

Which Route for Variations in the US – Where Have All the Suitability Petitions Gone?

Kathryn Wekselman, Lynn Gold and Ken Phelps tell companies developing variations on marketed drugs how to choose between the 505(b)(2) and ANDA regulatory pathways.

For pharmaceutical companies wishing to market in the US a product that is a variation on an already-approved drug, two regulatory routes might be appropriate: a new drug application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act or an abbreviated new drug application preceded by a suitability petition under section 505(j)(c) of the act.

Determining which route is best for a specific drug product requires strategic thinking based on a deep understanding of the similarities and differences between the two regulatory paths.

The processes involved in the 505(b)(2) route differ significantly from those in the ANDA path (the path traditionally used for straightforward generic drug approvals). There can also be a big difference in the time it takes to gain approval under each path.

In the last few years, a number of factors have combined to result in an increase in 505(b)(2) submissions and decrease of suitability petitions submissions.

Understanding the requirements of each regulatory route and the way in which the Food and Drug Administration has recently begun using its authority for variations is critical for choosing the appropriate path. This article describes the most important concepts that a drug developer needs to know to understand the difference between the suitability petition and the 505(b)(2) NDA submission.

505(b)(2) NDA

A 505(b)(2) application is an NDA for which one or more of the investigations relied upon by the applicant for approval “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted”¹. In other words, the 505(b)(2) route of application is used for drugs that are variations on existing approved drugs when some or all of the information necessary for approval is obtained from sources, such as published literature or FDA findings of safety and efficacy for the reference listed drug (RLD), to which the applicant does not have right of reference.

The kinds of changes to existing drugs that are appropriate for 505(b)(2) submissions include changes to dosage form, strength, route of administration or formulation and novel combinations of individually approved products. Pro-drugs or active metabolites of approved drugs may also be appropriate for this route.

As with any NDA submission, a successful 505(b)(2) application must satisfy the burden of proof for every requirement necessary for drug approval, including efficacy and safety. While some 505(b)(2) applications can succeed without any new clinical efficacy or safety trials, many require one or more new trials to demonstrate efficacy and safety of the variation on the RLD.

However, some or even most of the information submitted can come from existing sources.

ANDA suitability petition

An ANDA is ordinarily filed for a drug product that is identical to the RLD. An ANDA suitability petition allows a drug company to request that the FDA permit the filing of an ANDA for a drug product that differs from the RLD. The circumstances under which the FDA can approve a suitability petition include the use of a different route of administration; a different dosage form or a different strength of an already-approved RLD; or a different active ingredient in a combination product in which the other active ingredients match those of the RLD.

To succeed, a petitioner must obtain FDA agreement that no animal or clinical investigations are necessary to show efficacy or safety. That is, the information required for an ANDA will be sufficient to show safety and efficacy of the proposed product, even though it differs from the RLD in one of the ways listed in the statute.

As a practical matter, the kinds of changes to an RLD that the FDA is likely to approve without any efficacy or safety studies are things like an intermediate dose between two already approved

Determining which regulatory route is best for a variation requires strategic thinking

Changes to existing drugs that are appropriate for 505(b)(2) submissions include changes to dosage form

A suitability petitioner must obtain FDA agreement that no animal or clinical investigations are needed show efficacy or safety

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doses, a half dose of a drug that is already approved as a scored tablet, or the replacement of one approved ingredient in a combination product with another approved ingredient in the same pharmacological or therapeutic class.

The petition itself is very simple. The process for filing a suitability petition is described in the Code of Federal Regulations Title 21 (21 CFR 10.20), and the format for the content is described in 21 CFR 10.30.

The petition should explain why the requested change should be accepted

The petition should contain the requested change and explain why the change should be accepted. It should include the proposed labelling, which will differ slightly from the NDA labelling, and whatever clinical and non-clinical information exists, both favourable and unfavourable.

The suitability petition is not the ANDA; it is just the request for permission to file the ANDA. The FDA approval of the suitability petition does not necessarily mean the agency will approve the ANDA when filed. All ANDA requirements must still be fulfilled for approval.

Suitability petitions from 1999 onwards are listed on the FDA website². The list comprises petitions that are pending, approved, withdrawn or denied. Denial of suitability petitions is primarily due to a finding that efficacy or safety issues must be addressed via clinical studies. Most often, these applications should be 505(b)(2) NDAs.

505(b)(2) NDAs versus suitability petitions

It is obvious from their definitions that some features of suitability petitions and 505(b)(2) NDAs overlap, most notably in the kinds of changes to an RLD that may be made in the variation. Similarities and differences between the two regulatory paths are summarised in Table 1.

