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Teaser New drug applications (NDAs) using the FDA 505(b)(2) regulatory pathway can streamline and reduce nonclinical drug development requirements while potentially maintaining marketing exclusivity.

Streamlining nonclinical drug development using the FDA 505(b)(2) new drug application regulatory pathway

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In the USA, drugs are approved by the FDA by three main regulatory pathways: (i) 505(b)(1) new drug applications (NDAs); (ii) 505(b)(2) NDAs; and (iii) 505(j) abbreviated NDAs (ANDAs). The appropriate pathway depends on the active ingredient, already approved drug products, drug formulation, clinical indication, route of exposure, among other factors. The 505(b)(2) NDA pathway is a regulatory approval pathway that allows sponsors to use existing public data in lieu of conducting studies; thus, potentially offering significant drug development and marketing advantages. Nonclinical testing programs for 505(b)(2) submissions are often reduced and, in some cases, are not even required. This paper provides an overview of the 505(b)(2) regulatory pathway with a focus on how nonclinical programs can be streamlined and accelerated.

Introduction

In the USA, new drug products are approved by the FDA by three main regulatory pathways: 505 (b)(1) and 505(b)(2) new drug applications (NDAs), and 505(j) abbreviated NDAs (ANDAs). The focus of this paper is on 505(b)(2) NDAs that offer potential drug development and marketing advantages not afforded by the other two pathways. Nonclinical testing programs for 505(b)(2) NDA submissions are often reduced and sometimes not even required. For the purposes of this paper, 'nonclinical' refers to *in vitro* and *in vivo* testing conducted to support the nonclinical pharmacology, pharmacokinetic (PK) and toxicology sections of an NDA (i.e., modules 2.4, 2.6.1–2.6.7 and 4). The primary purpose of this paper is to provide examples of nonclinical developmental programs appropriate for the 505(b)(2) NDA submission pathway so that drug developers can understand nuances of the nonclinical requirements for 505(b)(2) NDAs. The approval of new drug products in the USA is codified in the Federal Food, Drug and Cosmetic Act (Federal FD&C Act), as amended [1]. The Federal FD&C Act prohibits the marketing of a new drug unless that drug meets certain safety and efficacy standards that are ultimately determined by the FDA during the NDA or ANDA drug review and approval process [1–3].

Brand-named drugs can be approved either through a 505(b)(1) NDA or a 505(b)(2) NDA [4,5]. 505(b)(1) NDAs are used for drugs that have been discovered and developed with sponsor-conducted studies; these are often for new molecular entities and new chemical entities (NMEs,

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NCEs) that have not been previously registered in the USA [5]. By contrast, a 505(b)(2) NDA contains full safety and effectiveness reports, including nonclinical information required for approval; however, at least some of the information required for NDA approval comes from studies not conducted by or for the applicant [6]. The 505(b)(2) NDA pathway was created, in part, to help avoid unnecessary duplication of studies, including nonclinical studies, already performed on an existing or previously approved drug(s) [e.g., a listed drug (LD)] [7]. The focus of this review is primarily on 505(b)(2) NDAs that rely on information from an LD because the majority of 505(b)(2) NDA approvals rely on nonclinical data from an LD in addition to sponsor-conducted nonclinical studies and published nonclinical information; however, some 505(b)(2) NDA approvals do not utilize an LD (e.g., they rely solely on published nonclinical information). To provide perspective and background information related to the relevance of the 505(b)(2) pathway in drug development, Fig. 1 provides a breakdown of the 505(b)(2) NDAs that were approved in 2017 by therapeutic area and Table 1 provides a comparison of the number of 505(b)(1) NDA versus 505 (b)(2) NDA approvals from 2003 to 2017.

In the case of NDAs for products that are compositionally equivalent versions of an existing approved product, generic drugs also enter into the approvals paradigm. Generic drugs are typically approved via an ANDA under Section 505(j). Generic drugs rely on much of the safety and efficacy data submitted by the reference listed drug (RLD) and must meet strict criteria that establishes the similarity to the RLD, such as chemistry, manufacturing and controls (CMC) and bioequivalence [2,8]. Specifically, an RLD is an approved drug product to which new generic versions are compared and the new generic must be shown to be bioequivalent to the RLD to be approved. In the 505(b)(2) setting, an RLD is generally referred to as the LD.

The 505(b)(1) NDA pathway requires a great deal of time, resources and capital, and has a high failure rate [9]. The advantage of a 505(b)(1) or 505(b)(2) NDA is that, in addition to any applicable patent protection(s), the FDA can grant periods of market exclusivity. The 505(j) (generics) ANDA pathway requires significantly fewer resources and capital and has a high success rate. However, patent protection often does not exist, FDA market exclusivity provisions for ANDA products are very limited and drug pricing considerations often result in limited profit margins. The 505(b)(2) NDA pathway offers potential advantages not afforded by the other two pathways: (i) nonclinical and clinical programs are often reduced compared with 505(b)(1) NDA programs; and (ii) approval success rates are typically greater than for 505(b)(1) NDA programs because safety and efficacy profiles of the drug substance are typically well-characterized. The main disadvantages of a 505(b)(2) program, however, are: (i) a sponsor's CMC program is accelerated compared with a 505 (b)(1) NDA program because the to-be-marketed (e.g., commercial) product should be used in sponsor-conducted nonclinical and clinical studies; (ii) other companies can target the same opportunity and gain approval first, thereby effectively forcing the other 505(b) (2) NDA product to submit through the generic, 505(j) NDA regulatory pathway; and (iii) the patent and exclusivity provisions of the LD(s), if referenced, can affect approvability.

The 505(b)(2) NDA submission pathway for new drug products provides a mechanism that allows the applicant of the new drug product to reference the published literature and, potentially, the FDA's findings of safety and/or effectiveness (e.g., as listed on the LD product's approved labeling, if used) to fulfill various registration requirements. From a nonclinical perspective (inclusive of sponsor-conducted *in vitro* and *in vivo* studies to support the nonclinical sections of an NDA), these sources of nonclinical safety data can reduce or even eliminate the amount of nonclinical testing required to support clinical trials and/or full registration of the new drug product. As part of the 505(b)(2) NDA development process, it is important to meet with the FDA early during development [e.g., a pre-investigational new drug application (PIND) meeting] because there can be varied and different options available to address the nonclinical requirements of a 505(b)(2) NDA drug development program. Meeting with the FDA affords the sponsor the opportunity to outline a proposed nonclinical program to the FDA and obtain their feedback and agreement on various program elements.

