How to turn a 505(b)(2) into an NDS/SNDS

CAPRA 2012 Symposium

Current Perspectives in Regulatory Toxicology and Safety

Agenda

- What is a 505(b)(2)?
- Considerations for a Canadian New Drug Submission (NDS) or Supplemental New Drug Submission (SNDS)
- Examples
- Status- Current and moving forward

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What is a 505(b)(2)?

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- Drug development pathway unique to US
- Designed to encourage innovation while protecting patent and exclusivity rights
- Section 505(b)(2) was added to the Act in 1984 with the goal of avoiding unnecessary duplication of preclinical and certain human studies.
- Division 8, Part C have NDS, ANDS in Canada.
- In US similarly for drugs 505(b)(1) and 505(j)
- 505(b)(2) is a hybrid
- Together with 505(j) replaced paper NDA policy
- Establish comparability to the reference drug.

What is a 505(b)(2)?

- New Drug Application that contains full reports of investigations of safety and effectiveness but where at least some of the information 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
- 505(b)(2) involves approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product
- Published literature- applicant does not have right of reference to raw data underlying studies
- Agency finding of safety and/or effectiveness for approved drug – makes Agency's conclusions that would support approval of a 505(j) application (ANDA) available to an applicant who develops a modification of a drug

Food and Drug Administration Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry Applications Covered by Section 505(b)(2). October 1999.

Kinds of 505(b)(2) applications

- New Chemical Entity/new molecular entity
  - Studies not conducted by or for the applicant and applicant does not have right of reference
  - For NCE likely to be derived from published literature studies rather than FDA's previous finding of safety and effectiveness (minority)
- Changes to previously approved drugs
  - Application may rely on Agency's finding of safety and effectiveness of previously approved product coupled with information to support the change (new studies conducted by the applicant or published data)

Food and Drug Administration Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry Applications Covered by Section 505(b)(2). October 1999.

Examples

- Dosage form
- Strength
- Route of administration
- Substitution of an active ingredient in a combination product
- Formulation
- Dosing regimen
- Active ingredient
- New Molecular Entity
- Combination product

Food and Drug Administration Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry Applications Covered by Section 505(b)(2). October 1999.

Examples cont…

- Indication
- Rx to OTC switch
- Naturally derived or recombinant active ingredient
- Bioinequivalence

Food and Drug Administration Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry Applications Covered by Section 505(b)(2). October 1999.

Considerations for Canadian NDS/SNDS

Considerations for Canada

- The 505(b)(2) NDA to the extent that the listed drug(s) and the proposed drug product differ must include sufficient data to demonstrate that the proposed drug product meets requirements for safety and effectiveness
- No 505(b) (2) in Canada.
- Can't cross-reference any Agency finding of safety and/or effectiveness for an approved drug product unless you have right of access to data (SNDS or NDS) or filing an abbreviated application (ANDS).
- Need to file as NDS or SNDS with applicable preclinical and clinical references
- Patent considerations
- Data exclusivity

Do I have sufficient data to file my 505(b)(2) in Canada?

Maybe. It depends.

What is required ?

- *C.08.002 A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following…*

  (g) detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended;

  (h) substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended;

- *C.08.003 (3) A supplement to a submission referred to in subsection (1), with respect to the matters that are significantly different from those contained in the submission, shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug in relation to those matters.*

What is required ?

- *C.08.005.1. (1) Every manufacturer who files a new drug submission… a supplement to any of those submissions shall, in addition to any information and material that is required under section C.08.002, C.08.002.01, C.08.002.1, C.08.003 or C.08.005, include in the submission or supplement*
- *(a) a copy of all clinical case reports respecting any subject of a study included in the submission or supplement if that subject has died, suffered a serious adverse reaction or an unexpected adverse reaction, or the study, insofar as it relates to this subject, has not been completed;*
- *(b) a sectional report in respect of each human, animal and in vitro study included in the submission or supplement;*
- *(c) a comprehensive summary of each human, animal and in vitro study referred to or included in the submission or supplement; and*

What is required ?

