Report from the FDA Pharmacy Compounding Advisory Committee meeting on 2-28-2015

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Bill Mixon, RPh, MS, FiACP, FACA
The Compounding Pharmacy
Hickory, NC 28602
wmixon@thecompoundingrx.com

Disclosures

Bill Mixon declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria."

Learning Objectives

At the conclusion of this program, the participants will be able to:
• Understand the composition of the FDA PCAC and how that affects the outcome
• Understand the agenda for the 2nd meeting of the FDA PCAC June 17-18, 2015
• Gain an understanding of other changes at the State and Federal level that affect pharmacy compounding from the speakers perspective.
• Understand how the FDA will define “Demonstrably Difficult” compounds

FDA PCAC Timeline

- Nov 21, 1997  FDA Modernization Act signed into law by President Bill Clinton
- Oct 8, 1998  First list was published in the Federal Register after consulting the (original) Pharmacy Compounding Advisory Committee (PCAC)
- Oct 14-15, 1998  First meeting of the original PCAC
- March 8, 1999  FDA finalized and codified the original withdrawn or removed list
- July 13-14, 2000  PCAC voted to include amitriptyline, astemizole, cisapride, grepafloxacin, and troglitazone to the list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective.
- FDA did not complete this rulemaking or further update this rule because of ongoing litigation concerning the validity of section 503A, which was resolved by the enactment of the Drug Quality and Security Act (DQSA) in 2013

FDA Pharmacy Compounding Advisory Committee

• First meeting of the “new” PCAC was February 23 & 24, 2015
  – Consider 2 drugs for exclusion for which comments were received (adenosine and chloramphenicol)
  – Consider 25 drugs for exclusion for which NO comments were received
  – Consider 6 drugs for addition to the List of Bulk Substances that we may compound with

FDA Public Hearing Room, from the visitors gallery
Overview of PCAC Committee

• 12 voting members
• 2 non-voting “industry representatives”
• 12 FDA Participants (also non-voting)
• We met in Silver Spring, MD at the FDA headquarters
• 2 day meeting, with 3 more meetings planned for 2015
• Meetings are open to the public, and can make comments during the Open Public Hearing time

PCAC Membership

• 12 Voting members:
  – Jürgen Venitz, MD, PhD, (Chairman) College of Pharmacy, VCU
  – Gigi Davidson, RPh (USP) NCSU College of Veterinary Medicine
  – Donna Wall, PharmD (NABP) Indiana University Hospital
  – Katherine Pham, PharmD Children’s National Medical Center
  – Allen Vaida, RPh Institute for Safe Medication Practices
  – Robert DeChristoforo, MS NIH (Chief, Clinical Ctr Pharmacy Dept.)
  – William Humphrey, RPh, St. Jude’s Children’s Research Hospital
  – Padmar Gulur, MD UC Irvine (anesthesiologist)
  – Michael Carome, MD Public Citizen (Ralph Nader’s organization)
  – John DiGiovanna, MD NIH (dermatologist)
  – Elizabeth Jungman, JD Pew Charitable Trusts
  – Stephen Hoag, PhD (professor) Univ Maryland Dept. Pharm. Sciences

PCAC Membership, continued

• Non-Voting Members
  – Ned Braunstein, MD Industry Representative (works for Regeneron Pharmaceuticals, maker of Eylea)

  – Bill Mixon, RPh Industry Representative (owns The Compounding Pharmacy, Hickory NC)

  – Jayne Peterson, RPh, JD Designated Federal Officer from FDA

Day 1, Session 1, of the PCAC

• Call to order, Conflict of interest statements, etc.
• FDA introductory remarks and historical review of the “Do Not Compound” list
• Consideration of addition of 2 drugs for addition to the “Do Not Compound” list
  – Adenosine Phosphate Added to Do Not Compound list
  – Chloramphenicol (for oral use only) Added to Do Not Compound list
Day 1, session 1, continued

Discussion and voting on 25 additional drugs to be added to the “Do Not Compound” list:

- Alatrofloxacin (all forms - Trovan)
- Aminopyridine
- Astemizole
- Bromfenac Sodium (except Bromfenac Na ophthalmic solutions)
- Cerevisatin Na
- Cisapride
- Esmolol HCl (all parenteral forms)
- Gatifloxacin (except ophthalmic solutions)
- Grepafloxacin
- Methoxyflurane
- Novobiocin Na
- Pemoline
- Perglide mesylate
- Phenylpropanolamine
- PEG 3350 with NaCl, Bicarb, KCl & Bisacodyl ER 10mg or >
- Propoxyphene HCl
- Raprocuronium Br
- Rofecoxib (Vioxx)
- Sibutramine HCl (Meridia)
- Tegaserod maleate (Zelnorm)
- Troglitazone (Rezulin)
- Trovafloxacin mesylate
- Valdecoxib (Bextra)
- Oxycodone HCl EXTENDED RELEASE products without Abuse-detterent properties

