product was not a commercial success, the area remains very dynamic particularly due to the high profile CAR T-cell, and T-cell treatments which have been valued so highly during recent acquisitions⁷

Collectively these drug technologies make up 18% of the Phase II+ biologic drug pipeline. It is still not clear which of these platforms will enter the mainstream. The performance of each particular technology class is somewhat dependent on the first few launches. If they fail to deliver clinically and commercially, these launches serve as warnings to investors for the platform as a whole. Existing marketed examples of cell and gene therapies have faced multiple challenges in commercialisation, particularly in the funding of treatment. The western world's first gene therapy, Glybera was priced at €1.1 million in Germany. Glybera is used to treat an ultra-orphan⁸ indication, lipoprotein lipase deficiency, but much of the pipeline similarly aims to cure disease, and will likely be priced highly. The challenges associated with the cost of ground-breaking curative treatments in the pipeline must be tackled proactively. Innovative approaches to funding will be a necessary pre-requisite of success when commercialising such valuable treatments.

Instilling payer confidence in a technology's curative promise is challenging given the inability for clinical trials to model a lifelong cure. Schemes such as the UK's Early Access to Medicines and the Accelerated Access Review can enable early collection of real-world data before approval and enable longer periods of evaluation.

Drug delivery: calls for change

Innovation in biologics is not limited to the therapies themselves. It can also be seen in the routes of administration for biologics. They can make delivery simpler, faster and more compliant. This has the material advantage of making biologics scalable for larger populations, often taking treatment out of the hospital and into the home. However it is important to note that some novel delivery mechanisms were developed for the functional necessity to target specific parts of the body, and therefore enable treatment where previously it was not possible.

There are currently two biologic delivery methods which are used for the great majority of biologic products, IntraVenous (IV) and subcutaneous. IV is one of the oldest/simplest routes of administration for many biologics. It requires health care professional presence to administer and treatment can take long periods of time. This makes IV burdensome for patients having to travel and wait during treatment. Similarly, using IV is more costly for healthcare payers who will have to staff and facilitate the treatment. This is particularly burdening if treatment is required on a frequent basis over a long period of time and for large patient populations. Perversely, with buy and bill models in the US, doctors can be incentivised to treat patients using inefficient delivery mechanisms.



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Figure 4: Innovation can also be in delivery



The challenge for novel delivery mechanisms is to reduce the burden of biologic treatment whilst maintaining (or improving) patient safety.

Today, many biologics have subcutaneous formulations available. This has the advantage of enabling patient self-administration and often cutting down on the delivery time. This solves many of the challenges of IV delivery, however, there is still room for innovation. In the diabetes space subcutaneous injection devices are extremely discreet, but patients can still feel stigmatised when moving away from oral treatments. This psychological barrier can lead patients to delay insulin/GLP-1 treatment and remain on small molecules for longer than may be recommended by their doctor.

Patient compliance also becomes a hurdle when we take drug treatment out of the hospital and into the home. Patients incorrectly administering, inappropriately storing or forgetting treatment can have serious medical consequences.

Several novel delivery methods have the potential further tackle these challenges:

- **Inhaled biologics:** There are two examples of inhaled biologics that have reached the market, both of which are inhaled insulins- Pfizer's Exubera, and Mannkind's Afrezza (previously licensed to Sanofi). These drug launches have not been successful despite backing from major pharmaceutical players, even though they provide simpler administration with comparable efficacy. Their failure to disrupt the subcutaneous status quo tells us that removing the stigma/inconvenience from subcutaneous treatment may not be enough to succeed. In this current environment payers are not interested in spending more and switching to medicines with longer patent lives in order to treat patients that are already adequately served. Inhaled insulins provide an important message for all novel biologic delivery mechanisms: clearly justifiable real-world therapeutic improvements over convenience
- **Implanted biologics:** Implanting a drug is an interesting concept which has seen use in small molecule hormonal control. Implants have the benefit of requiring extremely infrequent treatment, sometimes once a year. Their constant presence nullifies the threat of poor patient adherence whilst also providing a constant steady flow of medication, which may be clinically beneficial. A near-market example of an implanted biologic is Intarcia and Servier's implantable GLP-1 pump, which will only require replacement every 6-12 months. If patients are consistently well controlled using only this medication, the infrequency of administration makes this less a treatment and practically likened to a cure
- **Oral biologics:** This is the holy grail of biologic administration- to make administration the same as a small molecule. The simplicity of using oral biologics would enable more convenient and compliant treatment. The hope is that it would enable access to more patients that would benefit from treatment, but are discouraged by injections. There has been sustained effort by market leaders such as Sanofi/Novo as well as start-ups to develop oral insulins and GLP-1s. However, due to difficulty of working against fundamental human digestive physiology; achieving stability, absorption and distribution of oral biologics is likely to be some way off
- Several other biologic delivery mechanisms are in development, such as intranasal, microneedle patches and dissolving films. These have more niche disease-specific advantages, for example it has been shown that intranasal delivery of biologics have the potential of increasing bio-availability past the blood brain barrier

