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**EXHIBIT 8**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING  
ADVISORY COMMITTEE

Friday, July 14, 2000

8:30 a.m.

Advisory Committee Conference Room 1066  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852

## PARTICIPANTS

Randy Juhl, Ph.D., Chairperson  
Igor Cerny, Pharm.D., Executive Secretary

## MEMBERS

Loyd V. Allen, Jr., Ph.D.  
Elizabeth I. McBurney, M.D.  
Garnet E. Peck, Ph.D.  
Judith Martin Riffée, R.Ph.  
William J. Rusho, R.Ph.  
Sara L. Sellers, Pharm.D.  
Lawrence Trissel, F.A.S.H.P.  
Tony Welder, R.Ph.

## INDUSTRY REPRESENTATIVE

Joan M. LaFollette, R.Ph.

## CONSUMER REPRESENTATIVE

RoseEllen M. Hope, R.Ph.

## FDA

Kathleen Anderson, Pharm.D.  
Jane Axelrad  
Peter H. Cooney, Ph.D.  
Lana Ogram  
Capt. George Scott

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## C O N T E N T S

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General Counsel, Boehringer Ingelheim 4

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1 PROCEEDINGS

2 Call to Order

3 DR. JUHL: Good morning. Welcome to Day 2 of the  
4 Pharmacy Advisory Compounding Committee. Today we will be  
5 considering the portion of the agency's proposed White Paper  
6 on difficult to compound that deals with sterile products, a  
7 continuation of discussions that we began yesterday.

8 The first order of business this morning is to  
9 conduct an Open Public Hearing. We have a number of  
10 speakers that have requested before us. We will go through  
11 the list and, if there is still time remaining of the hour  
12 that we have allotted, we will give the opportunity to those  
13 who may not have scheduled themselves, an opportunity for  
14 brief comments, if they desire.

15 The first person that I have listed is Susan

16 Guzzo. Susan, are you here? Susan is from the Office of  
17 General Counsel at Boehringer Ingleheim Pharmaceuticals.  
18 She has requested ten minutes to talk with us. Welcome.

19 Open Public Hearing

20 MS. GUZZO: I apologize for yesterday and I  
21 appreciate your accommodating me for today. I am a  
22 registered pharmacist. Also I am an attorney and I am with  
23 Boehringer Ingleheim, Pharmaceuticals.

24 Of course, I would like to provide you with some  
25 information about products whose integrity we believe is

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1 drastically compromised when they are compounded and, as a  
2 result, do pose a serious threat to public safety.

3 The first area of concern that I would like to  
4 speak to you about is the unit dose inhalation vials. The  
5 FDA has long recognized the importance of sterility for  
6 these inhalation products. Nonsterile products that are  
7 introduced into the lungs pose a safety risk, but, often,  
8 these patients are already immunocompromised because they  
9 are either elderly or they have a disease.

10 Therefore, the FDA has always imposed the  
11 strictest standards of manufacturers to insure sterility.  
12 The manufacturing that we do is all done, or performed, in a

13 highcontainment filling area. This means that there are  
14 hepafilters that continually clean the air. It also means  
15 that access by personnel is extremely restricted and those  
16 that do enter must wear an airsuit gown before entering.

17 Also, all equipment, tanks and filling equipment  
18 are cleansteamed sterilized before each and every batch.  
19 Highpurity water is used in all preparations and there is  
20 a sterile filtration of the product.

21 The resins that we use in the vials are high  
22 temperature heated rendering them sterile and pyrogen free  
23 before they are filled. Procedures are in place to insure  
24 there are no traces of other drug product that could  
25 possibly contaminate the product and as well stability

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1 testing is done on every batch that can verify that the  
2 product is sterile eighteen months after preparation.

3 These are the standards that we impose and we meet  
4 to insure the public safety of inhalation products that we  
5 produce are sterile. Sterility has not waned as a public  
6 safety issue in the FDA's view and it is still evident  
7 because the FDA has recently issued that sterility  
8 requirement for aqueousbased drug products that becomes  
9 effective in May of 2002.