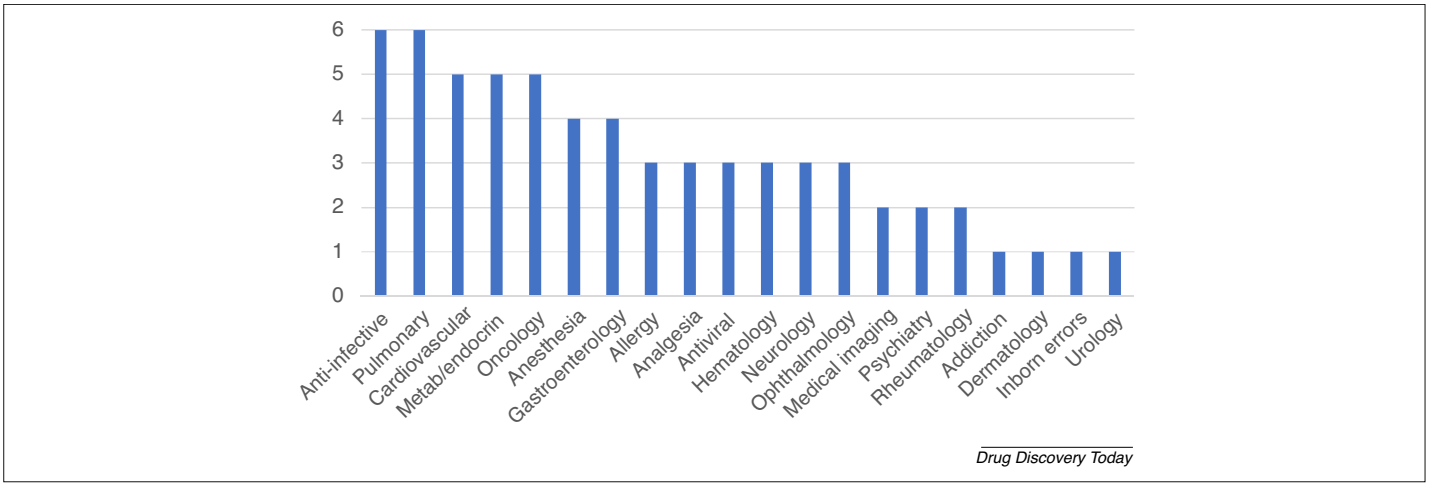

FIGURE 1

Comparison of the number of 505(b)(2) NDA approvals by therapeutic area in 2017. One NDA (208400) was counted twice because it was approved for two indications in two different therapeutic areas (oncology and rheumatology). Source of data was Camargo Pharmaceuticals Marketing Intelligence. Abbreviation: Metabo/endocrin, metabolism and endocrinology.

TABLE 1

Comparison of the number of 505(b)(1) NDA versus 505(b)(2) NDA approvals from 2003 to 2017

Pathway	Year														
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
505(b)(1) NDA	47	58	44	53	36	44	42	47	36	46	49	51	56	40	54
505(b)(2) NDA	19	44	30	35	30	33	38	29	43	37	39	43	47	47	65
Total	66	102	74	88	66	77	80	76	79	83	88	94	103	87	119

Source of data was Camargo Pharmaceuticals Marketing Intelligence.

Applicability of the 505(b)(2) NDA pathway and associated nonclinical information

The FDA has issued a draft guidance that helps sponsors determine the types of drug products are covered by 505(b)(2) NDAs [7]. A 505(b)(2) NDA contains full reports of investigations of safety and effectiveness, where at least some of the information (nonclinical and/or clinical) required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. For example, the applicant can rely on the FDA's finding of safety and/or effectiveness for an LD as provided in the approved LD labeling (also known as a package insert), such as nonclinical reproductive and developmental toxicity, genotoxicity and carcinogenicity information. However, the drug product must share characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication and/or conditions of use) in common with the LD but at the same time be different enough to not qualify for the 505(j) (ANDA) pathway (e.g., the new drug product could use a different salt form of the drug substance and have a different clinical indication).

To reference the FDA's findings of safety and/or effectiveness for the LD, a scientific bridge must be established between the sponsor's drug product and the LD. This is typically done by generating clinical comparative bioavailability data; however, nonclinical comparative bioavailability and/or distribution data are sometimes also required. With most 505(b)(2) NDA drug products, there are differences relative to the LD (e.g., different salt form of the drug substance, different clinical indication, varying excipients, different route of exposure, altered duration or frequency of dosing, etc.). To support these differences, nonclinical and/or clinical data must be generated or referenced to support these differences.

Information that can be relied upon

The strength of the 505(b)(2) NDA pathway is that publicly available nonclinical and clinical information can be relied upon for drug approval and can greatly reduce the nonclinical and clinical development requirements for supporting clinical trials and NDA approval. The following types of information can be relied upon for a 505(b)(2) NDA.

- Any specific information necessary for approval (e.g., published nonclinical and clinical studies) that is obtained from literature or from another source to which the applicant does not have a right of reference. This applies to studies that are considered pivotal for determining the safety and/or efficacy of the new drug product, not general published references or studies that provide background information or are just supportive.
- The FDA's previous finding of safety and/or effectiveness for a drug. This is embodied by the general approval of the LD and the approved labeling for the LD. Typical nonclinical information provided in the labeling that can be relied upon is often reproductive and developmental toxicity, genotoxicity and carcinogenicity studies. This approach was implemented to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug.

Regarding the FDA's previous finding of safety and/or effectiveness, a common misconception is that FDA Summary Basis of Approvals (SBAs) (e.g., the pharmacology and toxicology reviews for a drug product NDA) can be relied upon for a 505(b)(2) NDA. SBAs are technically considered opinions of the individual FDA reviewers responsible for authoring various SBAs and, therefore, are not considered to be the FDA's final determination regarding a drug product and cannot be relied upon for an NDA. However, SBA content can provide data considered sufficient to support the safety of a product [e.g., a 505(b)(2) NDA drug product with an LD identified] intended for introduction to the clinical setting. The SBA information can have fundamental safety information, appropriate for justification, in the conduct of new clinical studies for an investigational new drug (IND) but not an NDA.