- *(2) A sectional report referred to in paragraph (1)(b) shall include*
  - *(a) a summary of each study included in the submission or supplement;*
  - *(b) a summary of any additional information or material filed to amend the submission or supplement; and*
  - *(c) where raw data is available to the manufacturer in respect of a study,*
    - *(i) a summary of the data,*
    - *(ii) a cross-referencing of the data to the relevant portions of the sectional report,*
    - *(iii) a description of the conditions under which the experiments from which the data were obtained were conducted,*
    - *(iv) the details of the data treatment process, and*
    - *(v) the results and conclusions of the study.*
- *(3) The comprehensive summary referred to in paragraph (1)(c) shall include a summary of the methods used, results obtained and conclusions arrived at in respect of all studies referred to or included in the submission or supplement and shall be cross-referenced to the relevant portions of the sectional reports.*

What does this mean?

- Requirements variable
- Generally no Canadian specific guidelines
- Importance of ICH, FDA and EMA guidances
- Importance of experts
- Foreign reviews
- Regulatory precedent
- Need to bridge to originator product (comparative bioavailability)
- Each reviewing division decides how much data is required
- Importance of pre-NDS meetings

Enough data to support NDS/SNDS?

- Typically no additional nonclinical data is required for Canada
- If developing in a new dosage form/new indication and there are holes in the earlier nonclinical development program the Agency may ask that you address them.
- Importance of clear understanding of FDA strategy to build on for Health Canada
- Use of foreign agency reviews
- 505(b)(2)s may have 1 pivotal study- requirement for confirmatory study?
- Cases where bioequivalent to a comparator that is not a comparable dosage form- not ANDS
- Current safety concerns?
- For switch- actual use and label comprehension studies

Factors to consider

- Extent of reliance on nonclinical and clinical literature
- Need to update literature review from point of FDA decision onwards?
- Literature review strategy- limited literature, extensive literature
- Clinical experience where nonclinical data is lacking
- Negotiation of nonclinical overview section only where completely based upon published literature
- Population of Product Monograph
- Use of portions of existing Product Monographs for active ingredients (usually nonclinical section).
- Requirement for RMP

Additional typical nonclinical and clinical content differences

- Differences in practice of medicine, product availability/competitor situation, or marketing strategy (e.g., not all indications intended for all markets).
- Applicability of foreign clinical data in Canada and need for additional local studies.
- Need to make reference to prior meetings and agreements with each agency.
- Integrated Summaries of Efficacy & Safety (ISE and ISS) are U.S. documents. Canada requires Modules 2.7.4 and 2.7.3 as summaries of safety and efficacy
- Need to incorporate more recent safety and efficacy information due to a lag in filing time
- Applicability of priority review or Notice of Compliance with Conditions (NOC/c)

Patent considerations

- Patent listing for your product where NDS patent must contain:
  - a claim for the medicinal ingredient;
  - a claim for the formulation that contains the medicinal ingredient;
  - a claim for the dosage form; and/or
  - a claim for the use of the medicinal ingredient as defined in section 2 of the PM(NOC) Regulations
- new patent SNDS
  - a supplement for a change in formulation (this includes a change in strength);
  - a supplement for a change in dosage form;
  - a supplement for a change in use of the medicinal ingredient.

- Applicable active patents that should be addressed (most likely none)

Health Canada. Guidance Document: Patented Medicines (Notice of Compliance) Regulations. April 2012

Data exclusivity

- 505(b)(2)s eligible for
  - 3 years if one or more of clinical investigations (other than BA/BE studies) was essential to approval of the application and was conducted or sponsored by applicant
  - 5 years if for a NCE
- May also be eligible for orphan drug exclusivity (7 years) and for pediatric exclusivity (6 months)

- NDS/SNDS
  - Vast majority of 505(b)(2)s will involve medicinal ingredients that have been previously approved in Canada
  - Drugs that contain medicinal ingredients that have been previously approved in Canada, including drugs that have previously received an NOC and/or a Drug Identification Number (DIN), will not be afforded protection.

Food and Drug Administration Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry Applications Covered by Section 505(b)(2). October 1999.

Health Canada. Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations. October 2011

General NDA to NDS/SNDS items for consideration

Module 1: Administrative Regional Information

Module 2: Quality, Nonclinical, Clinical Summaries

Module 3: Quality

Module 4: Nonclinical Study Reports

Module 5: Clinical Study Reports

Module 1

- Within eCTD format there are 4 main elements required in Module 1 that are common to both regions:

  -Cover Letter

  -Administrative Forms or Application Form

  -Product Labelling

  - Location of foreign labels in Module 1 varies across regions

  -Location also varies across regions

- The content of each of these will differ

Module 1 Requirements - Canada

- Health Canada Summaries
  - Certified Product Information Document (CPID)
  - Comprehensive Summary: Bioequivalence (CS:BE)
  - Datasets for CS: BE studies are also to be provided in Module 1

