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GENERIC INHALERS: BEYOND REVERSE ENGINEERING

INTRODUCTION

The global pharmaceutical industry is an enormous market and generics are forming an increasingly important part of this sector. The generics market share by unit volume in North America rose from 52% in 2006 to 70% in 2016[1] with generics accounting for 23%[2] of a $446bn industry in the US in 2016[3].

Some observers forecast continuing growth towards a $380bn global generic market by 2021[4]. Regulatory bodies such as the FDA and the PMDA in Japan are actively encouraging generic entries into the market in order to increase competition, drive costs down and increase choice for patients.

A generic drug is one that can be substituted for a reference listed drug (RLD), by virtue of its equivalence in dosage, intended use, route of administration, side effects, pharmacokinetics and pharmacodynamics. Generics are often non-branded versions of off-patent formulations that can retail at a fraction of the branded price due to the vastly reduced development cost. A generic device is one that is substitutable for a reference device due to is similarity in the usability and drug delivery performance.

Many of the dominant pharmaceutical companies operate partly, or wholly, in the generic drugs market. In 2016, the generics divisions of Teva, Mylan and Novartis all reported revenues in excess of $9bn with the top ten manufacturers reporting nearly $50bn between them[5]. Whilst generic drugs are long-established, there are fewer players in the generic devices market, especially with high profile submissions from companies such as Hikma and Mylan being rejected by the FDA in recent years.

1 Change in the unit volume of generics market share worldwide between 2006 and 2016, by region: https://www.statista.com/statistics/864200/unit-volume-change-in-generics-market-share-worldwide-by-region/

2 Change in the value of generics market share worldwide between 2006 and 2016, by region: https://www.statista.com/statistics/864317/value-change-in-generics-market-share-worldwide-by-region/

3 Total nominal spending on medicines in the U.S from 2002 to 2016 (in billions U.S. dollars): https://www.statista.com/statistics/238689/us-total-expenditure-on-medicine/

4 Zion Market Research. (2018, March 21). Global Generic Drug Market Size & Share to Reach $380.60 Billion by 2021: Zion Market Research. Retrieved from Globe News Wire: https://globenewswire.com/news-release/2018/03/21/1443577/0/en/Global-Generic-Drug-Market-Size-Share-to-Reach-380-60-Billion-by-2021-Zion-Market-Research.html

5 https://www.statista.com/statistics/274660/revenues-of-top-global-generics-manufacturers-2011/

APPROACH

It is very easy to think of a generic device as being a replica of the original product and that reverse engineering the reference device will automatically be successful. This is an oversimplification and ignores the relationships between the drug, the engineering, the usability and the device performance, not to mention any outstanding IP surrounding the device. This not only risks missing the mark when it comes to replicating handling and performance, but also missing the opportunity to create a commercially optimised device.

GENERIC REQUIREMENTS

The drug delivered by a generic combination product must be similar to the reference drug in four key aspects:

- Same active pharmaceutical ingredients (API)
- Same strength, dosage form and route of administration
- Bioequivalence
- Same quality standard

The product also has the requirement that it must be substitutable for the reference device without the intervention of a healthcare professional and without any additional training.

Implications for the design of the device are that the drug must be delivered to the patient in the same way as the reference device and that the delivered drug must have characteristics that allow it to be absorbed in the same way by the patient e.g. the same fine particle fraction for Dry Powder Inhalers (DPIs) or the same needle depth and flow rate for injectables. Additionally, the patient must be able to use the device based on their existing knowledge of the reference device or the instructions for use (IFU).

These requirements mean that there are aspects of the device design that cannot be changed. For example, if the reference device is primed with a lever action then the generic device must also use a lever which is operated in the same way, and if the reference device is a dry powder inhaler then the reference device must also present the drug in powder form.

WHY INNOVATE AT ALL?

There are many reasons why engineers may want, or need, to redesign aspects of the device. It is worth recognising that most reference devices have been on the market for some time, and that technology, user preferences and regulations have all evolved at pace in recent years. One example of this is the 2003 introduction of an FDA regulation requiring dose counter mechanisms in Metered Dose Inhalers (MDIs)[6]. Another example is that, where it was once understood that medical devices should have a 'clinical' feel to them, it is now more common for patients to opt for a more stylised, consumer-focussed design that is less obviously medical.

