Best Practices for 505(b)(2) Applicants

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I want to help YOU provide

PERFECT patent certifications for

your 505(b)(2) application

Learning Objectives

- Describe what makes an application a 505(b)(2)
- Describe regulatory requirement differences between 505(b)(1) and 505(b)(2) NDAs and ANDAs
- Describe utilization of Orange Book for 505(b)(2) patent certifications

Comparison of 3 types of applications described under section 505 of the FD&C Act

505(b)(1) NDA	505(b)(2) NDA	ANDA
Preclinical	Preclinical	
Clinical	Clinical	
Pediatric Use	Pediatric Use	
Chemistry, Manufacturing, Controls (CMC)	CMC	CMC
Pharmacokinetics (PK) & Bioavailability	PK, Bioavailability, Comparative Bioavailability	Bioequivalence
Labeling	Labeling	Labeling
Patent Information	Patent Information	
	Patent Certification (if applicable)	Patent Certification
Exclusivity Request	Exclusivity Request	
	Exclusivity Statement	Exclusivity Statement

What is a 505(b)(2) application?

A 505(b)(2) application is an application that contains full reports of investigations of safety and effectiveness, where at least some of the information relied upon for approval comes from studies **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 (21 U.S.C. 355(b)(2)).

The bottom line - 505(b)(2) applications

The primary difference between a 505(b)(1) and a 505(b)(2) NDA is the *SOURCE* of the information relied upon for the 505(b)(2) application is *NOT OWNED* by the 505(b)(2) applicant or the applicant does NOT have a right of reference

The bottom line - 505(b)(2) applications

- 505(b)(2) approval standards are the same as 505(b)(1)

- Additional regulatory obligations for 505(b)(2) applications include patent certification and bridging (as applicable)

- 505(b)(2) applications do NOT have ANDA 'sameness' requirements

Patent Certifications for 505(b)(2)s

- Orange Book – primary tool to consult when considering patent certification
- Orange Book updates include newly listed patents OR changes to existing patent listings
- Certifications need to be maintained while 505(b)(2) application under review
- 505(b)(2) application may require updated certification when Orange Book changes occur

The ABC's

- Cite the correct regulation!
- 505(b)(2) patent certification – 314.50(i)(1)(i)
- ANDA – 314.94(a)(12)

505(b)(2) NDAs may rely on multiple sources

- In addition to literature reliance a 505(b)(2) may rely upon multiple listed drugs

- If more than one listed drug is relied upon, a patent certification is needed for each and every listed drug relied upon

- A patent cert if required even if there are no patents listed in the Orange Book for a listed drug relied upon

Piggyback and Reach Back

- Applicant may cross-reference a previously approved 505(b)(2) application for which it is the NDA holder to support approval of its new NDA

- Reach back (patent certification) to original listed drug relied upon in approved 505(b)(2) application held by applicant is required

Piggyback and Reach Back

- A 505(b)(2) application may rely on other listed drug(s) approved under 505(b)(2)

- Must include patent certification or statement for each patent for listed drug(s) relied upon

- Reach back (patent certification) to the original listed drug(s) relied on by the approved 505(b)(2) not required

Pharmaceutical Equivalent (PE) Patent Certification Requirements

Pharmaceutical equivalents (PEs) are drug products in ***identical dosage forms and route(s)*** of administration that contain ***identical amounts*** of the ***identical active drug ingredient***, *i.e.,* the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

See 21 C.F.R. 314.3

Pharmaceutical Equivalent (PE) Patent Certification Requirements

For 505(b)(2) applications submitted after 12/5/2016:

- If there is a pharmaceutical equivalent (PE) ***to the drug for which the original 505(b)(2) application is submitted*** listed in the Orange Book ***and*** approved prior to submission of the original 505(b)(2) **application**, the 505(b)(2) applicant *must* also rely on the PE [See 21 C.F.R. 314.54]

- Additional patent certification/statement may be necessary (if PE not already identified as relied upon listed drug)

Pharmaceutical Equivalent (PE) Patent Certification Requirements

- apply in absence of other listed drug reliance

- may not require an additional bridge if PE reliance only for regulatory compliance

Paragraph IV and MOU

Is patent certification congruent with proposed labeling?

- Are methods-of-use (MOU) in label retained for patents where PIV certification is provided?
- Are MOUs carved out of label for provided MOU statements?
- Is a split patent certification (PIV+MOU statement) needed for patents claiming drug substance and/or drug product claims in addition to MOU claims?

Amendments - Verification

- Each amendment must contain a verification statement in the cover letter to verify the proposed change in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1)
- Verification statement example:
  In accordance with 21 CFR 314.60(f)(2), CoronaVPharma verifies that any changes described in this amendment do not require a patent certification pursuant to 21CFR 314.60(f)(1)
- **OR……**

Amendments - Verification

- …. the amendment must include a patent certification or re-certification as applicable

Amendments – Certification/Re-certification

- If amendment includes a change described in 21 CFR 314.60(f)(2), applicant must provide patent certification and/or re-certification
- Example: Certification was provided in original NDA
  …Amendment for reformulation and new strength
  …….Certification needed for new strength
  ……..Re-certification needed for reformulation

Once 505(b)(2) always a 505(b)(2)

- A supplement to a 505(b)(2) NDA is a 505(b)(2) supplement even if the applicant is relying on their own information or literature for the supplement
- Supplement continues to rely on underlying information relied upon in original NDA
- New patent certification required for supplement (if listed drug reliance in original NDA and/or supplement)

Challenge Question #1

When submitting an amendment to a 505(b)(2) NDA, the applicant must:

A. Provide a verification statement in their cover letter if applicable

B. Provide a patent certification or recertification if applicable

C. Provide proof of notification

D. Both A and B

Challenge Question #2

Which conclusion is false?
Patent certification requirements for 505(b)(2) applications related to pharmaceutical equivalents (PEs):

A. provide FDA an option to refuse to approve a 505(b)(2) application if PE certification requirement not met

B. apply only when the PE product has unexpired patents

C. include timing caveats

D. apply to 505(b)(2) applications that only rely upon non-product specific literature

Summary

- Patent certification must be maintained while 505(b)(2) application under review, and should be updated to reflect Orange Book changes
- Patent certification requirements for 505(b)(2) and ANDA applications are similar but have distinct differences
- Consideration of distinct regulatory requirements for each abbreviated approval pathway is key to maintaining accurate patent certification

Resources

- 1999 draft Guidance for Industry *Applications Covered by Section 505(b)(2)*

- Federal Register Notice Final Rule (MMA) Oct 6, 2016 https://www.gpo.gov/fdsys/pkg/FR-2016-10-06/pdf/2016-22690.pdf

- Draft Guidance for Industry "Determining Whether to Submit an ANDA or a 505(b)(2) Application"

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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Closing Thought

Staying up-to-date with the Orange Book is key to maintaining certifications


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