For NDA approval, because only nonclinical studies listed in the LD-approved labeling can be relied upon (as nonclinical studies listed in the SBA are insufficient for this purpose as described above), gaps identified in available data, otherwise necessary for NDA approval, might need to be addressed by information contained in the published literature and/or by new nonclinical studies conducted with the new drug product under development. Importantly, LD-approved product labeling typically lists reproductive and developmental toxicity studies, genotoxicity studies and carcinogenicity studies that can be relied upon (if such studies were actually conducted in support of product approval). Some LD product labeling will include other nonclinical studies (e.g., pharmacodynamic and PK studies, repeat dose toxicity studies, juvenile toxicity studies and other relevant or product-specific nonclinical studies); however, these situations are more limited. As discussed in the later sections, various factors will determine the types of information (published or new study based) necessary to meet nonclinical requirements for a 505(b)(2) NDA submission.

Examples of drug products that qualify for the 505(b)(2) NDA pathway

The following are some examples of drug products that qualify for the 505(b)(2) NDA pathway because they do not meet the 505(j) ANDA requirements [7]:

- different form of the drug substance (active ingredient);
- dosage form changes and changes in the route of administration;

- formulation changes;
- changes in strength;
- new clinical indication;
- different dosing regimen;
- prodrugs or metabolites;
- combination products;
- prescription to over-the-counter (OTC) switch;
- bioinequivalence.

As evidenced by the list above, a wide array of changes to a drug substance or drug product can qualify it for the 505(b)(2) NDA pathway. Some of the changes are straightforward and clearly lead to a 505(b)(2) NDA regulatory pathway, such as a change in the salt of an active ingredient. However, some changes, such as using a prodrug of an approved drug, entail uncertainty and the final determination if the 505(b)(2) NDA pathway will be applicable might not be fully known until nonclinical and/or clinical data are generated.

Nonclinical drug development under the 505(b)(2) NDA pathway

Table 2 compares nonclinical drug development requirements for 505(b)(1) NDAs, 505(b)(2) NDAs and 505(j) ANDAs at a high level. As will be reviewed later, nonclinical development under the 505 (b)(2) NDA pathway entails consideration of a range of variables that are highly dependent on the number and types of changes to the new drug product as compared with the LD. Accordingly, this table should be used as a general guide. Examples are provided later in the publication to help in understanding some of the nuances associated with 505(b)(2) NDA nonclinical drug development programs.

For 505(b)(1) NDA drug development, the International Council for Harmonisation (ICH) has issued many safety and multidisciplinary guidelines that provide clear pathways for meeting nonclinical regulatory requirements in the USA and outside the USA [10]. The main guiding document for 505(b)(1) NDA drug development is ICH M3, which outlines the types of nonclinical studies that are generally required for all drugs and then some drug-dependent assessments that could be needed [11]. For 505(j) ANDAs, because the drug product is essentially the same as the RLD, including the clinical indication, route of administration, duration of dosing, among others, no nonclinical *in vivo* testing is typically needed; however, *in vitro* CMC data, such as dissolution testing, is often needed, and sometimes comparative *in vitro* nonclinical data (e.g., pharmacology) might be needed.

For 505(b)(2) NDA drug development, the nonclinical program typically focuses on: (i) filling any nonclinical data gaps that might exist (e.g., if the LD is an older drug and does not meet all the requirements of ICH M3); (ii) justifying the safety of any differences between the new drug product and the LD (e.g., justifying the local safety of a new route of administration); (iii) justifying the safety of the excipients; and (iv) qualifying impurities and degradants. The nonclinical development program for a 505(b)(2) NDA drug product is highly drug-product-dependent and many factors enter into whether nonclinical testing is required and the number and types of studies that might be needed. The FDA has issued a guidance document that provides general information on the types of nonclinical studies that might be required for reformulated drug products and drug products administered by an alternate route [12]. This guidance document is very helpful for assessing potential 505(b)(2) NDA nonclinical programs because many 505(b)(2) NDA drug products involve a new formulation and/or are administered by a new route. However, this is general guidance and there are many examples where more-limited or more-comprehensive nonclinical programs were conducted to support a new 505(b)(2) NDA drug product.

Some drugs developed via the 505(b)(2) NDA pathway could have extensive clinical safety data for the drug substance or drug product. Clinical data can reduce or even eliminate some nonclinical requirements under the 505(b)(2) NDA pathway; however, it is important to keep in mind that some endpoints are not readily monitorable in clinical trials and can only be assessed nonclinically (e.g., histopathology changes of a target organ for which there is not an adequate clinical chemistry endpoint). In these cases, nonclinical studies might be needed to fully assess the safety of endpoints of concern that cannot be readily monitored clinically.

Many 505(b)(2) NDA drug products use different excipients and/or altered levels of the same excipients in the formulation relative to the LD and these excipients require qualification. A document that is helpful for 505(b)(2) NDA drug development is the FDA's guidance document on the safety evaluation of pharmaceutical excipients [13]. If excipients in the new drug product are listed in the FDA's Inactive Ingredients Database (IID) [14] for the given route of exposure and the amount of the excipients in the new drug product are at or below IID maximum potency levels, in general, the excipients are often qualified and additional nonclinical testing is not required; however, it can be helpful to identify other approved drug products that contain a given excipient to ensure that the daily dose, dosing regimen and duration of use of the excipient are similar to that of the LD. If an excipient is novel (not listed in the IID), is only listed for other routes of exposure or is present in the new drug product at levels above the IID maximum potency level, then the excipient might need to be qualified with additional nonclinical testing. Also, it is important to keep in mind that IID maximum potency levels do not provide the clinical indication, maximum daily dose, dosing regimen or duration of use; so, even if an excipient is at or below IID levels, nonclinical qualification might still be required. Nonclinical qualification can range from including extra control groups in any new nonclinical studies (e.g., include sham and vehicle control groups so that the safety of the excipients can be clearly compared to the sham control), referencing published safety studies for the excipient to the need to conduct a full nonclinical toxicology assessment with the excipient, according to the FDA's excipient guidance [13].

The following are some considerations for various changes to a drug product that qualify it for the 505(b)(2) NDA pathway that could require nonclinical testing to support the safety of the differences between the new drug product and the LD.