Product development requirements are identical for both regulatory paths

Module 4 of the regulatory submission is required for a 505(b)(2) but not for an ANDA

Table 1. Comparison of typical ANDA (after granting of suitability petition) and 505(b)(2) NDA submissions		
	ANDA	505(b)(2)
Product development	Product development requirements are identical	
Stability	<ul style="list-style-type: none"> - 1 stability batch - 3-month accelerated stability testing 	<ul style="list-style-type: none"> - 3 stability batches - 12-month room temperature and 6-month accelerated stability testing
Clinical development	Phase I pharmacokinetic study usually required	
	<ul style="list-style-type: none"> - Phase II study: not required - Phase III study: not required 	<ul style="list-style-type: none"> - Phase II study: sometimes required - Phase III study: often required
Regulatory submission	Module 3 requirements are identical Module 5 included when needed for study reports	
	<ul style="list-style-type: none"> - Module 1: components specific to ANDA - Module 2: 2.3 only - Module 4: not required 	<ul style="list-style-type: none"> - Module 1: components specific to NDA - Module 2: very important; all sections needed - Module 4: required
Patent certification	Required for both	
Exclusivity	Both can be blocked by exclusivity and both can confer exclusivity	
	<ul style="list-style-type: none"> - First generic to file a successful Paragraph 4 certification is awarded 180-day exclusivity 	<ul style="list-style-type: none"> - Period of exclusivity awarded: <ul style="list-style-type: none"> - 3 years: clinical study essential to approval - 5 years: new chemical entity (never approved under NDA) - 7 years: orphan drug - 6 months: additional for paediatric studies
Pre-submission timeline	<ul style="list-style-type: none"> - Suitability petition response time is 90 days but can be delayed - Start of bioequivalence study to filing: Usually 4+ months 	<ul style="list-style-type: none"> - Pre-investigational new drug meeting 60 days from request (optional) - Investigational new drug 30-day review if no clinical hold - Start of last clinical study to filing: usually 12+ months

Table 1. Comparison of typical ANDA (after granting of suitability petition) and 505(b)(2) NDA submissions (continued)

	ANDA	505(b)(2)
Post-submission timeline	– Review time currently: median of 16 months; varies with FDA's Office of Generic Drugs workload, complexity	– Prescription Drug User Fee Act date 10 months after NDA acceptance; may be extended
Costs	<ul style="list-style-type: none"> – \$200k-\$3m depending on studies required – No user fee for suitability petition or ANDA – Typically no marketing/promotion done 	<ul style="list-style-type: none"> – \$750k-\$8m, depending on studies required – User fee (PDUFA) <ul style="list-style-type: none"> – Small business exemption for first submission – Successive submissions: <ul style="list-style-type: none"> – No clinical studies: half PDUFA fee – Clinical studies: full PDUFA fee – Marketing/promotion typically done

An ANDA requires no user fee while a 505(b)(2) does

It is notable that, in addition to differences in timings, the two regulatory routes differ significantly with regard to process. For a 505(b)(2) NDA submission, the process includes a pre-IND meeting with the appropriate division (optional), submission of an investigational new drug application, an end of Phase II meeting with the appropriate division (optional), a pre-NDA meeting (optional) and submission of the NDA. A Prescription Drug User Fee Act date is assigned, and the FDA attempts to provide an approval or complete response by that date.

In contrast, the process for the suitability petition is handled by the FDA in the same manner as a citizen petition. Once a petition is filed, a public docket is assigned and public input is allowed. Then the Office of Generic Drugs at the FDA's Center for Drug Evaluation and Research reviews the petition and comments and publishes its decision. The review time frame for suitability petitions is defined as 90 days. If the petition is approved, an ANDA can be filed. From this point, the standard ANDA review process is followed, with uncertain timing of the review and response from the OGD.

One important component of the difference in process is that an ANDA suitability petition is a very public process. Not only is the petition made public, but anyone who wishes to can file a comment. Once a suitability petition is approved, it is also open to use by anyone who wants to file an ANDA for the same change to that RLD.

A suitability petition is a very public process

With regard to content, the 505(b)(2) NDA and the ANDA regulatory pathways share identical formulation, analytical, specification and manufacturing requirements for Module 3 of the common technical document. Only stability requirements differ for the two pathways. The contents of Module 5 will depend on the requirement for clinical studies. If clinical studies are required for either type of submission, the study reports must be included here. Module 4 is seldom required for ANDAs, but will need to be part of any 505(b)(2) NDA. Requirements for administrative documents in Module 1 differ between the two types of submissions and are spelled out in applicable guidances and regulations.

