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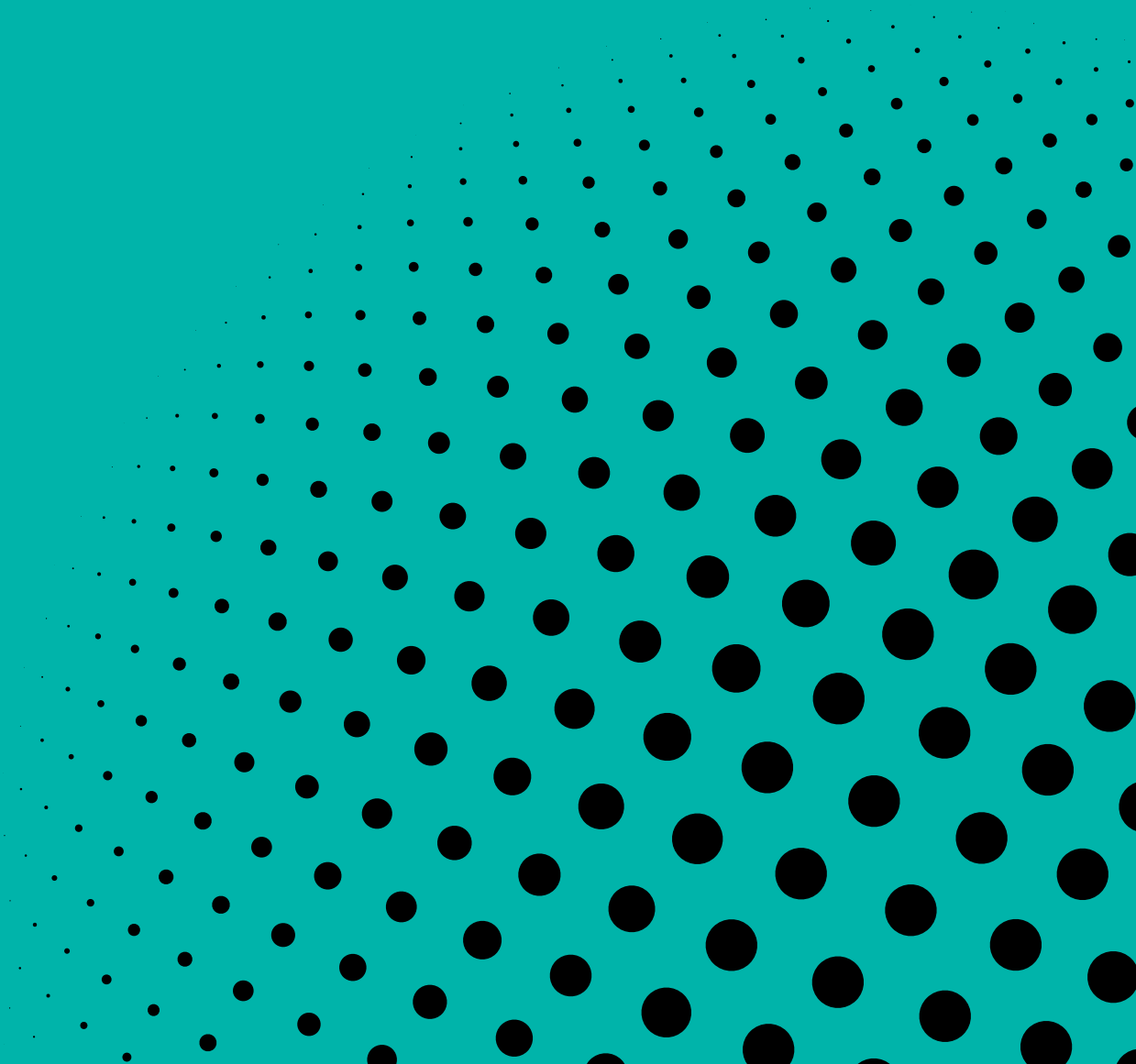
"(b)(2) or not to be, that is the question"

Strategies for patient-centric differentiation through the USFDA 505(b)(2) pathway

Whitepaper December 2021



USFDA 505(b)(2) submissions can be advantageous because they can often lead to faster routes to approval when compared to traditional development pathways while creating new, differentiated products with commercial value. Jamie Unwin, Commercial Insight Officer at Nanoform, sat down with Timothy Pang, Executive Director, Pharma Consulting at Informa Pharma Custom Intelligence to discuss unique performance insights from the last three years for key molecules approved by this pathway, and to reflect on how patient-centric drug development has generated commercial value. Further, they discussed their view on the future direction of the industry with regards to the adoption of 505(b)(2) approaches, and the key technological advances that can empower these.