Systemic exposure differences

If systemic exposure from the new drug product is less than or equal to the LD based on the PK parameters, C_{max} and AUC, then the new drug product can typically rely on all the systemic-type toxicity information for the LD such as general systemic toxicity, genotoxicity, carcinogenicity and/or reproductive and developmental toxicity. This is one of the main benefits of the 505(b)(2)

TABLE 2

Comparison of nonclinical development programs under the 505(b)(1) NDA, 505(b)(2) NDA and 505(j) ANDA pathways

Nonclinical category	Nonclinical studies required under designated pathway		
	505(b)(1) NDA	505(b)(2) NDA	505(j) ANDA
Pharmacology			
Primary pharmacology	Required	Typically known based on the LD but new studies might be needed for a new indication	Not required
Secondary pharmacology	Drug dependent	Typically known based on the LD	Not required
Safety pharmacology	Required	Typically known based on the LD nonclinical data and/or clinical use	Not required
Pharmacological drug interactions	Drug dependent	Typically known based on the LD	Not required
Pharmacokinetics			
In vitro metabolism	Required	Typically known based on the LD	Not required
Protein binding	Required	Typically known based on the LD	Not required
Absorption, distribution, metabolism and elimination	Required	Typically known based on the LD	Not required
Pharmacokinetic drug interactions	Required	Typically known based on the LD	Not required
Toxicology			
Acute toxicity	Not required	Not required	Not required
Repeat dose toxicity	Required – duration depends on clinical indication and duration of use	Might be required depending on various factors such as indication, route, formulation, etc. relative to the LD	Not required
Local tolerance	Required – typically included in repeat dose toxicity studies	Might be required depending on various factors such as route, formulation, etc. relative to the LD	Not required
Genotoxicity	Required	Typically known based on the LD	Not required
Carcinogenicity	Might be required depending on the clinical indication and duration of use	Might be required depending on various factors such as route, duration of dosing, formulation, etc. relative to the LD	Not required
Reproductive and developmental toxicity	Required	Typically known based on the LD	Not required
Juvenile toxicity	Might be required depending on the clinical population	Might be required depending on the clinical population	Not required
Photosafety assessment	Required	Might be required if not already assessed for the LD	Not required
Abuse liability	Drug dependent	Typically known based on the LD	Not required
Combination toxicity	Probably required if one or more NMEs or NCEs	Typically, not required if all drugs are already approved and well-characterized	Not required
Excipient qualification			
Excipients approved by FDA for the same route and used at the same or lower concentration	Studies probably not required	Studies probably not required	Not applicable
Excipients approved by FDA for the same route but used at higher concentration	Studies probably required to qualify the higher use level	Studies probably required to qualify the higher use level	Not applicable
Excipients approved by FDA for a different route	Studies probably required to qualify use by the new route of exposure	Studies probably required to qualify use by the new route of exposure	Not applicable
Novel excipients	Full nonclinical qualification program probably required	Full nonclinical qualification program probably required	Not applicable
Impurities and degradants			
Below ICH qualification thresholds	No studies required	No studies required	No studies required
Above ICH qualification thresholds	Genotoxicity and toxicity studies required if not qualified as part of the general toxicity program	Genotoxicity and toxicity studies required if not qualified as part of the general toxicity program	Approach must be discussed with the FDA

Abbreviations: ICH, International Council for Harmonisation; LD, listed drug; NMEs, new molecular entities; NCEs, new chemical entities.

NDA pathway because many nonclinical studies do not need to be repeated. However, as outlined in the following examples, additional nonclinical studies might be needed to justify other differences between the new drug product and the LD. If systemic exposure from the new drug product is higher than the LD, then new systemic-type toxicity studies might be needed depending on how the LD toxicity studies were designed and the resulting margin of safety for the new drug product.

Different forms of drug substance (active ingredient)

For some simple changes to a drug substance such a change from a sodium to a potassium salt, no new nonclinical studies are needed to support the 505(b)(2) NDA. However, some salts can raise concerns with the FDA, as will be provided in an example later, and can require a significant amount of nonclinical studies to justify the safety of the salt itself (e.g., if the salt alone is known to affect organ development or function). Prodrugs, such as esters of an active ingredient, often require nonclinical studies to demonstrate that the prodrug breaks down quickly and is not detected at appreciable levels systemically. Also, depending on the route of administration [e.g., intramuscular (IM) or subcutaneous (SC)], prodrugs can require local toxicity assessments owing to local exposure to the prodrug even if the prodrug is not detected systemically. If the LD is a racemic mixture and the new drug is a single enantiomer, comparative nonclinical toxicity testing is often required to ensure that the enantiomer does not exhibit greater toxicity than the racemic mixture. This often involves a comparative general toxicity study and a comparative developmental toxicity study.

Dosage form changes and changes in the route of administration

Some dosage form changes, such as switching from an oral tablet to an oral soluble film product presentation, might not require nonclinical studies. Also, switching from an immediate release (IR) to an extended release (ER) oral drug product presentation might not require nonclinical studies if it is demonstrated that clinical exposure for the ER product is equal to or less than the IR product based on the PK parameters, C_{max} and AUC, and there are no novel excipients, impurities or degradants that are of concern.

Changing the route of administration often requires nonclinical studies to demonstrate at least the local safety of the new route of administration. For example, if the LD is an oral tablet and the new route of administration is IM then a nonclinical toxicity study assessing the local safety of the IM injection should be conducted. In addition, if the IM injection is an extended-release injection, the animals should be followed for the entire duration of the extended-release interval and the fate of any materials associated with the formulation, typically ones that provide the extended-release properties, should be determined.

Formulation changes and changes in strength

Formulation changes might or might not require nonclinical studies; with such study requirements being highly dependent upon a range of factors. For example, for an oral solution that uses a different mixture of well-known excipients, nonclinical data will probably not be required. However, for a topical product that uses a unique excipient mix to enhance dermal penetration of the active ingredient, nonclinical studies would probably be required to demonstrate the local and potentially systemic safety of the new topical product owing to potentially increased local and systemic exposure occurring as a consequence of increased dermal penetrance. Changes in dose strength might not require nonclinical data if the clinical exposure is equal to or less than the LD.