Much of the work for innovative biologic delivery has been in the diabetes space.

This is because diabetes is a primary care area with an extremely large and growing patient population that could see significant benefit and increased compliance of insulin treatment should it be made easier. Once established, these technologies could spread to other disease areas. This will be particularly important in diseases with large patient populations like Asthma, COPD and hypercholesterolemia.

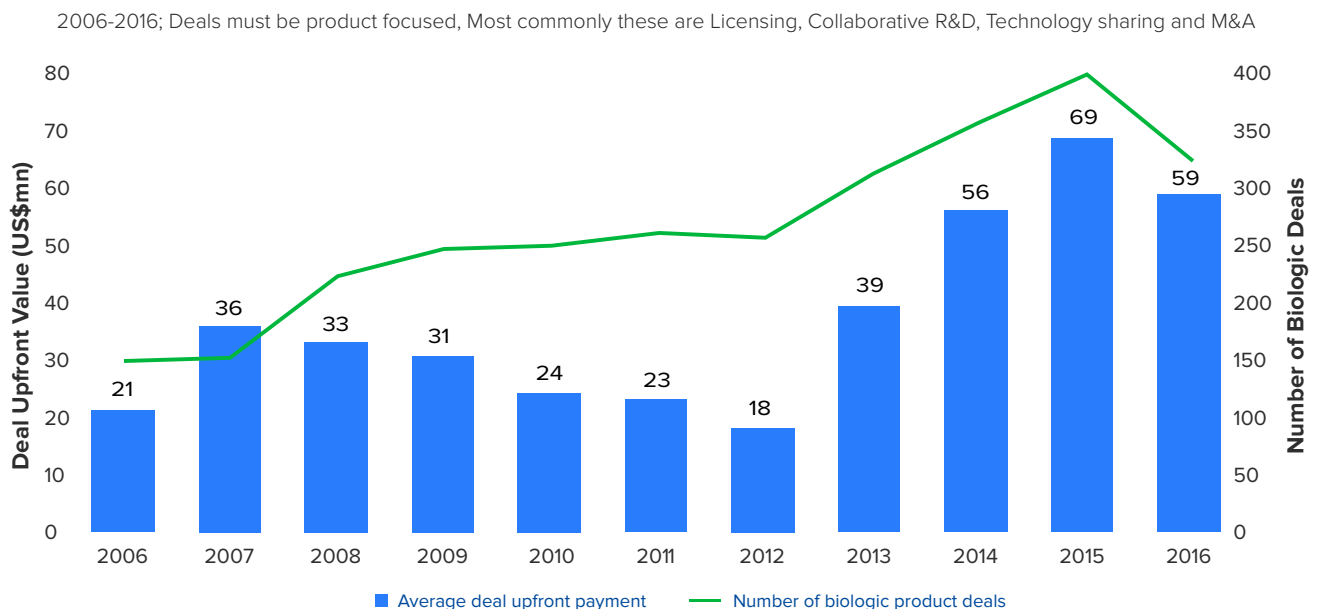
Biologic asset deal frenzy

As biologic pathway targets are validated, competition for the mode of action intensifies. In the 2012-16 period, the upfront value of a biologic product deal rose from ~\$20Mn to \$60Mn, tripling in four years. These valuations are raised due to three factors:

- Innovation output from biotechs has increased in scale and quality. This is possible due to greater scientific understanding of disease, advancement in scientific techniques and their wider availability
- Investment strategies are increasingly incorporating biologics into the pipeline with large pharma driving the trend. This competition, particularly between companies with deep pockets, is driving up deal values
- There has been prolonged availability of capital at low interest rates, promoting deal making across all sectors

The forecasted average value of a biologic deal in 2016 will be lower than 2015, a record year. The Valeant, Turing and Mylan pricing scandals attracted heavy criticism in late 2015 and 2016. The resulting attention from policy makers in the US has concerned investors, reducing expectations of future pharmaceutical market potential. This has contributed towards the fall of the NASDAQ biotech index by 21% since September 2015.⁹ President Trump's pronouncements after his election have served to increase the uncertainty of an already nervous sector.