Read on to find out more.

Jamie Unwin
Commercial Insight Officer
at Nanoform

Timothy Pang
Executive Director, Pharma
Consulting at Informa Pharma
Custom Intelligence

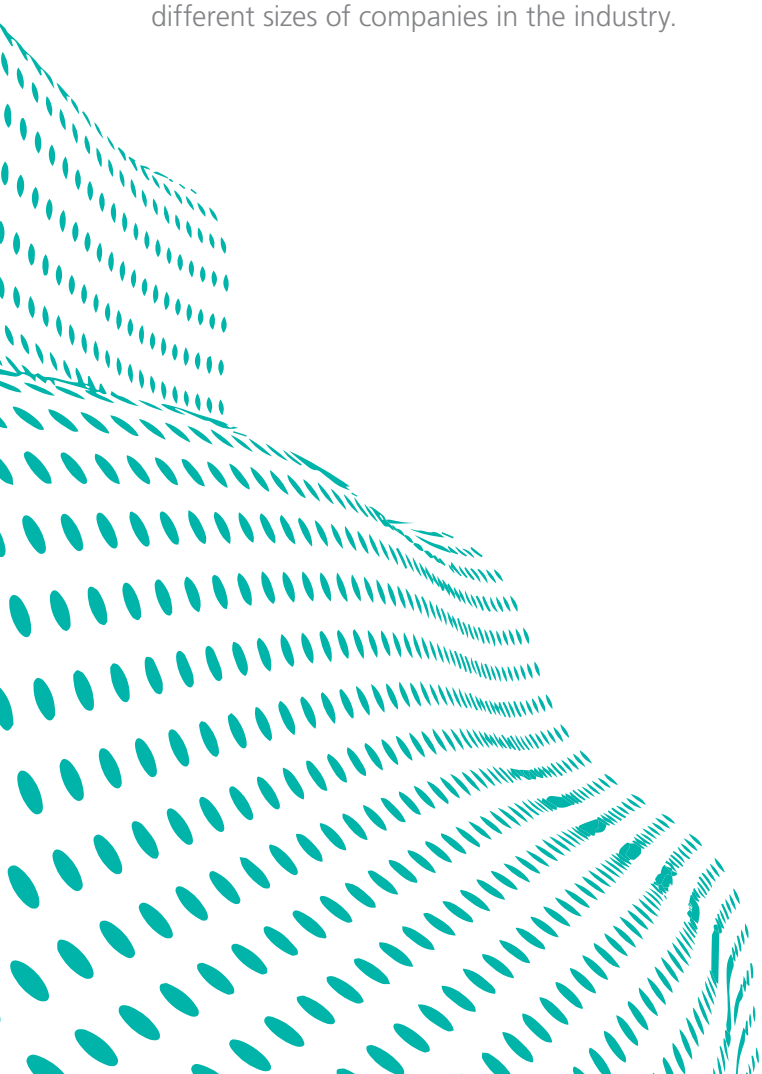
The evolution of 505(b)(2)

505(b)(2) submissions can be advantageous because they can often lead to a faster route to approval and increased opportunities for patient centricity. This has led to the 505(b)(2) drug pathway evolving as a preferred regulatory and commercial strategy.

Timothy Pang, Executive Director, Pharma Consulting at Informa shared his insights into the evolution of the 505(b)(2) pathway, highlighting that there is a significant difference now compared to even just five years ago. Indeed, 10 or 15 years ago, there was a perception in the industry that the 505(b)(2) route was less innovative, given that it doesn't involve new drug discovery.

Since that time, the volume of 505(b)(2) applications has expanded significantly, with the number of applications now exceeding that of 505(b)(1) applications.

In the past, 505(b)(2) firms tended to be relatively small, with larger players perhaps less active in that area. Some of the increase in volume we can now see can be accounted for by smaller firms, but also reflects increasing interest across different sizes of companies in the industry.



What are the advantages of 505(b)(2)?

In terms of the development of the lifecycle, there are clearly many advantages to 505(b)(2) in terms of the length of the development process. Another trend that can be observed in the industry is the increase in new chemical entities (NCEs) as candidates for the 505(b)(2) pathway. These type 1 approvals benefit from a period of exclusivity that is longer than more stereotypical reformulation-type 505(b)(2) applications, which likely contributes to interest in the industry.

Why is 505(b)(2) adopted less by Big Pharma?