10 Just to mention the same issues of sterility also  
11 apply to morphine for intrathecal use and also for cafcit  
12 oral solution which is administered to premature infants who  
13 don't even have a developed immune system.

14 A second reason why inhalation products should be  
15 considered seriously is because of the containers in which  
16 they are packaged. It has been demonstrated by FDA, by us  
17 and by others, that the lowdensity polyethylene vials allow  
18 impurities to migrate into the product. As a result, we, as  
19 manufacturers, are not even allowed to affix a label to  
20 these vials.

21 Rather, we have to emboss the name of the product  
22 on the vial and then we have to enclose all these low  
23 density polyethylene vials in a foil pack to prevent  
24 exterior contaminants from migrating in. Migration of  
25 contaminants is really a safety hazard, so much so that one

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1 manufacturer has recently recalled 60 of its own lots  
2 because there was a migration of packaging material into the  
3 product.

4 I have not even heard this being considered to  
5 date. Packaging and compounding would probably have to meet  
6 some kind of standards as well.

7 Another area of concern, however, and grave  
8 concern, quite frankly, is the use of benzalkonium chloride  
9 in many of these UDV vials. It is used as a preservative in  
10 many compounded formulations, but the difficulty is that  
11 this product has been used to show bronchoconstriction.  
12 This is exactly the thing that the medications are trying to  
13 prevent.

14 So we do not use this preservative in our  
15 component formulations exactly for this reason.  
16 Nonetheless, it is routinely used by compounders. Because  
17 it is an adjunct ingredient, it is not required that the  
18 compounding pharmacist reveal this or disclose this to the  
19 patient.

20 So, if the patient has bronchoconstriction, they  
21 don't know if it is from the benzalkonium chloride, or they  
22 say to their doctor the drug is not working. So that is  
23 another area that I hope you will consider.

24 Finally, at this time, anyway, there is no  
25 mechanism in place to gather adverse events on compounded

1 products. As manufacturers, of course, we are required to  
2 gather this information and report all these adverse events,  
3 but when you consider that approximately 50 percent of all

4 inhalation UDVs are being compounded in the State of Florida  
5 and there is no way of gathering this information as to the  
6 ill effects that the process may have, that is also a grave  
7 area of concern.

8       So, for these reasons, for sterility, stability,  
9 packaging containers and nondisclosure of potential of  
10 adjunct ingredients and, perhaps, not a safety reporting  
11 mechanism in place, I would hope that you would consider  
12 looking at UDVs as one of those products that would be  
13 placed on a negative formulary.

14       Do any of you have questions for me?

15       DR. JUHL: Questions from the committee?

16       DR. SELLERS: Can you comment on the quality of  
17 bulk materials that are used in manufacturing sterile  
18 products?

19       MS. GUZZO: I can, to some limited degree. I can  
20 tell you that, for instance, morphine for intrathecal use;  
21 we, as manufacturers, start with a sterile, dry powder  
22 product. Our morphine is sterile to begin with.

23       If, in fact, you come in with a nonsterile  
24 product, a bulk ingredient product, sterilization of that  
25 after the fact is almost impossible. So I don't know, Sara,

1 if that goes to your question. But, other than that, if you  
2 would need more information, I am happy to provide it for  
3 you at a later date.

4 DR. JUHL: I have a question. The compounded  
5 products that you are speaking against, and I guess without  
6 naming drugs or products, I am wondering are they  
7 essentially copies of commercially available products?

8 MS. GUZZO: Yes; exactly.

9 DR. JUHL: So that they are already in violation  
10 of the

11 MS. GUZZO: Yes; exactly. There is information  
12 that I can provide to you. I think we are not here today to  
13 talk about the difference between manufacturing and  
14 compounding, but when you walk into a nursing home,  
15 100 percent of those patients are receiving a compounded  
16 product when, in fact, commercial product is available, I  
17 think that that is directly the issue.