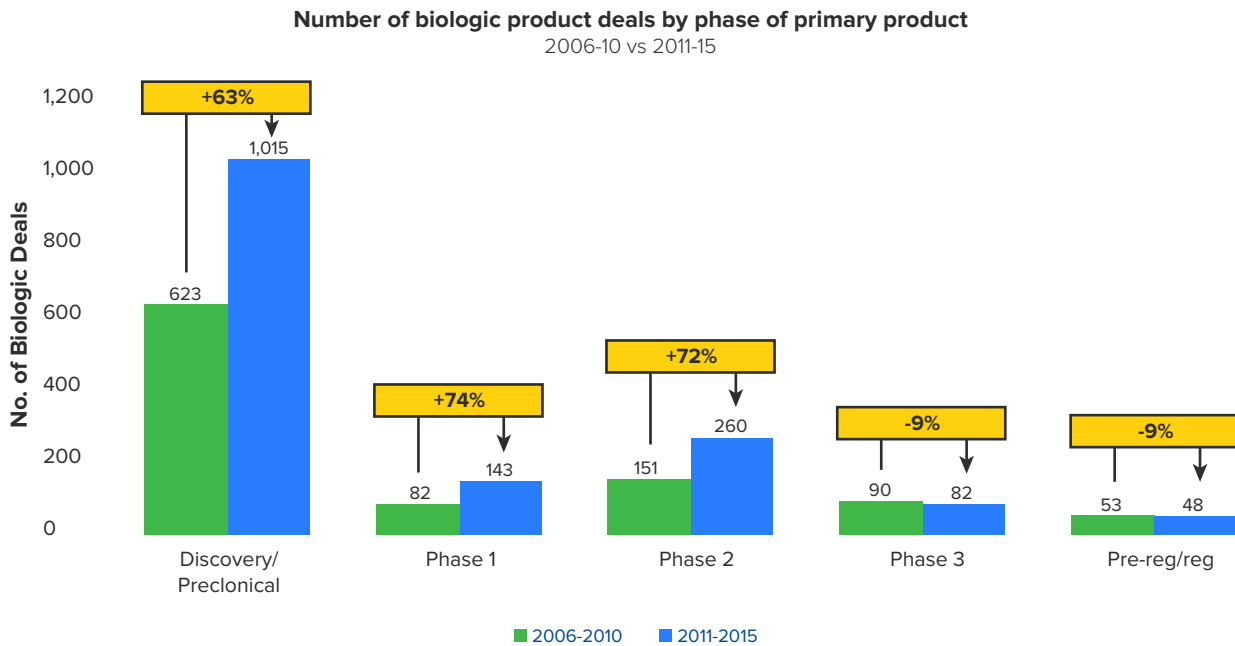
Figure 5: Value and number of biologic pipeline product deals



Source: Pharma Deals Nov 2016; 2016 no. of deals extrapolated to the expected full year figure

The number of biologic product deals signed has also risen. Between 2008 and 2012 these number was relatively stable ~250 deals per annum. However, in 2015 the number of deals announced reached at 400. Where are these biologic assets being sourced from?

Figure 5: Number of biologic product deals by phase of primary product



Source: Pharma Deals Q4 2015

Historically, the majority of biologic product deals have been executed early in the drug development cycle. This trend is becoming more pronounced. Between the 2006-10 and 2011-15 periods deals for biologic drugs in development to Phase II increased by over 60%. If we look at deal growth in absolute terms, the bulk of biologic deal increase is coming from very early stage, discovery/ preclinical (392 more deals, 71% of deal growth). This has several root causes:

71%

of absolute deal growth is in Discovery/Pre-clinical

- There are not many high-potential late stage biologics left to acquire. Demand for pipeline biologic therapies has increased but it will take several years before reactive supply will progress to the late stage
- High valuation of biologic products is pushing players who are unwilling to invest heavily to look earlier in development for promising candidates
- Players in the industry now have many years of experience developing biologics. They have taken them from scientific concept through to market blockbusters. As a result of this experience, more players have comfort conducting early stage deals
- The greater risk of early deal making has been balanced with the increased usage of contracted milestones within deals

The arrival of major biosimilars

Biosimilar immediacy

When small molecules lose patent protection generics enter the market, resulting in lower drug cost burden for payers. These savings are channelled into the funding of new innovative drugs and expanding access to older ones. The same innovation cycle for biologics is reaching maturity. Many biologic blockbuster products now have biosimilars lined up to take market share. Those biologic makers facing loss of exclusivity on a current marketed product can be partially comforted by the prospect of funding availability for future launches.