Ironically, some of the requirements for similarity to the reference product can also force changes within the device: the API must be identical but the excipient (binders, flavours, dyes and preservatives) may vary due to manufacturing methods or stability requirements, necessitating changes in the drug delivery engine to replicate the delivered drug characteristics and demonstrate bioequivalence. A key skill for generic device developers is the ability to identify the aspects of the design that they are forced to change in order to meet current regulations, those that they need to change to navigate any existing IP, areas they can change to improve the value proposition and, crucially, the areas that they must not (or must) change in order to be considered a generic.

STRIKING THE BALANCE

Given the conflicting drivers and requirements that permeate generic device developments, getting a product to market may not be as straightforward as it first seems. Is it even a viable business strategy?

There are in fact many good reasons for investing in generic device developments. Regulatory bodies are actively encouraging generics to enter the market in order to increase competition and choice for the patient[7]. Pharmaceutical companies are keen to enter the market because the cost of drug development is greatly reduced. Patients, healthcare providers and payers are keen to see prices driven down[8]. The market is still expanding rapidly, with revenues from generics expected to reach $500bn worldwide in 2021[9]. Additionally, the first 'substantially complete' Abbreviated New Drug Application (ANDA) for each drug product can enjoy 180 days of exclusivity in this lucrative market[10]. With these financial rewards on offer, any generic device programme must strike a balance between speed of development to capture the 'first to file' position, IP avoidance, commercial optimisation and meeting the requirements of a generic device.

Finding this balance is not trivial. Starting from a blank sheet of paper risks being beaten to the finish line and not meeting the usability requirements, while reverse engineering risks infringing IP and incurring unnecessary costs. The answer lies in the subtleties of the design itself. By gaining an understanding of when to replicate and where to innovate; what is crucial to the user interaction and what can be reimagined with no impact on performance; and what is covered by existing IP and how much it needs to change, companies are well positioned to develop an acceptable, viable, generic product. This process of 'Targeted Innovation' is key to success.

6 Brennan, Z. (2017, January 12). 180-Day Exclusivity for Generics: FDA Releases Draft Guidance. Retrieved from Regulatory Focus: https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/1/180-day-exclusivity-for-generics-fda-releases-draft-guidance

7 FDA. (2018, January 3rd). Statement from FDA Commissioner Scott Gottlieb, M.D. on new steps to facilitate efficient generic drug review to enhance competition, promote access and lower drug prices. Retrieved from FDA.gov: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm591184.htm

8 Gottlieb, S. (2017, June 21st). FDA Working to Life Barriers to Generic Drug Competition. Retrieved from FDA Blogs: https://blogs.fda.gov/fdavoice/index.php/2017/06/fda-working-to-lift-barriers-to-generic-drug-competition/

9 'The Pharmaceutical Industry and Global Health Facts and Figures 2017'. International Federation of Pharmaceutical Manufacturers and Associations https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf

10 Brennan, Z. (2017, January 12). 180-Day Exclusivity for Generics: FDA Releases Draft Guidance. Retrieved from Regulatory Focus: https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/1/180-day-exclusivity-for-generics-fda-releases-draft-guidance

TARGETED INNOVATION

The process of applying 'Targeted Innovation' begins with a thorough understanding of the reference device: how users interact with it, its performance, how it is made, what IP exists, etc. From that baseline, companies can begin to define the areas of the device that require change, those that prohibit change and those that provide an opportunity for change. The drivers for change are likely to fall into the categories of manufacturing, usability, product design and performance. The decision-making process for when to innovate will differ for each of these.