FDA handling of suitability petitions

As shown in Table 2, the number of suitability petitions approved increased yearly between 1999 and 2004, when a record 29 such petitions were approved. The number fell to 20 in 2005, and it has been well below that number every year since.

Table 2. Overview of FDA actions on suitability petitions*

Year of FDA action	No. filed	No. withdrawn	No. denied	No. approved	No. pending
1999	10	3	3	4	0
2000	38	6	5	27	0
2001	46	7	11	28	0
2002	32	4	8	20	0
2003	29	3	4	21	1
2004	62	10	8	29	15
2005	51	8	8	20	15
2006	42	7	4	5	26
2007	181	128**	2	14	38
2008	43	3	2	2	36
Q1 2009 (projected)	24 (96)	2 (8)	0 (0)	2 (8)	20 (80)
No Year Entry	8	2	0	0	6
Total	566	183	55	172	157

The number of suitability petitions approved fell in 2005

*Updated on FDA website, 21 March 2009.

**72 FR 8184, 23 Feb 2007, withdrawal of 128 based on Pediatric Research Equity Act requirement for studies in paediatric population.

The FDA does not maintain a listing of 505(b)(2) NDA filings. However, the number of 505(b)(2) NDA approvals in a given year can be estimated by a bit of detective work. Using the list of approved drugs available at Drugs@FDA.gov on the agency's website³, it is possible to obtain the list of drug approvals by month. From this list, one can select drugs that might have been eligible for 505(b)(2) submissions and verify by looking at their approval letters. Using this method, it has been determined that 33 505(b)(2) NDAs were approved by the FDA in 2009, a record number.

Implications of PREA

By far the most likely reason for the decrease in the number of suitability petitions since 2005 is the application of the Pediatric Research Equity Act of 2003 (renewed and extended by Title IV of the FDA Amendments Act of 2007).

Under PREA, a paediatric assessment is required for all applications submitted after April 1999 containing a new active ingredient, a new indication, a new dosage form, a new dosing regimen or a new route of administration. The paediatric assessment may result in a paediatric clinical trial requirement for approval. In addition to affecting the approval of suitability petitions going forward, this requirement actually caused the FDA to rescind approval of nearly 130 suitability petitions in 2007 because they did not contain paediatric assessments and no ANDAs had yet been filed pursuant to those particular petitions⁴.

Today, regarding RLDs for which sufficient paediatric studies have not been completed, it is no longer possible to plan only a demonstration of bioequivalence of the altered drug product to gain approval for a suitability petition. Many drug changes that would have been granted suitability petitions before PREA have become candidates for 505(b)(2) NDAs instead because of the need to conduct paediatric clinical studies. Both 505(b)(2) NDAs and ANDAs following a granted suitability petition require PREA assessments. However, only the 505(b)(2) pathway can be used if any clinical studies are required.

Other factors contributing to the decrease in the number of suitability petitions (and related increase in the number of 505(b)(2) drug development programmes) include speed to approval, pricing considerations and competition.

As already noted, approval of ANDAs and responses to suitability petitions are not governed by any time clock and can stretch out into processes that run over years. NDAs, in contrast, are provided with PDUFA dates, which should result in timely decisions, provided that the application is complete when filed and makes a convincing data-based case for safety and efficacy.

It is also a consideration that, as generic drugs, modifications to RLDs that have been approved under ANDAs are subject to greater pricing pressure than their non-generic counterparts. Generic drugs can typically expect rapid entry into the market of substitutable competitors, further increasing pricing pressures.

Identifying untapped opportunities

The general principles outlined in this article shed light on the most important considerations affecting the decision of whether to develop a variation under a suitability petition or a 505(b)(2) NDA. However, at the end of the day, it will be the detail in each drug development idea that will dictate which route is better, or even whether only one of the routes is possible.

Suitability petitions can still be an elegant, reasonably quick and very inexpensive way to get a new drug product that is a modification of an RLD onto the market. However, the proliferation of generic drugs, the increased expense of drug development for new chemical entities and the consistent application of PREA since 2007 have combined to create an environment where the number of 505(b)(2) submissions is increasing and the number of suitability petitions is falling. Today, drugs that are either not applicable to medical conditions in children or for which sufficient paediatric research has already been conducted probably present the best opportunities to use suitability petitions for modifications of RLDs.

The task for drug developers is to identify where these untapped opportunities exist, build strong supporting cases and move forward with the required submissions.

References

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The most likely reason for the decrease in suitability petitions is the application of the Pediatric Research Equity Act of 2003

Approval of ANDAs can stretch out into processes that run over years

The detail in each drug development idea will dictate which route is better