- **A jump in biosimilar availability and usage:**
 - The first biosimilar mAb, infliximab, has launched for all originator indications and has taken majority share in several European markets. There are now three competing infliximab biosimilar brands in Europe: Remsima marketed by MundiPharma, Inflectra by Pfizer/Hospira and Flixabi by Biogen
 - The list of biosimilar molecules that have gained FDA approval now includes filgrastim, infliximab, adalimumab and etanercept, with many more entrants expected before the end of the decade
 - A rich pipeline with over 240 biosimilars in development (including only those which are announced publically) will mean that launches will be coming with increasing frequency and there will be greater competition within each molecule
- **Stakeholders will have biosimilars high in their priorities. They will gain a lot of experience in the space of a few years:**
 - Regulators will be clarifying guidance for biosimilar manufacturers. Many regulatory bodies are aligning guidelines to those of the EMA
 - Country medicines agencies will be assessing the clinical evidence over time. Important decisions on stance for switching patients will be applied as a result
 - Payers will be grappling with barriers to biosimilar uptake in order to find savings and increase leverage
 - Physician and patient groups will express their views. These will form the backbone of public opinion on biosimilars, and can influence agency guidance
 - The biopharma industry, innovative and biosimilar players, will develop new strategies of competition. The level of discounting that a biosimilar business model can sustainably provide will be better understood

The decisions and opinions developed during this transitional period will set precedent moving forwards. As a result, keeping up to date with this rapidly changing space will be important for strategic decision making for the short and the long term.

State of the biosimilar market

Many of the top 20 biologics are already exposed to biosimilars competition. An estimated 6/20 have lost exclusivity in the US and 7/20 in Europe. By 2020, these figures will increase to 15/20 and 14/20 respectively.¹⁰

Where are all the biosimilars?

Seven of the twenty largest biologic products have gone off patent in Europe. It would be expected for these high revenue products to be top priority targets for biosimilar makers, and that market entry would be rapid. Yet, as of November 2016, biosimilars have launched for only three of the seven (infliximab, insulin glargine, etanercept), with launches late by many months after patent expiry.

Why haven't biosimilars launched for the other four off-patent molecules?

- **Cost:** The high expense of developing and launching a biosimilar has led to a less competitive environment, slowing progress. Development costs are higher than for small molecules due to greater clinical trial requirements, requirement for larger and more sophisticated manufacturing facilities, promotional activity, and drawn out expensive patent litigation lawsuits.

The skill set and investment required to develop and launch a biosimilar resembles those needed to launch a new biologic brand, rather than a generic small molecule. Finding biologic/biosimilar talent is a major hurdle for the many small generic companies who are interested in entering the space.

Large biologic players have been tempted in to a biosimilar play due to their existing infrastructures. There are important synergies to be found in manufacturing, expertise in molecule development and regulatory approval

- **Market opportunity:** Market opportunity for players remains uncertain. Uptake is slower and lower than for small molecule generics; this will improve but it is uncertain to what extent.

The biosimilar space has become crowded relative to the investment required for entry. Price discounts have been unexpectedly high in some markets. Merck Group has reportedly shown interest in divesting its biosimilar drug business due to this strong competition¹¹

- **Patent uncertainty:** Biosimilar makers face a wide range of outstanding Intellectual Property (IP) patents if they seek to bring a product to market. The majority of this IP goes beyond protecting the molecule, also protecting formulations, devices and importantly the manufacturing processes. For biologics, the exact manufacturing processes used are influential in the final structure and function of the drug. The complex structure of biologics and their high sensitivity to their manufacturing conditions is why the process can define the structure. Biosimilar manufacturers will attempt to find alternative ways around these additional process patents. However, if this is taken too far they risk the drug no longer being truly biosimilar.