MANUFACTURING

When considering the manufacturability of a device, there may be many opportunities to redesign elements to strengthen the commercial viability of the product. There have been major improvements in manufacturing processes and materials technology in recent years. A reference device may rely on clips and detents which add complexity to the tooling, whereas the generic version may consider ultrasonic welding as a retention technique. Previously unavailable materials may offer new possibilities for friction reduction or dimensional stability, making some of the features

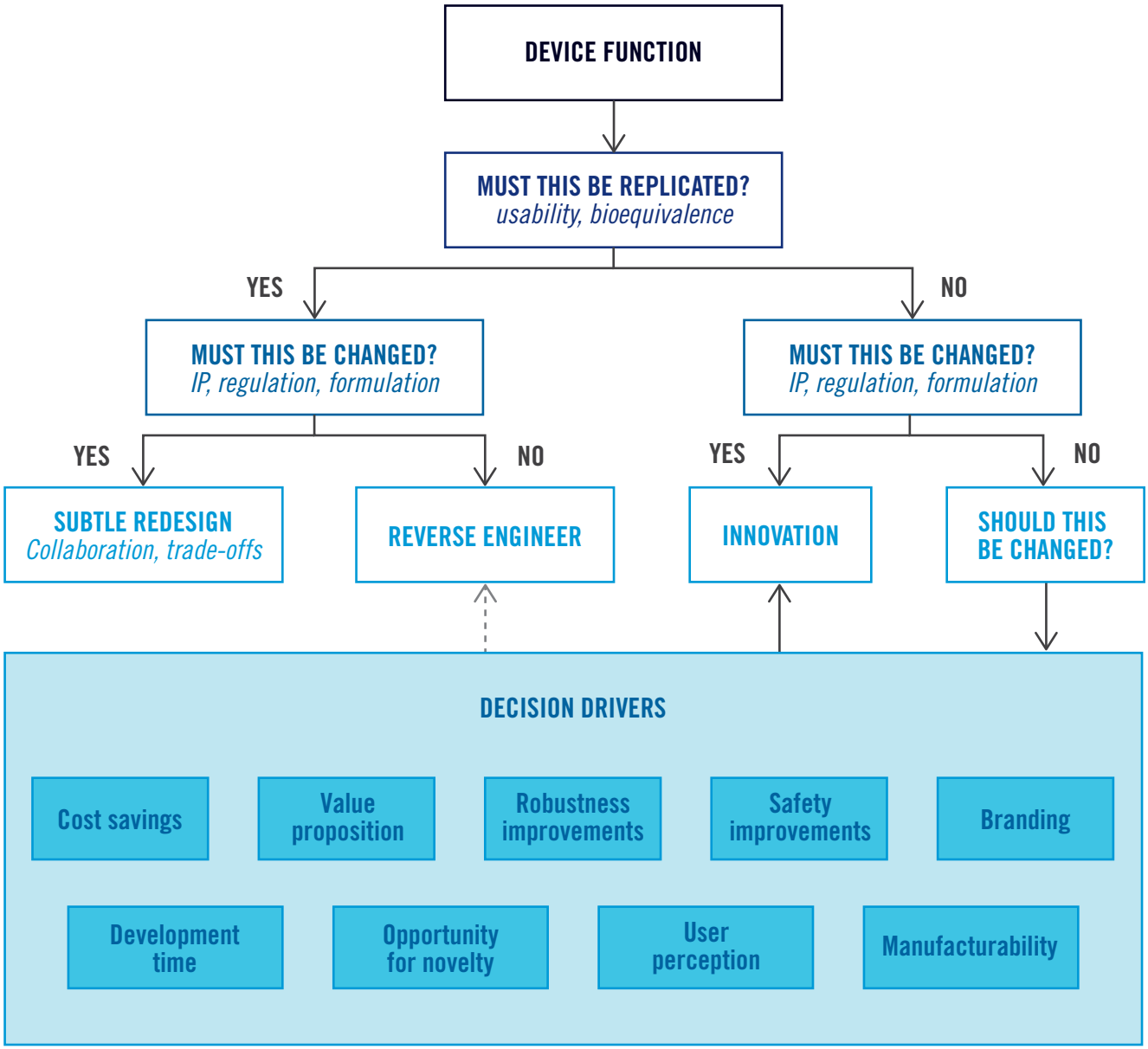

Figure 1: Targeted Innovation decision process

of a reference device redundant. As well as considering alternative processes, there may also be opportunities to design with the capabilities of the manufacturer in mind to reduce capex or part cost. For example, there may be merit in combining functionality to reduce the part count in the device, thereby reducing the number of tools, albeit with a more complex tooling strategy for the remaining parts. Alternatively, reducing part complexity to keep the tooling simple, therefore improving yield, may be the best approach. With a clever understanding of the component interactions there may be opportunities to reduce tolerance stacks which could, in turn, allow control of dimensions to be relaxed – this opens up more options for manufacture when less precision is required.

