R&D and clinical trial strategy for 505(b)2 asset development to advance broader clinical impact

Could the evolving 505(b)(2) pathway offer biotech companies a faster and more strategic route to bringing internationally developed therapies – and new indications – to the US market?

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Drug approvals via 505(b)2 are far from a new phenomenon today. However, compounds most known in this context are usually line extension products of already approved medications, mostly at additional dosing options or with new delivery or application systems.[1]

Few are aware of the increasing use of the 505(b)2 pathway to introduce innovative medications into the US market. Metformin, arguably the most common diabetes compound used, is one such example.[2,3] Approved in 1999, Metformin was introduced 11 years after its EU approval. The common narrative holds that an investment infrastructure, innovation-centric thinking and the commercial propects of US market introduction have turned the US into the inevitable first market for introducing innovative medications. That narrative, while still largely valid, has nevertheless seen several exceptions, most recently during the COVID-19 pandemic.

It is also true that, with rapid evolution in research and therapeutic compound development, some treatment options see the light of day in circumstances that are not optimal. Thalidomide, initially developed for nausea and vomiting during pregnancy with dramatic consequences in Europe especially, started a second therapeutic life as one of the more successful treatments of multiple myeloma.

There are few source markets for international drug transfers into the US, as the regulatory and clinical trial development standards have to be adequate for the US Food and Drug Administration (FDA) to accept an application under 505(b)2. Most international drug transfers originate from the EU.

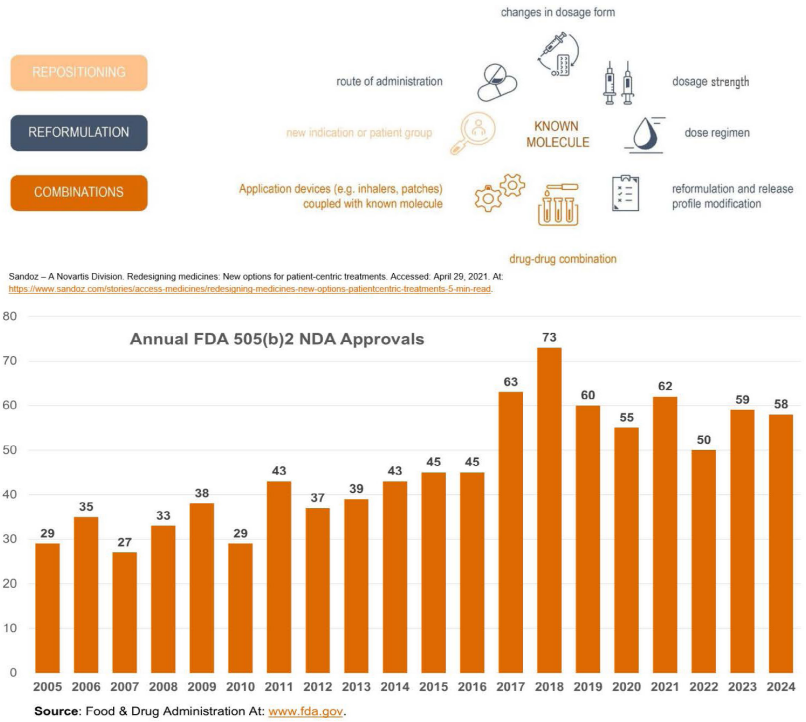
Molecules, mechanism of action and pleiotropic effects

Not infrequently, as in the case of metformin, the compound applying for approval in the US under 505(b)2 has already been in clinical use for some time. If the mechanism of action (MoA) is well understood and demonstrates utility beyond the initial core indication – independent of the MoA supporting use in that first indication – this 'pleiotropic effect' can serve as the basis for additional clinical trial development. If additional clinical evidence already exists that demonstrates potential use in other clinical indication areas, it can further support any additional new drug approval (NDA) applications to be developed within the market exclusivity period provided by the first approval – either again under 505(b)2 or another applicable FDA approval pathway. Viable commercial opportunities for additional indications depend on market size and reimbursement scenarios. But provided that the analysis of these factors is favourable, it can be challenging, especially for smaller biotech companies, to take advantage of these prospects, given the limited market exclusivity period provided even in the best-case scenarios under 505(b)2. This article will discuss how – if such opportunities exist for any given sponsor – to approach them in the context of the original 505(b)2 approval and R&D process.

Clinical trial demands for NME approval under 505(b)2 for international product transfers

The benefits of the 505(b)(2) pathway are compelling and include shorter clinical development timelines, greater regulatory predictability, potential periods of market exclusivity and significantly lower costs. International compound transfers under 505(b)2 are usually medications not yet approved in the US and are thus considered new molecular (NMEs) or clinical entities (NCEs). The FDA will frequently accept already available clinical trial results – if conducted within the standard parameters the agency sees as acceptable – and the burden for additional clinical trials is therefore

Figure 1. Types and Volume of 505(b)2 Approvals[1,2]



considerably lower by comparison. Critical here is a bridging trial to link the already existing clinical data of the reference label product (RLD) to the 'new' compound seeking approval in the US.

