Notice: Archived Document

The content in this document is provided on the FDA’s website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.
Excipients:  
A Regulatory Support Prospective

Iain Margand, RPh  
Senior Regulatory Project Manager  
October 20, 2010
Overview

• Justification
• Specific Dosage Forms
• Control Correspondences
• Special Considerations
• Summary
Justification

• Consults
  – Sent to Office of New Drugs (OND) for review with available pharm/tox information once acknowledged
  – May take two to three months for a review

• Review available internal databases
  – Inactive Ingredient Database
  – Original NDA or ANDA submissions
Justification cont.

- Products required to be Q1/Q2 may be within ±5% of an approved ingredient, but cannot exceed the highest amount within our databases.
- Each inactive ingredient must be justified unless it is ≤0.1% of the total drug product weight.
- Dose vs MDD justification.
Statistics

- FY 2010: Received 813 RTR = 14%
- FY 2009: Received 859 RTR = 9%
- FY 2008: Received 830 RTR = 15%
- FY 2007: Received 877 RTR = 11%
- FY 2006: Received 796 RTR = 8.5%

RTR = Refuse to Receive ANDAs
RTR Breakdown

(25) Bioequivalence requirement(s) not being met

(23) Clinical

(13) Packaging

(10) Inactive ingredient levels

(10) MISC — Micro, Container Closure, Batch Records, etc.
RTR Breakdown Cont.

(8)  Stability
(7)  Submission format
(5)  Not Q1/Q2 – Ophthalmic
(4)  Basis of Submission
(3)  Not Q1/Q2 – Injection
(3)  Not Q1/Q2 – Nasal and other
(2)  Receipt date of DMF
(2)  Multiple minor issues (between ~10-20 issues)
Solid Oral Dosage Forms

- Must be justified via the same route of administration as proposed product
  - i.e. Buccal, Sublingual, Oral
- Route may be influenced by absorption site
  - Orally Disintegrating Tablet
  - Some Buccal products
- “Generic” descriptions do not always justify an inactive
  - Inactive may be a different grade or different product
Oral Solutions

• Not required to be Quantitatively (Q1) or Qualitatively (Q2) the same as the RLD
• Eligible for Bio Waiver under 21 CFR 320.22(b)(3)
• Be aware of the amounts of some inactive ingredients
  – Sugar Alcohols (Sorbitol, Mannitol, Glycerin)
  – May cause a change in Bioavailability
Ophthalmics

- **Required** to be Q1 and Q2 with the RLD

- 21 CFR 314.94(a)(9)(iv) no longer applies
  - Determination that changes in the formulation may adversely affect the efficacy of the drug product

- If you decide to make any change to the preservative, buffer, tonicity adjuster, thickening agent
- BE study must submitted at time of filing

- If no BE study is submitted we will Refuse to Receive your application

- 505(b)(2) option
Ophthalmics cont.

- Provide the amount of Benzalkonium Chloride as amount of Benzalkonium in the product
  - Ex: if using a 50% Benzalkonium Chloride solution, 0.5 mL would contain 0.25 mg of Benzalkonium

- When using a different hydrate of an inactive than in the RLD, provide the equivalent amount of the two inactives
  - Ex: Xdihydrate used in RLD = Xheptahydrate in generic
Topical Products

- Includes lotions, ointments, creams, solutions, foams, gels
- Generally, solutions do not need to be Q1/Q2 with the RLD under 21 CFR 320.22(b)(3)
  - Some products that fall under the Bioequivalence Waiver will still need to provide Bioequivalence and/or Clinical studies
Topical Products cont.

• Creams and Ointments do not need to be Q1/Q2 with the RLD
  – Not eligible for Bio Waiver
  – Will need to provide Clinical studies regardless
Topical Products cont

- Must demonstrate product is a solution when administered for some products to receive a Bio Waiver
  - Example: Foam

- Changes in amounts of inactive ingredients from the RLD may require additional studies or pharm/tox data
Nasal Sprays

• Must be Q1/Q2 with the RLD

• Still need to provide *in-vitro* studies
  – Plume geometry, droplet size, dispersion, etc.

• If the product is a suspension, will need to provide additional *in-vivo* studies
Metered Dose Inhaler (MDI) Nebulizer Solution

- MDI recommended to be Q1/Q2 with the RLD
- 21 CFR 314.94(a)(9)(v) allows for changes but must demonstrate changes do not affect safety or efficacy
- Products for nebulization are not required to be Q1/Q2 under 21 CFR 320.22(b)
- MDI’s are not eligible for a waiver
• Q1/Q2 to the RLD is always preferred
• May make changes in the formulation under 21 CFR 314.94(a)(9)(iii)
  – Buffer, Preservative, Antioxidant
• pH adjusters are not considered exception excipients
  – If the RLD has pH adjusters in the labeling, they must be included in the generic formulation and production batch records even if they are not utilized
  – 21 CFR 201.100(a)(iii) does not require a parenteral to list pH adjusters in the labeling
Transdermals