Production volumes will also play a role in the decision-making process. A reference device may be manually assembled, but the reduced cost of automation and the growth in the market may make a semi or fully automated assembly process a wise investment. Some redesign work would probably be necessary to accommodate a change in assembly strategy.

Any changes in the approach to manufacturing and assembly from that of the reference device would need to be considered in the context of the business case. Since new tools would need to be procured and qualified for any new production line, there may be a limited appetite for introducing any changes which could impact timelines. Conversely, investing in new tools could be the perfect opportunity to maximise the financial potential of the device and to introduce technology that may already exist in-house.

USABILITY

The design of a generic device from a human factors perspective is a study in improving the user experience without impacting the usability. The aim of a generic program is to develop a device which can be submitted via an ANDA 505(j) (for the US market) in the most expedient and efficient way, i.e. passing a Threshold Analysis without the need for supplementary user studies or design changes. To achieve this, it is imperative that the design team fully understands the user interaction with the device, can identify and isolate the features that are key to that interaction, and can define the characteristics of those features that lead a user to act in a particular way. By understanding these elements, the team can assess the non-critical features of the device against any known use problems to propose design changes that could deliver an improved user experience. Human factors teams should also be aware of any changes in patient demographics from the reference device – for example, an aging population, or an increase in prevalence of other conditions in some territories (diabetes, visual impairment), can change the typical characteristics of a target patient for some devices.

There are strong dependencies between the work of the human factors engineers and the device designers to ensure that usability is preserved in light of other changes that may be made. The most significant of these is the avoidance of existing IP. It can be the case that a critical feature that defines a user step is protected by an enduring patent. In these instances, an experienced, integrated team can identify a solution that navigates the IP whilst minimising the impact on the user and the regulatory approach.

PRODUCT DESIGN

The industrial design of any device serves three important functions: it creates desirability; it defines the way the patient interacts with the product and; it also reinforces the patient's interpretation of the IFU. However, the styling, form factor or colour scheme can be protected under design rights and so the very features that encourage correct and consistent use of the device may be impossible to replicate.

Designers, therefore, need to tread a fine line to enable users to apply their knowledge of the reference device to use the generic whilst at the same time creating a new identity. There are many factors that will influence the product design. For example, there may be a desire to incorporate existing branding to identify it as part of a particular product family. There may also be opportunities to create a design that enhances user perceptions of certain characteristics, e.g. quality or robustness. Designers should also be aware of changes in user preference since the launch of the reference device. For example, patients may prefer their devices to have more of a consumer product feel to them, or for their rescue medication to stand out easily in a cluttered handbag.

Achieving this blend of originality and consistency with the reference device is a challenge for design teams. It involves close working relationships with everyone from usability experts (to understand the user experience), to engineers (so that form and function complement each other), to marketing representatives (such that the generic device's positioning in the product portfolio is well communicated).

PERFORMANCE

Device performance is non-negotiable. The foundation of the generic market is that the combination product must deliver the same benefit to the patient as the reference device. This

means that the device must work in tandem with the drug to match the efficacy of what has gone before, and this means that any differences in the characteristics of the drug are likely to require a different delivery mechanism.

There are a number of reasons why there may be differences between the reference and generic drug formulations. The most significant of these will be differences in the infrastructure and processes used by the drug manufacturers, and their suppliers, that could result in different stability requirements, different preservatives or even different dyes being used in the excipients. The important point is not that there are differences but that those differences are understood and their implications for the device can be determined.

The main function of the device design is to deliver the drug into the patient in a way that can be absorbed into the body. Using DPIs as an example, this involves matching the device resistance, fine particle fraction and evacuation performance of the reference device by creating a deagglomeration engine and air path that work for the specific formulation. There are other characteristics of the medication that will need to be considered too: the moisture, light or time sensitivity of the drug will impact the way it is stored and presented to the patient; the electrostatic properties or viscosity may affect materials choices; and all of the above will need to be considered against a backdrop of existing IP. This means that even if the formulations are identical it is likely that some innovative thinking will be required to match performance.