New clinical indication

If the route of exposure, dose, dosing regimen and duration of use are the same for the different clinical indications, then no new nonclinical studies might be needed. However, if there are any differences from the approved indication (e.g., switching from an acute to a chronic dosing indication) then nonclinical studies of appropriate duration would probably be required.

Different dosing regimen

Using a different clinical dosing regimen might not require nonclinical data if the clinical exposure using the new dosing regimen is equal to or less than the exposure for the LD dosing regimen. If exposure for the new regimen is higher then nonclinical testing might be needed; however, it might be possible to leverage existing toxicity studies, even if they did not use the new dosing regimen, because they often use a maximum tolerated dose (MTD) or maximum feasible dose (MFD), which can support different dosing regimens owing to the high exposure that can be produced by either an MTD or MFD.

Combination products

Combination products can involve the combination of a drug, biologic and/or device. For a combination of two approved drugs, nonclinical testing might not be required assuming that the route of exposure, dose, dosing regimen and duration of use are the same as for the approved drugs. If any of these parameters are altered, nonclinical studies might be needed to support the proposed change(s). For a combination of a drug and an approved 510(K) device, nonclinical testing to support the safety of the drug itself might not be required; however, biocompatibility of the device in combination with the drug product will probably be required. Biocompatibility testing often follows FDA and ISO-10993 guidance on device biocompatibility testing [15,16]. In addition, leachable and extractable testing and assessment is required for the device when used with the drug product.

Potential challenges associated with the 505(b)(2) NDA pathway

Although the 505(b)(2) NDA pathway might provide reduced nonclinical study requirements for drug approval, there can be challenges with the 505(b)(2) NDA pathway that can make drug development more difficult than initially envisioned. The following points are provided to reflect areas that can present unique or unexpected challenges when developing a product in accordance with the 505(b)(2) NDA submissions pathway. Several of the following points are addressed later in the publication wherein various examples of drug products developed using the 505(b)(2) NDA pathway are described.

- Longer than expected repeat-dose toxicity studies might be required (e.g., instead of a 90-day repeat-dose rat toxicity study, a 6-month repeat-dose rat toxicity study could be required for approval).

- Repeat-dose toxicity studies are required in two species (rodent and non-rodent) even though many 505(b)(2) NDA programs rely upon a single species toxicity study using the new drug product formulation.
- Novel excipients can require extensive qualification. This often occurs when ingredients used in cosmetics are used for the first time in drugs because cosmetic use carries none to minimal weight on the acceptability of the excipient for drug product use.
- Coating technologies (e.g., drug particle encapsulation in an extended-release matrix) can require injection-site-specific, extended-duration nonclinical toxicology studies to assess local effects of the new drug product as well as to demonstrate full clearance (or biodegradation) of a coated or encapsulated product from a site of administration.
- Nonclinical PK/biodistribution bridging studies between the new drug product and the LD might be required in addition to clinical bridging studies. This can occur if exposure to the new drug product is best represented by local tissue exposure versus systemic exposure.
- The LD has limited nonclinical data owing to the age of the drug and basic nonclinical data gaps need to be filled (e.g., genotoxicity, reproduction and developmental toxicity) in addition to any nonclinical studies required for the new drug product formulation itself.
- The clinical population and indication could require specific nonclinical studies (e.g., juvenile toxicity studies for pediatric patients and wound-healing studies for drug products used in surgical wounds).
- The drug product formulation, and not the drug substance, might need to be tested in nonclinical studies to fully assess the safety of the new drug product and/or qualify any novel excipients. This could require larger nonclinical species to aid with dosing (e.g., if the new drug product is an extended-release tablet that cannot be administered to rodents).
- For combination products consisting of two or more drugs, there can be concerns with additive or synergistic toxicity, especially if the mechanisms-of-action or clinical effects are similar, requiring combination toxicity studies.
- Products developed that provide a fundamental change in delivered product characteristics (e.g., aqueous inhalant versus dry powder inhalant product) can require acute and chronic toxicology study support.

Obtaining consensus with the FDA on the nonclinical program

Because there are often different options for addressing the nonclinical requirements for a 505(b)(2) NDA drug development program, it is beneficial to the sponsor to discuss the proposed drug development program with the FDA during a PIND meeting. During the meeting, the sponsor can ask for further clarification on the FDA's position and nonclinical requirements. Sometimes after a discussion with the FDA about their position in the preliminary meeting comments, different approaches can be proposed to the FDA to address the nonclinical requirements and concerns that allow the sponsor more flexibility and still provide the FDA with the data they require. As product development continues, additional meetings to discuss and confirm the direction of the nonclinical program are beneficial, such as an end-of-Phase-II (EOP2) meeting and then a pre-new-drug application (PNDA) meeting.

Examples of 505(b)(2) NDA nonclinical drug development programs

This section provides a summary of various nonclinical packages that have been successfully utilized to support 505(b)(2) NDA drug product development programs. This section is intended to give a flavor for the variances in the nonclinical programs deemed appropriate to support various changes relative to the LD. Some examples provide full details of the drug product and clinical indication because they were obtained from the FDA SBAs for the approved drug product, and the presented information is, therefore, publicly available. For other products, only nonconfidential details are provided because the drug products are (or might be) still under development and have not received an NDA approval; however, sufficient information is provided so that the reader can understand the relevance of the nonclinical program to the changes in the new drug product compared with the LD.

Different form of the drug substance

As mentioned previously, some simple changes to a drug substance, such as switching from a sodium to a potassium salt, might require no new nonclinical studies to justify the change from the LD. A good example is the approval of Cambia® (diclofenac potassium sachet for oral solution) that relied on two LDs [Voltaren® (diclofenac sodium delayed-release oral tablet and extended-release oral tablet NDAs) and Cataflam® (diclofenac potassium oral tablet NDA)] along with published literature to meet all the nonclinical requirements [17]. No additional nonclinical studies were conducted. This approval also shows that different dosage forms, multiple LDs and discontinued LDs (Voltaren® delayed-release oral tablets were discontinued, but not for reasons of safety or efficacy) can be relied upon for the NDA.