The uncertainty and accompanying threat of patent litigation further increases risk for biosimilar investors. However, increased use of pathways such as the US's Inter Partes Review procedure and Arrow declarations in Europe may enable biosimilar players to challenge biologic patents more efficiently

- **Regulatory difficulties:** The regulatory evolution of biosimilars is still relatively immature. The EMA published the world's first biosimilar guidelines in 2005, with the FDA publishing 2012. The convergence between these and other regulatory guidelines has been slow, preventing single cost-effective biosimilar development. Biosimilar legislation is only in its infancy. The Hatch-Waxman Act in 1984 did not lead to an immediate mature generic market, and neither will biosimilars. As regulatory bodies and biosimilar manufacturers gain experience in bringing biosimilars to market, regulatory difficulties will have a smaller impact

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- **Complexity in development:** Biologics vary greatly in structure. Unlike many small molecules, biologics are not always consistent or well-defined. Each batch of biologics has the potential to be slightly different due to the large number of variables that could change. This means that an originator biologic can vary significantly, particularly when manufacturing processes are altered, which occurs more than once a year for many products. Achieving biosimilar approval for these poorly defined molecules can be challenging. The originator molecule structure may have changed between discovery and Phase III of biosimilar development. The biosimilar manufacturer must show that any differences are not clinically significant from the several iterations of originator structure. In addition, gaining enough doses of successive originator product can itself be challenging. These same hurdles during development must be overcome independently by each biologic manufacturer, not a particularly efficient model for increasing competition

Players have gained experience developing and taking biosimilars through regulatory procedures. This combined with a greater understanding of the biosimilar business model has meant that biosimilars are now being developed earlier and with greater competition than was the case previously. Moving forwards the lag between biologic loss of protection and biosimilar launch will decrease.

Biosimilar uptake tracking

The space is changing very quickly, so it is important to understand the dynamics for the biosimilar environment and the possible resulting scenarios. We will analyse the historic performance of biosimilars in three molecules: infliximab, insulin glargine and etanercept. These molecules have been chosen because their launches have been relatively recent (since 2014), and therefore reflect the current biosimilar environment. Additionally the sales for the originator brands of these molecules are all within the top 10 brands globally, so parties are likely to be using best competitive practice, providing an analogue for future large biosimilar launches.

Figure 6: Europe, Japan, Canada, US - Biosimilar share of molecule treatment days

		Biosimilar treatment day share (August 2016)				
		Country	Infliximab	Insulin Glargine	Etanercept	
EU5	UK		54.3%	1.4%	11.8%	
	France		19.2%	0.3%	–	
	Germany		23.8%	4.1%	10.6%	
	Italy		38.1%	9.9%	–	
	Spain		30.2%	5.7%	–	
High Penetration EU	Finland		88.8%	0.6%	–	
	Norway		93.2%	1.8%	59.1%	
	Poland		99.8%	22.6%	–	
	Denmark		97.5%	3.1%	76.2	
	Japan		3.0%	27.7%	–	
	Canada		0.7%	0.6%	–	
	US		–	–	–	

Source: QI MIDAS Monthly August 2016

Infliximab

Infliximab biosimilars have been on the market for the longest, have the highest uptake and therefore provide the most insight. Uptake has varied by country, the European tender markets, including the Nordics and Poland, have achieved almost full usage within two years, for Denmark it took under 6 months. This is due to the ability to switch the bulk of infliximab patients from the originator to the biosimilar tender winner. EU5 markets have had slower, more incremental uptake. The majority of patients using biosimilar infliximab in these markets are infliximab treatment naïve. There are some countries such as the UK and Italy which have regions or individual hospitals which have switched much higher, in some cases 100% of, patients.

Medicines agency opinions on switching have become increasingly positive. Many of these agencies were explicitly waiting for the results from switching studies such as the NOR-SWITCH trial. The trial results were announced in October 2016, and they showed no significant difference in efficacy or safety between Remicade and Remsima for the 400+ patients.¹² This will give confidence in infliximab switching to policy setters, and will also incrementally contribute to the growing positive sentiment towards biosimilar switching as a whole.

Etanercept

The etanercept biosimilar has only been on the European market for a short period of time, launching in Feb 2016. However, in this time uptake has been relatively strong. If we normalise the launch dates for etanercept biosimilar and infliximab biosimilars, etanercept uptake is faster in the majority of countries including the UK and Germany. This suggests that payers are gaining experience with biosimilars and, in the absence of barriers, the rate of biosimilar uptake will increase.

Insulin glargine

The insulin glargine biosimilar launched after the first infliximab biosimilars. Uptake has been far lower for the insulins. In Europe uptake has been particularly slow, with all EU5 members under 10% biosimilar usage¹³.