OTHER CONSIDERATIONS

It is not just the drug that will drive changes in the internal design of a generic device. Recent regulations mandating the integration of a dose counter may introduce new requirements for some devices. It may be decided that device robustness could be improved, or drug wastage could be reduced, by changing features within the device. Existing IP may force an entirely new internal mechanism. Additionally, there may be opportunities to improve the user experience by making the operation smoother, or manufacturability by making it simpler, which should be considered in the context of development time and risk.

HOW TO DELIVER 'TARGETED INNOVATION'

Delivering 'Targeted Innovation' is not just about understanding where to explore novelty and where to replicate an existing feature. It is important to have a broad experience of the relevant market in order to navigate a very congested IP landscape and to avoid the common pitfalls that device designers encounter.

Of course, it is not just the designers who are critical to the development of a generic device. Without the right testing infrastructure and expertise, it is impossible to demonstrate equivalence and the engineering teams will effectively be designing blind. These testing and feedback mechanisms include particle size measurement techniques using Next Generation Impactor (NGI) and Spraytec equipment; the use of load cells and cycling rigs to characterise the physical performance; and well designed, conducted and reported studies to understand the user interaction. By integrating these testing activities into the device development there is a continuous flow of feedback into the process which ensure an optimised and robust design.

The final piece in the generic jigsaw is the project leadership. Setting the tone and the direction for a generic device development requires a deep understanding of the requirements of the device, the relevant regulations and standards, and how to balance these with the need to optimise speed and cost. Knowing when to encourage creativity to solve a problem, when to reign in the originality, and where there is a commercial opportunity is the crux of a development that negotiates the conflicting requirements of 'the same but different'.

It is vital to have all of these skills working as a cohesive team. The interdependencies between the requirements management, engineering, product design, human factors and the design for manufacture - all brought together in a feedback loop of testing, user trials and design review - are key to delivering a successful product, quickly and efficiently.

CONCLUSION

The generics market continues to thrive and developing a generic device can bring great rewards. A combination of market knowledge, usability expertise, design and engineering skills can help to strike the right balance between reverse engineering and innovation. Bringing those capabilities together on a foundation of regulatory knowledge and thorough device and user testing can be the difference between success and a rejected application.

The generics market presents some unique challenges. Understanding where and when innovation is necessary and targeting it at the right device functions to make an impact can help companies capitalise on these specific, generic opportunities.

GLOSSARY

ANDA 505(j) ..... **Abbreviated New Drug Application**
A regulatory submission proposing a product that has certain identical characteristics to a previously approved product

API ..... **Active Pharmaceutical Ingredient**
The chemically-active component of a drug product

Combination Product ..... **A product that involves a medical device and a drug/biologic**

Device ..... **A method of administration of a drug**
e.g. a dry-powder inhaler or a pre-filled syringe

DPI ..... **Dry Powder Inhaler**
A device to deliver inhaled drug in powder form into the lungs

Excipient ..... **The chemically-inactive component of a drug product**

Generic ..... **A product that is the subject of an ANDA submission**

IFU ..... **Instructions For Use**

IP ..... **Intellectual Property**
i.e. patents

MDI ..... **Metered Dose Inhaler**
A pressurised inhaler that delivers a specific amount of medication into the lungs

NGI ..... **Next Generation Impactor**
An item of test equipment to characterises particle size distribution in a sample of air or gas

RLD ..... **The Reference Listed Drug**
i.e. a previously approved product that is cited by the generic version

Spraytec ..... **Droplet size measurement using laser diffraction**

For more information, or to discuss how this approach could fit your business, please contact:

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About Cambridge Consultants

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With a team of more than 800 staff in the UK, the USA, Singapore and Japan, we have all the in-house skills needed to help you – from creating innovative concepts right the way through to taking your product into manufacturing. Most of our projects deliver prototype hardware or software and trials production batches. Equally, our technology consultants can help you to maximise your product portfolio and technology roadmap.

We're not content just to create 'me-too' products that make incremental change; we specialise in helping companies achieve the seemingly impossible. We work with some of the world's largest blue-chip companies as well as with some of the smallest, innovative start-ups that want to change the status quo fast.

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