Although salt changes can seem relatively straightforward, some salts can raise safety concerns with the FDA and lead to targeted nonclinical studies. Esomeprazole strontium was approved through the 505(b)(2) NDA pathway using Nexium® (esomeprazole magnesium) as the LD [18]. The FDA had concerns about the use of esomeprazole strontium in pregnant and lactating women and pediatric patients owing to the potential for adverse effects of strontium on bone growth and development, because strontium in high doses can induce adverse bone effects similar to rickets. The sponsor conducted reproductive and developmental toxicology studies in rats, comparing esomeprazole strontium (ES) to esomeprazole magnesium (EM). Bone effects of treatment with ES and EM were assessed in all developmental toxicology studies. The applicant conducted a rat Segment-II embryo-fetal development study, a rat Segment-III pre- and post-natal developmental toxicity study with an emphasis on bone development, a rat Segment-III pre- and post-natal developmental toxicity study in animals receiving a calcium- and vitamin-D-deficient diet and a rat juvenile toxicity study. All studies included a toxicokinetic (TK) analysis of esomeprazole and TK and distribution data for strontium and calcium. Because bone is the most sensitive target organ for strontium, bone morphometry and detailed histopathological analyses were included in the Segment-III and juvenile toxicity studies. These studies demonstrated that ES caused similar effects

to EM and the new drug product was approved after these targeted nonclinical studies were submitted.

Prodrugs of an approved drug substance can present unique challenges depending upon whether they are detected in the systemic circulation. As an example, a single dose but long-acting IM depot formulation of a prodrug of a pain reliever was being developed as a new 505(b)(2) NDA drug product relying upon an immediate release form of the active moiety as the LD. After discussions with the FDA, the ultimate nonclinical program hinged upon whether systemic levels of the prodrug were detected in the systemic circulation and whether the prodrug would be considered an NME and require extensive nonclinical testing to demonstrate the systemic safety of the NME [i.e., similar to a 505 (b)(1) NDA package]. During a PIND meeting, the FDA and sponsor cooperatively developed different scenarios of what the nonclinical program might require given different considerations (e.g., no circulating prodrug, 'low' levels of the prodrug or 'high' levels of the prodrug). Regardless of the circulating level of the prodrug, nonclinical studies were required to demonstrate the local safety of the long-acting IM depot formulation, the fate of the long-acting formulation and the genotoxicity potential of the prodrug to local tissues. The FDA recommended including systemic safety assessments in the local safety studies because that would help to assess the safety of the prodrug if any prodrug was found to circulate in clinical trials.

Dosage form changes

A new chronic-use psychiatric drug product was developed under the 505(b)(2) NDA pathway with the difference from the LD being that the new drug product was an oral soluble film (OSF) whereas the LD was approved as various oral and parenteral presentations. Because the excipients in the OSF were within the IID maximum potency levels for oral administration and the clinical dose, dose regimen and indication were the same, no new nonclinical studies were required to support the dosage form difference from the LD for the IND and NDA stages of development. A similar scenario occurred for Syndros® (dronabinol oral solution), which relied upon Marinol® (dronabinol oral capsules) as the LD [19]. No new nonclinical studies were required to support the Syndros® NDA approval under the 505(b)(2) NDA pathway and the safety of the formulation (excipients) was assessed by a combination of listings in the IID and published literature.

For another drug product to help with fatigue and mental focus, no nonclinical studies were needed to support a new extended-release drug product bridging to an immediate release LD. However, the FDA did state nonclinical studies would be needed if there were any unexpected or potential interactions between the excipients, degradants and/or impurities in the extended-release formulation. By contrast, the same psychiatric drug listed above was developed under the 505(b)(2) NDA pathway as a chronic-use dermal patch. To support initial clinical trials (i.e., IND-enabling studies), the sponsor conducted a repeat-dose rabbit skin irritation study and guinea pig skin sensitization study using the drug product formulation. These studies were sufficient for the IND; however, for an NDA, the following studies were needed: (i) phototoxicity assessment per ICH S10; (ii) 9-month repeat-dose local toxicity study in minipigs using the clinical patches; and (iii) dermal carcinogenicity. However, the dermal carcinogenicity study would only be required if pre-neoplastic and/or proliferative findings were noted in the minipig study or there were other causes for concern such as genotoxicity or positive carcinogenicity findings for other approved routes of exposure.

Clobex® (clobetasol propionate) lotion, Olux® (clobetasol propionate) foam, and Olux®-E (clobetasol propionate) foam are dermal products containing the potent glucocorticoid clobetasol and are indicated for various dermatoses. All three products were approved via the 505(b)(2) NDA pathway and referenced the topical products Temovate® (clobetasol propionate) cream and/or Temovate® E (clobetasol propionate) cream as the LD(s). All of the drug products have similar durations of use and drug substance concentrations (0.05% clobetasol). However, the formulations varied between the products qualifying them for the 505(b)(2) NDA pathway. Olux® (approved in 2000) did not conduct any new nonclinical studies to support approval [20]. By contrast, Clobex® (approved in 2003) conducted the following nonclinical studies: *in vitro* dermal penetration, dermal Segment-II developmental toxicity study in rats, eye and skin irritation studies in rabbits, skin sensitization in guinea pigs, and a 13-week dermal toxicity study in hairless mice, which was a range-finding study for a photocarcinogenesis study [21]. Clobex® also had post-approval commitments to conduct a dermal carcinogenicity study and photocarcinogenicity study. Olux®-E (approved in 2007) was tested in a battery of genotoxicity studies and skin and eye irritation studies in rabbits for approval [22]. In addition, Olux®-E had post-approval commitments to conduct a dermal carcinogenicity study and photocarcinogenicity study. Despite all three products having the same concentration of clobetasol, the nonclinical programs varied and this could have been due to the FDA's evolving nonclinical requirements, specific concerns with the varied formulations or other unknown factors.

Different route of administration

A different route of administration to the LD often necessitates nonclinical studies to at least assess the local safety of the new drug product. Sometimes systemic safety is also required depending on what is known about the LD and other factors such as route-specific metabolic differences (e.g., switching from an oral tablet to a parenteral or sublingual dosage form that avoids first-pass hepatic metabolism). A new prolonged-release pain-relieving drug product was developed under the 505(b)(2) NDA pathway for intraarticular (IA) joint administration. The LD was for oral administration and had a robust nonclinical database. To assess the safety of the IA administration and effects of long-term retention of the drug product in the joint, nonclinical studies were conducted in a rodent and non-rodent and involved extensive assessments of the joint and surrounding tissue. The studies included systemic TK and were of sufficient duration to follow the complete elimination of the drug product from the joint space.

