Final Minutes

July 13 and 14, 2000 – 3rd Meeting of the
Pharmacy Compounding Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research
Advisory Committee Conference Room, Room 1092
5630 Fishers Lane, Rockville, MD

Objectives: The committee will review five drug products for inclusion on a list of drug products that cannot be compounded because they have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.

The committee will discuss and provide FDA with advice about drug products that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of those drug products.

The meeting was held in the CDER Advisory and Consultants Conference Room. Prior to the meeting, the members, consultants and guests had reviewed the background information from the FDA. There were approximately 50 persons in attendance. The meeting started at 8:30 a.m.both days and ended at approximately 4:15 p.m. on July 13th and at approximately 10:30 a.m. on July 14th.

Attendance:
PCAC Members Present: Randy Juhl, Ph.D., Chair, Lloyd Allen, Jr., Ph.D., R.Ph., Elizabeth McBurney. M.D., Sarah Sellers, Pharm.D., Garnet Peck. Ph.D., William Rusho, R.Ph., Lawrence Trissel, F.A.S.H.P., Joan LaFollette, R.Ph.(Industry Representative, non-voting), Rose-Ellen Hope, R.Ph. (Consumer Representatiave), R.Ph.(Industry Representative, non-voting), Judith Martin Riffee, R.Ph., Tony Welder, R.Ph.

PCAC Members Absent: Christopher Rhodes, Ph.D., Carmen Catizone, M.S., R.Ph., David Liebman, D.P.A., R.Ph. (Industry representative, non-voting).

FDA Participants: Kathleen Anderson, Pharm.D., Jane Axelrad, J.D., Peter Cooney, Ph.D., Amit Mitra, Ph.D., Lana Ogram, Brian Rogers, Ph.D., George Scott, R.Ph., Vinod Shad, Ph.D.

Non-FDA Speakers: Andrew Blight, M.D. (Acorda Therapeutics), Veronica Mallon, Ph.D., (Acorda Therapeutics)

Open Public Hearing Speakers:
7/13/00:
Jana Nestlerode, J.D., patient, representing herself, argued against inclusion of DMPS on the bulks list. Committee chair Juhl asked FDA to report about their second look into DMPS at the next Pharmacy Compounding meeting.
Larry Sasich, Pharm. D.,Public Citizen Health Research Group, generally supported the concept paper, but cautioned about the use of non-sterile ingredients to make sterile products)
Shelly Capps of the International Academy of Compounding Pharmacists (IACP) stated that IACP would be submitting scientific comments to the Agency. But, they were disappointed with the late issuance of the concept paper, and also wished there to be a discussion of drugs versus drug products.
7/14/00:
Susan Guzzo , R.Ph., J.D., Office of the General Counsel, Boehringer Ingelheim Pharmaceuticals, Inc. stated that sterile products (esp UDVs) should be added to the difficult to compound list.
Henri R. Manasse, Jr., Ph.D., Sc.D., Executive Vice President and CEO, American Society of Health-System Pharmacists (ASHP) suggested the Committee consider both the ASHP sterile compounding guidelines as well as USP chapter 1206.
Greg Jones, R.Ph., Pharmaceutical Programs Manager of the Florida Department of Health. Bureau of Pharmacy Services, discussed some of the abuses his department has encountered in the compounding of mostly copies of commercial products, mostly in the areas of inhalants, sterile products, and controlled-release products.

Committee Discussion/Vote:
Issue #1: Withdrawn or Removed List of Drug Products:
The Committee debated adding the following products to a list of drugs that may not be compounded because they were either withdrawn OR removed from the market because the drug or component of drug was found unsafe or not effective: aminopyrine, astemizole, cisapride, grepafloxacin, and troglitazone. All 5 were added to this list by the following votes:

For aminopyrine, astemizole, grepafloxacin, and troglitazone: 9-0 to add;
For cisapride: 8-1 to add.