Timothy went on to share his thoughts on some reasons why Big Pharma is less dominant in the 505(b)(2) space and whether that might change in the future. He explained that there are some natural reasons for this. While the 505(b)(2) market is certainly making a non-trivial contribution, in terms of average product revenues this might still be somewhat below the targets Big Pharma has for its pipeline. There is also a long legacy of drug discovery in Big Pharma, and a deeply rooted way of thinking about drug development in terms of drug discovery of new chemical entities, or new mechanisms or targets. Nevertheless, Big Pharma has always been heavily involved in 505(b)(2) drugs in certain areas.

Historically, this has been in women's health in oral contraceptives, in dermatology and particularly topical dermatology. These markets have always been and likely will always be primarily 505(b)(2) markets. Most topical dermatology drugs are reformulations. While they might be reformulated to a cream, gel or ointment, in these cases we are often working with molecules that have been around for a long time. The same thing is true of areas such as hormone replacement therapy, oral contraceptives and other areas of women's health.

As a result, large franchises and pharmaceutical companies have been built on the 505(b)(2) pathway. While oral contraceptives or hormone replacement therapies may not be considered the hottest corners of the pharma market, Timothy explained they are products that have an important impact on patients and have, over time, generated significant revenue in the industry.

A commercial perspective on how 505(b)(2) has changed in the industry

Jamie Unwin, Commercial Insight Officer at Nanoform, expanded on the increasing proportion of drug approvals on the 505(b)(2) pathway for drugs classified as type 1 NCEs. From 2018 to 2020, he explained that the data shows that the proportion of type 1 NCE approvals on the 505(b)(2) pathway has increased from just 2% to around 18% in 2020 (see Figure 1) and can be expected to continue increasing from that baseline.

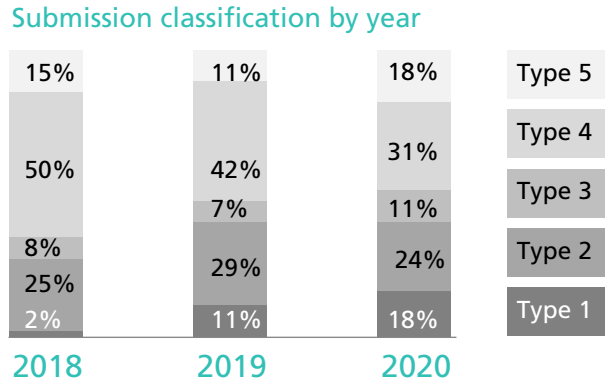


Figure 1. Submission classifications of 505(b)(2) approvals by year

Looking at IQVIA sales (see Figure 2), it is fclear that 505(b)(2) brands make a significant contribution to the US Pharma market, totaling $2.2 billion in US sales in the second quarter of 2021. That contribution is spread across a large number of brands, but 31% of the sales are from just two products. Individually, 505(b)(2) brands typically achieve modest sales, generating on average $8 million per quarter.

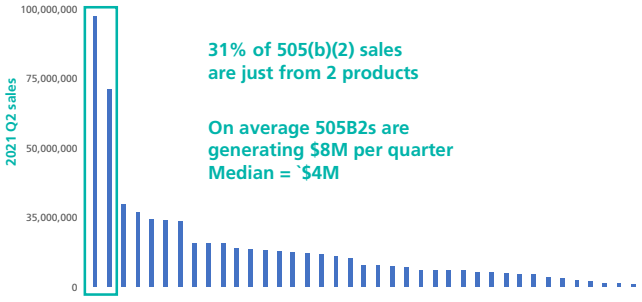


Figure 2. IQVIA sales performance analysis (approvals 2018-2020)

Looking at this from a commercial perspective, the question then becomes – is this a low value market? Would an Abbreviated New Drug Application (ANDA)-type strategy create better returns? And finally, just how competitive are 505(b)(2) brands in these markets?

To answer this, Nanoform completed a cannibalization analysis (Figure 3) and in a simple form, looked at the share of market dollars for all presentations of a particular molecular type. While this is subject to the usual caveats of dealing with IQVIA data, rebates and discounts, it nevertheless generates useful insights. When looking at the share of 505(b)(2) molecules as a percentage of all other molecule sales, including branded and generic, it can be seen that 505(b)(2) brands punch well above their weight.