- Proof of GMP compliance for foreign sites and Health Canada Establishment Licence for Canadian sites
- Letters of authorization for DMFs
- RMP
- Environmental Risk Assessment, Statement or Waiver
- Look-alike/Sound-alike

Health Canada. Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format. June 2012

RMP

- REMs may be discussed at End of Phase 3/pre-NDA
- Typically the discussion around RMPs and need for them occurs at time of preNDS meeting
- REMS not required to be submitted with NDA in most cases
- The REMs does not address all 3 required elements of the RMP and a European RMP may not be available
- Experience where the review would not be initiated until RMP was received

Module 2 and Module 3 Quality content differences

- For Canada, it is preferred that chemistry and manufacturing information be summarized in a Health Canada (QOS) template .
- Key is that all information identified in template is captured in 2.3 & included in M3
- Differences in Module 2.3 will also arise due to different CMC requirements in Module 3 across the regions
- Drug Substance Drug Master File (DMF) reference will be different for each region
- Extent of information that must be included in M2 and 3 vs by reference to DMF differs
- In U.S. USP/NF only accepted versus USP/NF, Ph.Eur, Ph.F, BP in Canada
- Lag time in filing between Can and US may require inclusion of CMC amendments/supplements (e.g., as a result of process improvements, validation, analytical method changes, stability updates, etc)

Unique M3 “Drug Substance” Requirements Canada

Module	Content
3.2.S.4.1 Specifications	Signed and dated specifications on company letterhead from company responsible for DS release
3.2.S.4.4 & 3.2.P.5.4 Batch Analyses	CoAs for at least 2 batches of DS and 2 batches of DP (from pivotal nonclinical and clinical or comparative BA studies)

Unique M3 “Drug Product” Requirements Canada

Module	Content
3.2.P.3.1 Manufacturer(s)	Canadian distributor with Health Canada Drug Establishment Licence Number
3.2.P.5.1 Specifications	Signed and dated specifications on company letterhead
3.2.P.8.3 Stability	NDS needs to contain 12 months long-term and 6 months accelerated stability data on 3 batches (each strength) per ICH or scientific justification.

Module 3.2.R Regional Information

U.S.	Canada
Executed Production Documents	Executed and Master (Blank) Production Records
Comparability Protocols	Lot Release Information (Biologics Only)
Methods Validation Package	
	Description of medical device used to deliver drug product (if applicable)

Publishing aspects

- Movement CRFs out of study reports to 5.3.7
- eCTD identifier
- Study tagging files
- Literature references
- Level bookmarking in study reports
- NDA study reports often don’t have consistent unique identifiers and consecutive pagination across entire study

Examples NDSs that were 505(b)(2)s

Examples NDSs that were 505(b)(2)s

- Omnitrope (somatropin), NOC April, 2007. NDS (with a reduced clinical package) was filed as a Subsequent Entry Biologic (SEB) submission, as the sponsor claimed comparability between Omnitrope and Genotropin® [an innovator drug that was issued a Notice of Compliance (NOC) on January 19, 1998, for marketing in Canada but was never marketed in Canada].
- Caldalor (ibuprofen), NOC Nov, 2011. Priority clinical and C&M NDS indicated for the reduction of fever in adult patients where non parenteral antipyretic medication is inappropriate or impossible
- Testim (testosterone) gel, initial NOC May, 2006. NDS indicated in testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

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Status- Current and future

Approvals by fee category & NOC type (NDS/SNDS)

	07-08	08-09	09-10	10-11	11-12
Clinical or nonclinical & C&M	19/20	12/18	14/11	23/8	24/11
Clinical or nonclinical only	0/122	0/99	1/74	2/67	0/52
Comparative studies*	1/12	0/9	0/11	4/17	1/12
NAS	21	12	18	17	28
Published data only					0/3

Health Canada. TPD Annual Drug Submission Performance Report: April 1 2011-March 31 2012.

Future?

- An increasing number of approvals via the 505(b)(2) pathway in the US and as a result this group will comprise an increasing percentage of NDS and SNDSs
- Continued development of guidelines addressing the need for clinical and nonclinical studies depending upon product changes
- Legislative renewal
- Possible consideration of an analogue of the United States Food & Drug Administration (US FDA) 505(b)(2)2 process for certain types of products/applications
- Changes to data exclusivity provisions in Canada

Thank You

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