Day 1, session 2-
The “Positive List”

- FDA introduction to the “new” List of Bulk Substances That Can Be Used to Compound Drug Products Under 503A, a.k.a. The Bulk Drug Substance List, or “The Positive List”

Nominations to the list:
1. Thymol Iodide
2. Silver Protein Mild
3. Squaric Acid Dibutyl Ester
4. Diphencyclopropenone
5. Cantharidin
6. Pirectam

Day 1, Session 2, continued

- Per DQSA, section 503A states that the criteria for determining which substances should appear on the bulk drug substances list “shall include”:

  1. Historical Use
  2. Reports in peer reviewed medical literature, or
  3. Other criteria the FDA may identify

Day 1, Session 2, continued

- Conditions for Bulk Drug Substances Used to Compound under 503A per DQSA:
  - Bulk drug substances (i.e. typically active ingredients) used to compound must:
    - Comply with the standards of an applicable USP/NF monograph, if one exists, and the USP Chapters on pharmacy compounding
    - Be a component of an FDA-approved drug, if an applicable USP/NF monograph does not exist, or
    - …must be on a list developed by FDA through regulation
    - Be made at a facility registered with FDA, and have a valid Certificate of Analysis
Day 1, Session 2, continued

2015 Proposed 503A List Evaluation Criteria:
- The physical and chemical characterization of the drug with respect to purity, identity and quality.
- Any safety issues raised by the use of the substance in compounded drug products
- The historical use of the substance in compounded drug products...for medical conditions published in peer-reviewed medical literature
- The available evidence of effectiveness, or lack thereof, if it exists.

Day 1, Session 2 and Day 2

Discussion of the following nominations for inclusion on the “Positive” List
- Thymol lodrde (Approved)
- Silver Protein Mild (not approved)
- Squaric Acid Dibutyl Ester (Approved)
- Diphenylcyclopropenone (DPCP) (Approved)
- Canthardin (Approved)
- Piracetam (not approved)

In all cases, the vote followed the recommendation of the FDA

2nd meeting of the “new” FDA PCAC meeting

- All of the previous slides related to the first meeting in February
- The second meeting is scheduled for next week on June 17 and 18, 2015
- Meetings are open to the public, are broadcast live, and are recorded for future viewing

June 17-18, 2015 meeting

- Federal Register, May 22, 2015-announcement of the following agenda items:
  - Update on expanded access to investigational drugs
  - Consideration of 4 additions to the “do not compound” list
  - Discussion of 4 bulk drug substances to include on the “Positive” list
  - Discuss criteria FDA is proposing to evaluate drug products or categories as “demonstrably difficult to compound”

June 17-18, 2015 meeting

Proposed addition of 4 drugs to the “Do Not Compound” list:
- Aprotinin (bovine pancreatic trypsin inhibitor-Trasylol)
- Ondansetron HCl for IV doses of >16mg
- Bromocriptine mesylate for prevention of lactation
- Acetaminophen all drugs with > 325 mg per dose

Drugs to be considered for inclusion on the 503A Bulk Drug Substances List during the next meeting

- The FDA received information on 64 Bulk Drug Substances that was sufficient for Evaluation for Inclusion on the 503A Bulk Drug Substances List:
- 4 bulk substances will be discussed at the June 17-18 meeting:
  + Brilliant Blue
  - Tranilast
  - N-acetyl-D-Glucosamine
  - Oxiriptan (a.k.a. 5-hydroxytryptophan)
Drugs to be considered for inclusion on the 503A Bulk Drug Substances List during the next meeting

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA's Recommendation to the committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brilliant Blue</td>
<td>Add to &quot;positive&quot; list</td>
</tr>
<tr>
<td>Tranilast</td>
<td>Do Not Add to &quot;positive&quot; list</td>
</tr>
<tr>
<td>N-acetyl-D-Glucosamine</td>
<td>Add to &quot;positive&quot; list for topical use</td>
</tr>
<tr>
<td>Oxitriptan (5-HTP)</td>
<td>Do Not Add to positive list</td>
</tr>
</tbody>
</table>

June 17-18, 2015 meeting

"During the morning of June 18, the committee will discuss the criteria FDA is proposing to use to evaluate drug products or categories of drug products for identification as demonstrably difficult to compound."