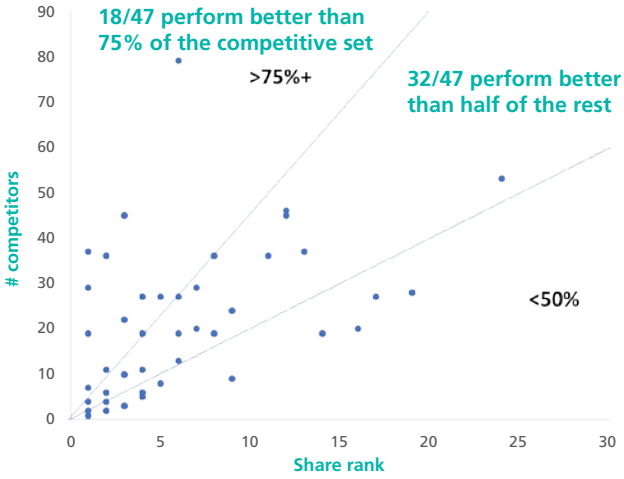


Figure 3. Cannibalization analysis (molecule for molecule)

Out of those analyzed, 32 out of the 47 analyzed performed better than half of their competitive sets, and 18 out of 47 performed in the top quartile. Even though these are small markets, there is evidently the opportunity to be highly competitive within them.

A good case study is a new micronized abiraterone drug, YONSA®, approved by the FDA on the 505(b)(2) pathway in 2018 and launched in face of 16 generic competitors. It was differentiated based on dosing simplicity and food effects. What can be seen by the data in Figure 4 is that even though YONSA® addresses only 2% of patients or 2% of market volumes, through clever market access and pricing strategy and clinical differentiation,
it was able to represent about 7% of market dollars. The drug offers an excellent value density.

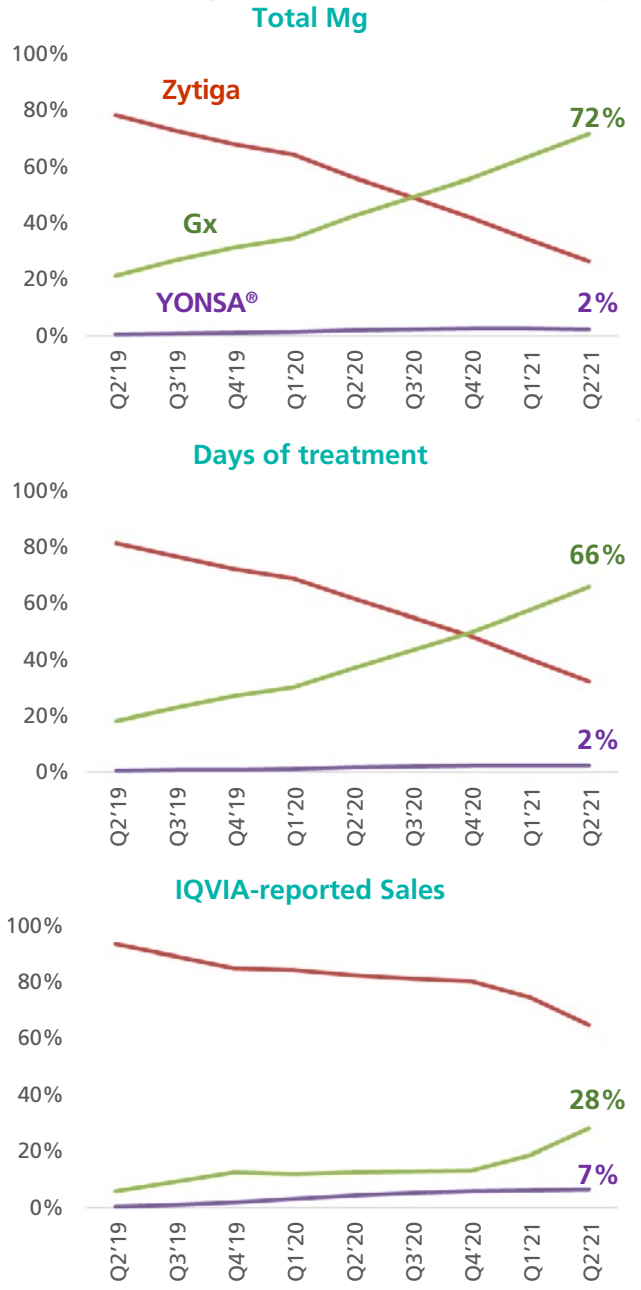


Figure 4. Performance of YONSA® in comparison with Gx and Zytiga

However, while differentiation is important, alone it is not enough. Jamie emphasized the importance of a continued commercial push. 505(b)(2) brands react exactly the same way as NCE brands, with the brands that gain more market share one or two years after launch being those that have a very strong commercial push behind them. Enduring consideration of market access and commercial activities is critical for long-term launch success – see Figure 5.