We have identified four reasons insulin glargine uptake has been slow:

- 1. Primary care treatment:** In most mature markets insulins are retail products, being prescribed by primary care physicians, reimbursed from the retail budget. Without the use of physician incentives or automatic pharmacist substitution, switching patients will be more difficult than in the hospital sector. In hospitals, lead physicians and lead pharmacists will communicate and collectively agree on whether to switch patients or not. This level of communication does not occur in retail, as a result the procuring pharmacist has less influence. Additionally, as the prescribing power lies with the physicians in retail, substantial biosimilar player investment would be required to promote to the large population of primary care physicians. Within EU5 the number of detailing visits for Abasaglar is seven times larger than that for all three marketed infliximab biosimilars combined¹⁴
- 2. Lifelong disease:** Diabetes is a chronic disease which the majority of sufferers will take treatment indefinitely. This means that the proportion of treatment naïve patients in the patient pool is relatively small. Since the majority of physicians in major European countries are currently not switching patients from Lantus, uptake may continue to increase slowly. If insulin glargine switching became common, this barrier could be lessened
- 3. Player ambition:** A key factor for slow biosimilar uptake could be the goals of the player that is marketing it, Lilly/BI are both heavily invested in the diabetes space. They may not be interested in bringing deep disruptive discounts to the area. Abasaglar can be thought of as a hybrid of a biosimilar and a line extension since Lilly/BI did not previously market a long-acting insulin. As more biosimilar insulins enter the market (one has recently received CHMP¹⁵ approval) the impact of competition from a market disrupter will encourage uptake
- 4. Follow-on protection:** Sanofi innovation on the Lantus franchise has protected a proportion of the market. 10% of Sanofi US and EU5 total insulin glargine sales is protected under the Toujeo brand, and the share is growing.¹ This limits the market available to insulin glargine biosimilars. However, disruptive pricing in the space does have the potential to draw patients back from Toujeo

While uptake has been low generally, some regions in Slovakia and Poland have successfully switched patients to the biosimilar. Interestingly, Japan uptake is far higher than in Europe, and the usage of biosimilars is consistently increasing with some pace. This is because the Diagnostic Procedure Combination (DPC) payment system provides greater reimbursement for biosimilar insulin glargine. Additionally, Lilly actively enrolled Japanese patients in the Phase III ELEMENT-1 trial.

The US will not behave like a typical European market with respect to biosimilar insulin uptake. Insulins already have very high levels of off-invoice discounting and rebating. Pharmacy Benefit Managers (PBMs) have demonstrated an ability to use formulary design to induce switching between branded modern insulins over the past five years. That performance suggests strongly that PBMs will be effective in influencing the usage of their preferred product, which in some cases will be the biosimilar. It remains possible for an originator to negotiate a preferred position ahead of a biosimilar, and that will likely happen, but the result will be lower insulin net costs in the market, whether biosimilars are used in high proportions or not.

United States biosimilar developments

The US holds the majority of biosimilar potential. Almost 60% of global biologic sales come from the US. The biosimilar environment is currently behind with only three marketed biosimilars but will catch up quickly. By 2021 ten molecules are estimated to have biosimilar competition¹⁶ (dependent on ongoing patent litigation), most with multiple biosimilar entrants.

Biosimilar pricing and market access in the US will also differ greatly from the European markets, particularly in the retail space. Pharmacy Benefit Managers (PBMs) have been very outspoken in their plans to utilise biosimilars interchangeably, even without official FDA interchangeable status. PBMs will be able to leverage the current pricing environment to push through formulary exclusions, encouraging deeper price cuts in return market share. PBMs also have the ability to use patient co-pays to financially deter patients from staying on the originator, incentivising switching. However, PBM biosimilar leverage could also be impacted by factors such as FDA biosimilar interchangeability status and politically driven healthcare policy changes, among others.