Criteria for the “Demonstrably Difficult to Compound” list

1. Complex Formulation
   - A formulation in which the APIs or excipients must have unique properties to achieve and maintain the proper performance of the drug.
   - It might contain ingredients that have certain properties or functions to allow or prevent certain outcomes.
   - Crystalline forms and particle size might be critical to the safety or efficacy of the drug.
   - Complexity increases likelihood of adverse effect on safety or efficacy of the compound.

2. Complex Drug Delivery Mechanism
   - Refers to the way the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect, such as passing through the stomach without dissolution or absorption or achieving permeation through the skin at a specific rate.
   - May include coated beads, polymeric matrices, or liposomes.
   - Complexity of the delivery mechanism increases likelihood of an adverse effect.

3. Complex Dosage Form
   - Complex dosage form refers to physical dosage units with characteristics that are difficult to consistently achieve and maintain.
   - The formulation may be simple (single API or simple delivery system, such as an injection).
   - Examples may include a propellant based aerosolized product or dry powder inhalers.
   - A complex drug delivery system could increase the likelihood of an adverse effect if done incorrectly.
4. Bioavailability

- Refers to the rate and extent an active ingredient is absorbed from a drug product and becomes available at the (desired) site of action.
- Drug products may be considered difficult to compound if bioavailability is challenging to achieve because of the characteristics of the API or compounded formulation (low permeability or low solubility)
- Inconsistent bioavailability could increase the likelihood of an adverse outcome.

5. Compounding Process Complexity

- This refers to whether compounding the drug requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product.
- …multi-particulate dosage forms of solid oral beads that require wet granulation, extrusion, drying, coating, curing before being processed into their final dosage form
- Process errors can lead to adverse outcomes

6. Physicochemical or Analytical Testing Complexity

- Refers to challenges presented with confirming the end-product testing for batch to batch uniformity, potency, purity, and quality of a drug product.
- Testing complexity requires specialized testing equipment or special training to perform the test
- May include cell-based assays, testing using NMR, mass spectrometry, and/or X-ray powder diffraction.
- Drug quality defects would be difficult to detect.

Unique Drug Products or Categories of Drug Products Nominated for the Difficult to Compound List

- Advair Diskus & Advair HFA
- Alprostadil injectable
- Ampyra ER tablets
- Atropine
- Azithromycin IV
- Baclofen intrathecal
- Bio-identical hormone Pellets
- Dry powder inhaler products
- Enteric-coated preparations
- Estradiol, oral and topical
- Estriol
- High Potency Drugs
- Low Dose Drugs
- Modified Release drug products
- Morphine intrathecal
- Nitroglycerin Ointment
- Non-sterile to sterile compounding
- Progesterone, oral and topical
- Progesterone with Estradiol oral and topical
- Papaverine injectable
- Sterile Drugs
- Sterile products for ophthalmic use
- Testosterone Pellets
- Transdermal Delivery Systems
- Wellbutrin SR tablet
- Zyban SR tablet
- …there are plenty more on the list of nominations…

Nominations for the Difficult to Compound List, continued

- Advair Diskus & Advair HFA
- Alprostadil injectable
- Ampyra ER tablets
- Atropine
- Azithromycin IV
- Baclofen intrathecal
- Bio-identical hormone Pellets
- Dry powder inhaler products
- Enteric-coated preparations
- Estradiol, oral and topical
- Estriol
- High Potency Drugs
- Low Dose Drugs
- Modified Release drug products
- Morphine intrathecal
- Nitroglycerin Ointment
- Non-sterile to sterile compounding
- Progesterone, oral and topical
- Progesterone with Estradiol oral and topical
- Papaverine injectable
- Sterile Drugs
- Sterile products for ophthalmic use
- Testosterone Pellets
- Transdermal Delivery Systems
- Wellbutrin SR tablet
- Zyban SR tablet
- …there are plenty more on the list of nominations…
Thank you for allowing me to represent you in this role on the FDA Pharmacy Compounding Advisory Committee

Need More Information?

Bill Mixon RPh, MS, FIACP, FACA

The Compounding Pharmacy
750 4th St. SW, Hickory, NC 28602
(828) 324-4115
wmixon@thecompoundingrx.com