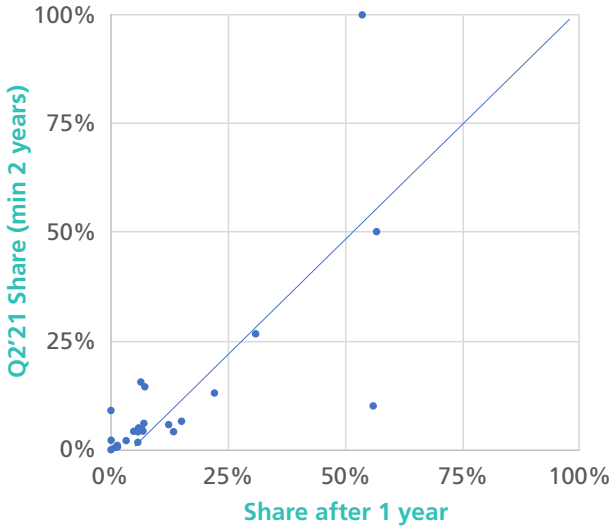


Figure 5. Enduring consideration of market access and commercial positioning activities is critical for long-term 505(b)(2) launch success

Emerging trends in 505(b)(2) and wider drug development

Jamie went on to highlight trends that he has noticed among Nanoform's own clients. He pointed out that fewer people come to Nanoform talking about only 505(b)(2) drugs, but are instead looking at life cycle management (LCM) at the earliest stage and looking at their portfolios as a whole. Another key trend Jamie shared was an absolute focus on the empowerment of patient centricity, as well as a demand for predictions regarding whether an approach will succeed.

Looking at each of these in turn, firstly from an LCM point of view, Jamie explained that there has been a shift from looking at whether it's possible to increase a specific molecule's bioavailability using Nanoform's approaches, to looking at whether Nanoform can empower patient-centric lifecycle management. Partners are beginning to look beyond their first launch, and instead look ahead at the incremental formulation steps that need to be taken and the fundamental particle aspirations that need to be built to make the drug work for patients.

A key trend is a desire to move away from an approach that involves setting a closed target product profile (TPP) for a molecule, with just one formulation and one indication, and then worrying about LCM later. Instead, there is a desire to look at the one aspect that is needed to conceptually empower any formulation route. At Nanoform, Jamie explained that the key ingredient is nanoparticles. By building fundamental particles with infinite possibilities that are highly bioavailable, there is no closed trajectory and companies can decide later down the line to formulate them to address many different patient-centric needs.

Finally, Jamie expanded on the demand for predictive certainties to understand when a proposed approach is going to fail fast. With R&D budgets more squeezed than ever, AI-based platforms such as Nanoform's STARMAP® platform are of great benefit to give pharmaceutical companies an understanding of whether a technology can work before even opening the lab doors.

Looking to the future

Looking to the future, Timothy shared his perspective of 505(b)(2) drugs as "the gift that keeps on giving." The pathway has evolved considerably over time, and the amount that can be accomplished on the 505(b)(2) route is constantly changing – a testament to the innovativeness of the industry. Timothy explained that he sees the 505(b)(2) pathway as constantly expanding into new areas. These include being applied to different types of molecules, as well as to different types of companies or business models; not only formulation or platform technology companies, but a wide variety of firms that find they can generate significant profits in this space.

Jamie expanded on this by highlighting that the regulatory flexibility granted by the FDA's 505(b)(2) pathway is helping to breed industrial ambition from a formulation point of view. The heterogeneity of formulation routes for products in the 505(b)(2) space is significantly greater than it was 3-4 years ago, suggesting exciting times ahead from a technical, regulatory and particle engineering point of view.

If you would like to learn more about the 505(b)(2) pathway and discover the opportunities created by Nanoform's game-changing nanoparticle engineering technologies, get in touch.

Jamie.Unwin@nanoform.com

About us

Nanoform is an innovative nanoparticle medicine enabling company. Nanoform works together with pharma and biotech partners globally to provide hope for patients in developing new and improved medicines utilizing Nanoform's platform technologies. The company focuses on reducing clinical attrition and on enhancing drug molecules' performance through its nanoforming technologies and formulation services. Nanoform's capabilities include GMP manufacturing, and its services span the small to large molecule development space with a focus on solving key issues in drug solubility and bioavailability and on enabling novel drug delivery applications.

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Contact us
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potential of
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nanoform.com
info@nanoform.com
+358 29 370 0150
@NanoformF
Nanoform

Cultivator II
Viikinkaari 4
FI-00790 Helsinki
Finland