Biosimilars in Emerging markets

The Emerging markets typically have relatively low access to biologic medicines when compared to developed markets. Patients in these markets stand to gain the greatest increase in access as a result of biosimilar competition. This has caused Emerging market health authorities to put significant effort into encouraging use of Non Original Biologics (NOBs). NOBs are copy-biologics which have not gone through a biosimilar pathway with strict regulatory scrutiny such as the biosimilar guidelines for the EMA, FDA or WHO. They have been preferred in the Emerging markets due to their early access and lower price relative to true biosimilars. NOB uptake has been significant, the market was worth \$2.1billion in 2015 relative to \$1.1billion globally for true biosimilars¹⁷. They equate to 18% of all biologic sales in Pharmerging markets, and are growing at almost twice the speed. However, the biosimilar regulatory environment in the Emerging Markets is changing rapidly. There has been a marked push for increasing quality of copy biologic medicines, but increasing access and affordability will continue be the top priorities for policy setters.

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Conclusion

The biologic market is large and rapidly expanding. It accounts for over a quarter of pharmaceutical spending, giving it increasing payer attention. The pipeline contains a growing share of biologic drugs preparing to launch into therapy areas which have seen very little biologic use historically, such as alzheimer's, asthma and cardiovascular. Extremely large patient populations in these areas will accelerate biologic budget growth.

Additionally, novel therapeutic technologies in the pipeline such as gene therapies and autologous cell therapies will also be launched with greater frequency. The high cost per patient for some of these potentially curative products will pressure budgets further.

- When launching a biologic into this payer environment pharmaceutical companies should look seriously at alternative funding mechanisms. Pay for performance schemes have successfully been implemented in the US. However, other novel mechanisms should be explored, with different mechanisms varying in effectiveness depending on the specific treatment. Examples include: differential pricing, which can be based on which indication a drug is used for or the severity of the patient; payment in instalments, which spreads an acute one-off budget impact into manageable portions e.g. in indications with patient warehousing
- Larger patient populations and budget constraints favour a strategy based on volume growth. The growth of biologic manufacturing capability in the Far East has enabled the production of cheaper biologics. Companies should look at opportunities to reduce manufacturing costs with the primary ambition of expanding access, particularly in less developed markets where drug cost is more likely to limit access
- Launching a biologic into a non-traditional biologic indication creates unique challenges which must be actively overcome. For example, the majority of patients for these biologics will historically have been treated by primary care physicians, who may have had little exposure to biologics. Without appropriate education these gatekeepers may not efficiently refer patients through to the appropriate specialists who can carry out treatment. A coordinated, multichannel approach can supplement physician education whilst maintaining commercial cost effectiveness

Older products in traditional biologic therapy areas are being joined by competitors, both original and biosimilar, fragmenting the at-present concentrated market and applying downwards pricing pressure. The scale of the biosimilar pipeline will ensure that in the future off-patent competition will come rapidly after key patent expiry, giving originators little hope of maintaining unprotected biologic revenue.

- Originators planning to protect a franchise from biosimilars must ensure that follow-on biologics are a strong value proposition for payers. Players should direct the development of follow-ons to improved efficacy, reduced side effects or effectiveness in patients not clinically satisfied with current biologics. Easier administration or patient support services are nice to have but may not make the difference between a low cost biosimilar and a more costly newer agent

The on-patent innovative biologic market will also be under greater competitive pressure. Recent launches of biologics have more quickly been followed by other originator competitors, often with the same mechanism of action. The pipeline follows this trend with more launches forecast for autoimmune indications, diabetes combinations, oncology checkpoint inhibitors, EGFR inhibitors and respiratory biologics.

- In this more competitive landscape first to market advantage will be short lived. Rapidly maximising market share is more important than ever and promotional strategy should reflect this. However, expectations for biologic launches should still be adjusted accordingly and pragmatically applied during business development

The acquisition cost for a pipeline biologic is very high, with the upfront deal value tripling since 2012. However, in 2016 this trend flattened largely due to political factors impacting the pharmaceutical sector as a whole. 2017 may therefore represent opportunities for companies with an appetite for risk.

- Players should carefully plan the timing of a product acquisition. The stabilisation of deal price in this political environment may present favourable opportunities
- Companies should look earlier in development for acquisition targets. Strong competition and relatively high prices have left fewer valuable late stage assets. Additionally, the launch of an early phase product may be in a future environment with a different, less stigmatised political focus
- It will be increasingly important for companies to strengthen the competencies required to nurture a biologic pipeline candidate, particularly if they have historically been small molecule focused

Ranging from incumbent biologic drugs, to areas with no currently available biologics, the market is undergoing an unprecedented period of change. Leadership will be at stake. As more companies bring biologics into the mainstream of their portfolio, and biologics become mainstream across more and more therapies, the companies which thrive will be those that are bold in their investments, effective in their product differentiation, and innovative in their commercial model.



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