Issue #2: Demonstrably Difficult to Compound:
The following Questions (in *italics*) were asked of the Committee, and the following recommendations were obtained (in **bold**):

1. *Do you agree that the following are the appropriate factors to use in evaluating drug products or categories of drug products to determine if they should be included on the difficult to compound list?*

    i. ***Drug delivery system**: Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility? Is the safety or efficacy of the product a concern if there is product-to-product variability?*

    ii. ***Drug formulation and consistency**: Is a sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility? Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve? Is the safety or efficacy of the product a concern if there is product-to-product variability?*

    iii. ***Bioavailability**: Is it difficult to achieve and maintain a uniformly bioavailable dosage form? Is the safety or effectiveness of the product a concern if the bioavailability varies?*

    iv. ***Complexity of compounding**: Is the compounding of the drug product complex? Are there multiple, complicated or interrelated steps? Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?*

    v. ***Facilities and equipment**: Are sophisticated facilities and/or equipment required to ensure proper compounding of the drug product? Is there a significant potential for error in the use of the facilities or equipment that could affect drug safety or effectiveness?*

    vi. ***Training:** Is specialized, highly technical training essential to ensure proper compounding of the drug product?*

    vii. ***Testing and Quality Assurance**: Is sophisticated, difficult to perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing? Is there a significant potential for error in the testing of the drug product that could affect safety or effectiveness?*

The Committee voted yes (9-0) to this question.

If not, what different or additional factor(s) would you suggest we use in the evaluation?
The Committee suggested that risk versus benefit considerations should be added as factors. Also, the Committee suggested that some of the nebulous terms (such as "sophisticated" or "complex") be clarified.

Do you think that the difficulty or importance of achieving stability should be considered as a factor?
The committee suggested that stability should be considered as a factor, especially its relationship to packaging components. When the committee was asked whether or not stability should be made a separate (8th) factor, or placed within one of the seven factors (e.g., numbers *ii* or *iii* above), the committee voted 9-0 to place stability *within* one of the seven factors.

2. *Do you agree that the class of metered dose inhalers should be included on the list of drug products that may not be compounded because they are difficult to compound properly?*
   The Committee voted 9-0 to add metered dose inhalers to the list of products that may not be compounded because they are too difficult.

3. *Do you agree that the class of dry powdered inhalers should be included on the list of drug products that may not be compounded because they are difficult to compound properly?*
   The Committee voted 9-0 to add dry powdered inhalers to the list of products that may not be compounded because they are too difficult.

4. *Do you agree that the class of transdermal drug systems, as defined in the concept paper, should be included on the list of drug products that may not be compounded because they are difficult to compound properly?*
   The committee added the phrase "…and commonly called patches…" in between "*as defined in the concept paper*" and "*should be included on the list…*" and with this change voted 9-0 to add transdermal products the list of products that may not be compounded because they are too difficult.

5. *Do you agree that the class of sterile drug products that are not compounded in accordance with USP Chapter 1206 should be included on the list of drug products that may not be compounded because they are difficult to compound properly?*
   The committee was in favor of using a MODIFIED USP Chapter 1206 (see below). Thus, the Committee agreed with the above question 9-0 that sterile drug products that are not compounded in accordance with USP Chapter 1206 should be included on the list of drug products that may not be compounded.

   Concerns with this chapter were raised. This chapter is seen more as a guideline and thus would need to become an enforceable entity strengthened. The chapter would need to remain flexible to changing technology. Also, some potential problems with the chapter were pointed out such as no mention of the LAL test, and a lack of description of various procedures.

Is USP Chapter 1206 an appropriate standard? If not, what other standard would you suggest we use?
Concerns with this chapter were raised. This chapter is seen more as a guideline and thus would need to become a strengthened enforceable entity. The chapter would need to remain flexible to changing technology. Some potential problems with the chapter were pointed out such as no mention of the LAL test, a lack of description of various procedures, and a lack of discussion of standards for bulk actives & excipients. Overall, the Committee voted 9-0 to make this chapter the standard and urged all other organizations such as the ASHP to participate in the revisions of 1206.

Should compliance with USP Chapter 1206 be required for the compounding of relatively low-risk sterile products from sterile components?
This question was tabled.

The Committee recommended adding the following types of products for the Agency's consideration as potentially demonstrably difficult to compound: Sustained release capsule/tablets/suspensions; enteric-coated products; antibiotics for pediatric use with flavoring agents added; biotech products covered under 505.

Lastly FDA agreed to pursue solutions to the 4-AP issue (since Acorda was not able to initiate an open-label expanded access program) in cooperation with IACP.

A verbatim transcript of this meeting will be available on the FDA's Docket's Management Branch Website approximately 30 days after the meeting. The address is: HTTP:/www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the July 13 and 14, 2000, meeting of the Pharmacy Compounding Advisory Committee and that these minutes accurately reflect what transpired.

Igor Cerny, Pharm.D. Acting Exec. Sec., PCAC	Date	Randy Juhl, Ph.D. Chair, PCAC	Date