A new chronically administered drug product was developed for intravenous (IV) administration to provide vasodilation effects; whereas, the LD was only approved for inhalation use, but had a robust nonclinical package. In the SBA for the LD, an IV 1-month large-animal toxicity study was summarized even though most studies used inhalation administration. To support clinical trials of 1 month or less, *in vitro* blood compatibility studies were required for the new IV drug product. The FDA allowed the reliance on the

IV 1-month large-animal toxicity study in the SBA to support clinical trials of 1 month or less. However, for the NDA, a chronic IV toxicity study was required in a non-rodent.

A final example is a new drug product being developed for chronic intranasal (IN) administration to treat a neurodegenerative disease. The LD was approved for chronic parenteral administration for a different indication. Owing to a large amount of published off-label clinical data (using IN administration of the LD), clinical trials were allowed to proceed without a requirement for additional nonclinical studies. However, to support an NDA submission, sub-chronic IN toxicity studies in rodents and non-rodents were required; to be followed by a chronic IN toxicity study in the most sensitive species.

Pediatric population

Depending on the clinical experience associated with use of a given LD in the pediatric population, juvenile toxicity studies might or might not be needed to support clinical trials in pediatric patients. The FDA has provided guidance as to when nonclinical juvenile toxicity studies are needed and general study design concepts applicable to such studies [23]. In addition, the ICH E11 pediatric clinical trial guidance provides a breakdown of typical pediatric age ranges that need to be considered when designing a juvenile toxicity study to support clinical use in different pediatric ages [24]. In general, the age ranges for pediatric patients are as follows per ICH E11:

i. preterm newborn infants;
ii. term newborn infants (0 to 27 days);
iii. infants and toddlers (28 days to 23 months);
iv. children (2 to 11 years);
v. adolescents [12 to 16–18 years (dependent on region)].

If a juvenile animal toxicity study is required to support pediatric clinical trials, the developmental age of the animals used in the study will need to be representative of the youngest pediatric age that will be enrolled in the clinical trial and listed in the new drug product labeling. As an example, a new drug product was developed under the 505(b)(2) NDA pathway for a rare genetic disorder that occurs in children. The LD was essentially used only by adults so there was limited pediatric clinical experience with the LD. Therefore, a juvenile rat toxicity study using appropriately aged animals was required before pediatric studies in children under the age of 12 could proceed.

Endogenous molecules

Some new drugs consist of endogenous molecules intended to treat conditions associated with inadequate levels (or utilization) of the endogenous molecule (or upstream or downstream molecules). Some of these drugs rely solely on literature for approval and do not have an LD to rely upon. Cholbam® (cholic acid capsules), for example, was approved under the 505(b)(2) NDA pathway for the treatment of bile acid synthesis disorders [25]. There was no LD relied upon to support the approval and no nonclinical studies were required for approval. The FDA made this determination because cholic acid is the most abundant bile acid in humans, there was minimal concern about its safety and Cholbam® only restored cholic acid in the patients to levels measured in healthy people. By way of contrast, another endogenous molecule was developed for a rare genetic disorder. Very high doses of the molecule were required to overcome the defective pathway and resulted in exceeding endogenous levels of the molecule in healthy people. Based on published nonclinical and clinical data for the molecule, clinical trials were allowed to proceed without new nonclinical studies; however, for NDA approval the following studies were required: (i) chronic toxicity in a rodent and a non-rodent; (ii) genotoxicity battery; (iii) carcinogenicity in a single species; (iv) complete reproductive and developmental toxicity battery; and (v) juvenile toxicity in rats or inclusion of appropriately aged animals and endpoints in the chronic rat study.

Excipient qualification

Many 505(b)(2) NDA drug products use different excipients in their formulation relative to the LD, which is often one of the main reasons these products qualify for the 505(b)(2) NDA pathway and are not 505(j) ANDA products. If the excipients in the new drug product are listed in the IID for the given route of exposure and the amounts in the new drug product are at or below IID maximum potency levels, then additional nonclinical qualification of the excipients is typically not required. However, it is important to keep in mind that the IID listings are not ideal because they do not provide the clinical indication, maximum daily dose, dosing regimen or dosing duration of an excipient so, even if an excipient is listed in the IID, qualification might still be required (e.g., the IID listed excipient is only used in acute products and the new drug product is for chronic administration). Ideally, it is best to use the IID to first identify whether an excipient is listed for the proposed route of exposure. Then, other search tools, such as DailyMed searching of approved drug labeling [26], can be used to try and identify other approved drug products that contain the excipient, using the same route of administration, to ensure that the use levels in the new drug product are equal to or less than other approved products. However, this can be difficult because the actual amount of the excipient in some dosage forms is not provided in drug labeling. Reviewing approved drug labeling does provide a comparison of the clinical indications, dosing regimens and durations of use to ensure that the current approved excipient uses are similar to the proposed use for the new drug product.

If a given excipient is not listed in the IID, or an excipient is listed in the IID but not for the new route of exposure, or if it is listed at levels higher than the maximum potency level in the IID, then nonclinical testing will probably be needed to qualify the excipient. This can range from including appropriate control groups in any new toxicity studies to using published safety data for the excipient to support the new use to a full nonclinical program to qualify the safety of the excipient as outlined in the FDA's excipient guidance [13].

For a new chronically administered inhalation drug product for blood vessel dilation, a couple of excipients were used that were listed in the IID but not for inhalation use. As part of the required 6-month inhalation toxicity study, sham air and vehicle-treated control groups were included along with three clinical formulation treatment groups to qualify these excipients. The two control groups allowed the safety of all the excipients, including the ones not listed for inhalation use, to be assessed and qualified. For a topical anti-infective drug product, several excipients were included that were not listed in the IID for any route of exposure. The

excipients were commonly used in topical cosmetic applications; however, to qualify the excipients for drug product use, a full nonclinical program would have been required, including a full reproductive and developmental toxicity package. Owing to this high hurdle, the excipients were removed from the new drug product.