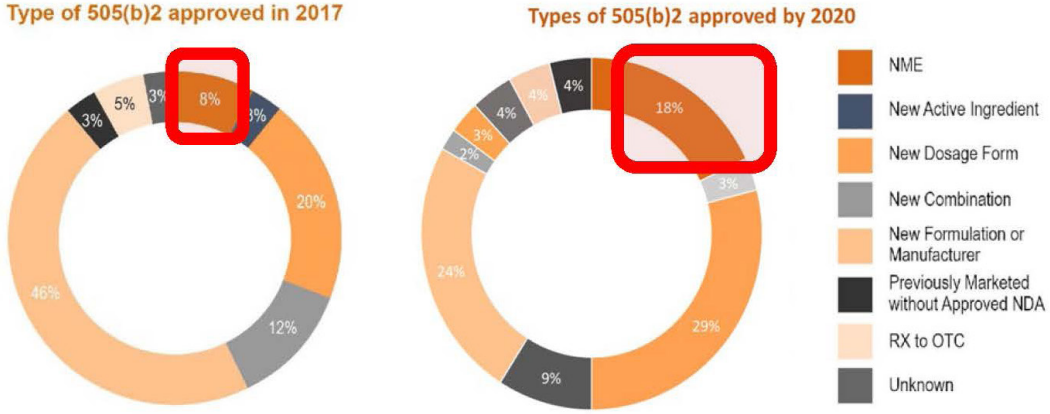
For transfer compounds that do not change dosing and application, it can be as low as conducting a phase 1 bioequivalence trial. For 505(b)2 compounds that include some innovative elements that differ from the RLD (ie, new galenic formulation, dosing or application method changes, combination products) and apply with a bioavailability trial, since the pharmacokinetics (PK) and pharmacodynamic (PD) parameters will be different from the reference product, the requirements also frequently include a phase 3 safety and efficacy trial (see **Figure 2**). But that also means that the first clinical indication for such a medication is usually their core indication. Market exclusivity for an NME under 505(b)2 is five years for a regular or seven years for an orphan disease indication. It is important to note that market exclusivity is separate from – and, in the case of additional indications under the 505(b)2 pathway, may be granted on top of – intellectual propety protection developed by the sponsor of the new drug.

Many products developed as modified or controlled-release versions of older immediate-release products have specific requirements. Clinical development for a controlled-release 505(b)2 typically includes: a food-effect study comparing fed and fasted PK of the new formulation; a multiple-dose steady-state PK study establishing the accumulation profile; a bioequivalence or PD equivalence study relative to the reference product. If reduced dosing frequency is included as a labelled claim, supportive adherence or tolerability data may be required, often derived from phase 3 trial evidence or patient preference studies, and potentially supported by comparative label claim data from existing literature.

Clinical trial demands for additional indications

If the compound has inherent additional clinical indication potential, the original market exclusivity period for the first indication may just be long enough to conduct additional clinical trial development. Any new indications would, in effect, extend the exclusivity period. That, however, requires a lot of strategic and clinical trial planning effort to chose the best development and commercial

Figure 2. Approved 505(b)2 Type Breakdown



roll-out approach. If a potential additional indication stays within the approved core indication – for example, to address specific patient sub-populations – a simple phase 3b clinical trial approach may suffice. If the new indication is outside of that window, the critical evidence standard usually applies and requires – in addition to necessary proof-of-concept clinical trials – phase 3 trial development to be eligble for approval (see **Figure 1**). Close cooperation with the FDA is instrumental in shaping the optimal design of such a clinical development programme.

Time saving-options under 505(b)2

Several options are available to help make effective use of the limited time, with one of the most critical being the conduct of a pre-investigational new drug (IND) meeting with the FDA to discuss both eligibility and clinical trial requirements for the first indication. In this context, FDA guidance will allow for a clear pathway to IND filing and eventual NDA approval success. If the compound requires additional preclinical development, FDA can provide a waiver that allows the sponsor to conduct these studies after initial approval or at least further into the overall clinical development process.[4] This approach is more likely to be approved by the FDA review division if the reference product has been in clinical use for some time in the originating country of first approval. One such example is the approval of lofexidine, approved in 2018 for opioid withdawal.[2,5,6] The FDA review division postponed requested additional toxicology studies for the compound, which was orginally approved in the UK in 1992, until after approval based on the already availble data and the long human use history.

Meetings with the FDA review division can be conducted for additional guidance such as – again – a pre-IND meeting or Type C meetings to gain additional input. The FDA can also provide ongoing guidance via its NextGen portal through Advice/Information Requests. The FDA review divisions can be quite responsive and will answer within a short turnaround time of 60 days to outline expectations for clinical trial design, trial endpoints, patient population criteria, analytical methods, etc. If phase 2 studies are required, the FDA can allow the combination of phase 2 and 3 trial phases – often seen in oncology trials – to save time and resources. If the sponsor does not have regulatory resources available in-house, it is advisable to conduct these meetings in partnership with a specialised consultancy, given the complexity and communications requirements the FDA expects. Chemistry, manufacturing and controls (CMC) is another critical element. The number one reason why 505(b)2 NDA applications fail is due to issues with the manufacturing process. Preparing a sound CMC process with ongoing input from the FDA review division is critical and can save the development programme from delays and the NDA application from failure.

Summary and conclusions

The 505(b)2 pathway has evolved considerably over the past decades and now includes a number of different types. International product transfers are one of the more complex 505(b)2 applications, especially if the application involves innovative updates to the RLD. Nonetheless, the 505(b)2 pathway platfrom has evolved enough regulatory flexibility that it allows for a development of the full clinical and commercial potential of such a transfer compound even if that includes additional clinical indications. For small biotech companies developing such a compound regulatory clarity – which the FDA can provide via several routes of communication – this can significantly aid in the process of fundraising for such R&D programmes.

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