• The most difficult products to justify inactive ingredient
  – Backing Film, Release Liners, Adhesives, etc.
  – Components rarely in our databases
• If the components have been used in a previously approved product, let us know
  – Provide DMF numbers and approved product NDA or ANDA number(s)
Control Correspondence (CC)

- Regulatory Support Branch has responded to 381 CC for FY 2010

- The current turnaround time is 60 days

- Limits will be place on CC in the near future regarding the amount of controls that can be submitted by one firm per year and the expected response time

- We no longer respond by e-mail to a CC. We will respond by telephone call
(CC) cont.

- We will not respond directly to CC from outside the US. Firms that are outside the US must submit their CC to OGD through their US Agent.

- Do not send duplicate CC.

- We have seen the same requests sent to the Generic Drugs e-mail account and the CDER DRUG INFO account or other means of submission.

- Causes additional delays and confusion.
(CC) cont.

- Provide all the required information with request

- Determination is made similar to a filing review justification
  - May include additional steps for justification such as requesting the original NDA submission from storage
(CC) cont.

• Do not send Pharm/Tox information. We will not pre-review this information
  – If we cannot justify your inactive ingredient, pharm/tox information will need to be submitted in the ANDA submission

• We will not review formulations other than for Q1/Q2 sameness
  – Reminder - CC reviews are a courtesy extended to industry
Percent Amount

• Issues may occur when using percentage to justify an inactive ingredient
  – Especially prevalent with Oral solutions, Parenterals and Topical Products

• Example: The IID states an inactive ingredient is used at an amount of 90%
  – Unable to determine from this if the ingredient is presented as weight/volume (w/v), weight/weight (w/w) or volume/volume (v/v) or if this is amount per container or per dose
  – Always provide amounts in mg/mL whenever possible
Pharmacology/Toxicology

• When in doubt, provide pharm/tox information in the original ANDA submission

• Must provide complete studies of the inactive ingredient *via* the same route of administration
  – No summaries or reference to locations of studies
  – If a DMF contains all the studies, provide copies of the studies, **do not** reference the DMF
Pharmacology/Toxicology cont.

- Submit pharm/tox information in **electronic format only**
  - If ANDA is paper, provide a separate CD
  - If electronic, provide an easily identifiable location or section
  - Paper copies of the pharm/tox information **will not** be acceptable
- Studies must use Rodent and Non-rodent subjects at a minimum
  - See Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005*
Flavoring/Fragrance Ingredients or Agents

- The components and composition for these products must be provided at the time of submission
  - Reference only to a DMF/LOA is not sufficient

- Most flavorings and fragrances are not in the IID or the internal databases
Flavoring/Fragrance Ingredients or Agents cont.

- The applicant may provide the components and composition for only the portion of the formulation that is $\geq 0.1\%$ of the total drug product weight

  - This also applies to Natural and/or Artificial components within the product formulation
Iron

• If an inactive ingredient contains an iron (ferric) component, the daily elemental iron intake must be taken into account
  – Occurs most often with coloring agents

• May not exceed 5 mg/day of elemental iron
  – 21 CFR 73.1200(c)

• Provide justification within the components and composition section (3.2.P.1) to demonstrate the daily amount does not exceed the daily limit
DMF

- May be used to provide the formulation certain inactives
- The DMF **must** be in electronic format, have been previously submitted to the Agency and must be up to date
- Need to specify where the formulation can be located in the DMF
- We will not review the DMF itself, only the formulation
- If we are unable to locate the formulation or searching through a DMF is too time consuming, we will request a copy of the inactive ingredient formulation components and composition
- Currently only in preliminary stages
Summary

• The more information at the time of submission, the better

• Develop internal inactive ingredient database

• Do your homework!

• If an inactive ingredient is accepted by Regulatory Support, either via an ANDA submission or a Control Correspondence, does not imply there will not be issues during any one of the Divisional reviews
Contact Information

• Martin Shimer, Branch Chief (240) 276-8675

Regulatory Management Officers:
• Kwadwo Awuah (240) 276-8678
• Peter Chen (240) 276-8977
• Rebekah Granger (240) 276-8724
• Shannon Hill (240) 276-8650
• Tim Jetton (240) 276-8677
• Craig Kiester (240) 276-8968
Contact Information cont.

Regulatory Management Officers:

- Iain Margand (240) 276-8676
- Saundra Middleton (240) 276-8973
- Ted Palat (240) 276-8982
- Felecia (Lisa) Tan (240) 276-8679
- Linh Vo (240) 276-8978
- Johnny Young (240) 276-8977

Support Staff:

- Jean Grimes (240) 276-8154
- Eda Howard (240)-276-8954
- Eddie Washington (240)-276-8957