Including LD comparator groups

It can be beneficial for nonclinical studies for a new drug product to include the new drug product along with LD-treated groups, even if the routes of administration are different. This allows a direct comparison between the effects of the new drug product and the LD so that it can be conclusively determined that any potential adverse effects by the new drug product are no worse than the LD and provide the same benefit:risk ratio. For example, a new drug product was developed for chronic oral administration. The sponsor conducted a 1-month non-human primate study. Unfortunately, the sponsor's study was not definitive with respect to findings, resulting in the sponsor program being placed on partial clinical hold. To address prior study limitations, a subsequent 9-month non-human primate study was conducted by the sponsor, which included new-drug-product-treated (oral product) and LD-treated (IV product) groups. The results of this 9-month study demonstrated that the new drug product exhibited the same safety profile as the LD. As mentioned previously for esomeprazole strontium, an LD comparator group (esomeprazole magnesium) was included in the various nonclinical studies and this was pivotal for determining that the new drug product had the same benefit:risk ratio as the LD.

Bendeka® (bendamustine hydrochloride) IV injection, a chemotherapeutic drug, was approved via the 505(b)(2) NDA pathway using Treanda® (bendamustine hydrochloride) IV injection as the LD. Bendeka® qualified for the 505(b)(2) NDA pathway because the formulation was different from Treanda® and the infusion duration was shorter for Bendeka® (10 min for Bendeka® versus 30 min for Treanda®). As outlined in the SBA, the sponsor compared the local tolerance of Bendeka® to Treanda® in rabbits, including intended (IV) and unintended [perivascular (PV)] administration [27]. This study demonstrated that Bendeka® had a similar safety profile as Treanda® for the intended route of administration (IV); however, Bendeka® caused irritation after PV administration, which was not observed with the LD (Treanda®). In addition, an *in vitro* hemolysis study compared Bendeka® to Treanda®; with no hemolysis being observed for either drug product. Despite greater PV irritation induced by Bendeka® in rabbits, as compared with Treanda®, the intended route of administration (IV infusion) demonstrated a similar safety profile for both drug products, which supported approvability of Bendeka®.

Nonclinical bridging studies

For most 505(b)(2) NDA drug products, establishing a clinical bridge between the new drug product and the LD allows reliance upon the LD's nonclinical information in the approved labeling, particularly for systemic effects. However, for some drug products, a specific nonclinical bridge needs to be established. A new topical ocular drug product was developed that had a slightly different formulation than the LD (also an ocular drug) but the indications and doses were different. A clinical bridge was going to be established by comparing systemic exposure for the new drug product relative to the LD in a clinical trial. This was acceptable for relying upon the clinical pharmacology and clinical safety information for the LD; however, this was not sufficient for relying upon the nonclinical information. To rely upon the LD nonclinical information, a nonclinical ocular biodistribution study had to be conducted to ensure that the new drug product produced ocular tissue and fluid levels that were equal to or less than the LD.

Combination products

Combination products can consist of multiple drugs, biologics and/or devices. If two or more approved drugs are being combined into a new combination drug product and the nonclinical programs supporting the individual components are robust then combination toxicity studies are often not required. However, if data on one or more of the drug actives are lacking, combination toxicity studies might be required. For example, an oral three-drug combination product was developed for a chronic metabolic indication. Nonclinical data for one of the drugs was sufficiently robust to support a chronic indication; however, the nonclinical data for the other two drugs were limited to acute use and were incomplete owing to the age of the drugs (e.g., time since original approval). To support clinical trials and eventual NDA approval, a combination toxicity study had to be conducted. This study involved multiple groups that compared the safety of each drug, individually, to the combination at several dose levels. Because the drug formulation presentation was novel, a large animal had to be used so that the clinical formulation could be administered successfully (i.e., administration of the actives in a tox-specific vehicle was not acceptable for the safety assessment of this drug product).

In addition, it is relevant to note that ever-increasing numbers of drug products are being packaged or delivered with drug-product-specific devices and subsequently evaluated via the 505(b)(2) NDA pathway. For a pre-filled syringe, especially one using well-known materials, more-limited biocompatibility testing is typically required. However, for a more-complex device with multiple fluid paths and materials that contact the drug product and/or patient (e.g., an infusion pump), a more comprehensive biocompatibility testing program would be needed along with leachables and extractables testing and assessment. For one 505(b)(2) NDA drug product delivered using a proprietary parenteral administration device, an extensive number of leachables and extractables were measured. This required extensive analytical work, data searching for relevant toxicity data and eventually nonclinical testing to qualify unidentified compounds above de minimis thresholds.

Orphan, QIDP, RPD, fast tract, breakthrough, priority review and accelerated designations

A new 505(b)(2) NDA drug product might equally be able to obtain orphan, qualified infectious disease product (QIDP), rare pediatric disease (RPD), fast tract, breakthrough, priority review and/or accelerated designations, as appropriate. These designations can help with overall drug development from time, cost and market exclusivity perspectives. However, the nonclinical requirements are often not affected by a given designation and remain the same as a new drug product that is not designated.

Concluding remarks

As emphasized by the examples provided in this manuscript, the 505(b)(2) NDA pathway for new drug product approval requires careful understanding and strategic input related to designing appropriate nonclinical programs that will meet applicable regulatory requirements and be accepted by the FDA. Vetting a proposed nonclinical program during a PIND meeting with the FDA provides buy-in by the FDA into the nonclinical program; however, it is important to provide a reasonable nonclinical approach and program so that the FDA can provide adequate feedback and the program can be tailored to meet the sponsor's and FDA's needs. For a 505(b)(2) NDA drug product, a proposed nonclinical program is highly drug-product-dependent and requires extensive nonclinical expertise and insight to understand the potential differences between the new drug product and the LD that need to be addressed nonclinically. Because some safety endpoints cannot be readily monitored clinically, even if extensive clinical data are available, nonclinical studies might still be necessary to assess specific endpoints of concern. Overall, the 505(b)(2) NDA regulatory pathway provides mechanisms to potentially reduce the nonclinical program for a new drug product, streamline drug development and approval, and support patent protection and potential market exclusivity.

Conflicts of interest

No funding source to declare for the writing of this manuscript. Drs Salminen, Wiles and Stevens are employees of Camargo Pharmaceutical Services. Camargo Pharmaceutical Services did not require the preparation or submission of this manuscript as part of their employment. All three authors contributed to the drafting, analysis, editing and submission of the manuscript.

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