18 As you know, I am a pharmacist and there is a need  
19 for compounded products, but this may be that line that you  
20 are speaking of, Randy.

21 DR. JUHL: The venue in which these products are  
22 used are primarily nursinghome, institutional, settings,  
23 outpatient or is it a variety that

24 MS. GUZZO: It is a variety. Yes.

25 DR. JUHL: Thank you.

10

1 Other questions or comments?

2 MS. GUZZO: I appreciate the time. Thank you very

3 much.

4 DR. JUHL: Thank you.

5 Next we have comments from Shelley Capps,

6 International Academy of Compounding Pharmacists. Shelley?

7 MS. CAPPS: Good morning. Thank you. Initially,

8 the International Academy of Compounding Pharmacists was

9 prepared to make a scientific presentation today. Upon

10 reading the issues for this meeting, we asked our previous

11 representative at this meeting, Gina Ford, to attend and

12 speak.

13 Gina is compounding pharmacist who would have

14 addressed the more practical concerns that were talked about

15 yesterday. However, because this committee has already

16 voted and made recommendations on all but one issue, we did

17 not want to waste your time and, instead, will just submit

18 comments to the FDA by the August 15 deadline.

19 Instead, what I would like to do today is to

20 discuss our disappointment in the procedural design of this

21 meeting. I would like to offer some suggestions about how  
22 the Academy can and would like to work with this committee  
23 in the future.

24 Ideally, the concept paper would have been  
25 published well in advance of this meeting. The public would

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1 have been given at least 45 days to comment on this paper  
2 and then the committee would have been apprised of the  
3 public comments prior to the meeting.

4 As it now stands, the committee has made  
5 recommendations only a few days after the concept paper was  
6 published without the benefit of thoughtful comments from  
7 practitioners in the industry that will be directly affected  
8 by this concept paper. The public was given less than 15  
9 days notice of this meeting. The public was only given two  
10 days to respond and request to present at this meeting.

11 The concept paper was released on June 29. This  
12 is only two business days prior to requesting participation  
13 here today. FDA's extensive bibliography has still not been  
14 put on display at FDA dockets. This makes it far more  
15 difficult to review the references cited by FDA. All of  
16 these factors have severely hampered input to this panel.

17 In addition, no agenda was provided. If it had

18 been given, Gina would have requested to participate in the  
19 first day's discussions and would have been available to  
20 address practical concerns.

21       The issues you have addressed are critical to our  
22 membership, pharmacists who work with tens of thousands of  
23 physicians who treat millions of patients. This network of  
24 professionals and patients puts us in a unique position to  
25 provide this committee with information.

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1       For example, yesterday, the committee had  
2 questions about 4AP. If ICP had been notified in advance  
3 of this discussion, we would have been prepared to assist  
4 the committee. The committee suggested a stability study  
5 for this substance. With three months' notice, we could  
6 provide this information to the committee.

7       In closing, we believe this committee has been  
8 greatly disadvantaged because public comment here has been  
9 limited. As I stated yesterday, ICP believes strongly that  
10 this concept paper strays from Congressional intent for  
11 determining what is to be considered demonstrably difficult.

12       As stated twentyfive times in the legislation,  
13 including four times related to demonstrably difficult, a  
14 drug product and not a technique or class of delivery

15 systems must be proven demonstrably difficult. For this  
16 reason, we believe that the concept paper, itself, is  
17 flawed.

18 Had notice been given and public comment allowed  
19 prior to this meeting, this legal argument could have been  
20 made and resolved. I only address these issues I know you  
21 have pointed out that it is a legal issue, but I only  
22 address them because I want to convey to the committee that  
23 we very much want to work within this forum and help this to  
24 be an effective meeting.

25 Thank you.

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1 DR. JUHL: Thank you very much.

2 Let me kind of go through by point. We will have  
3 some additional information on 4AP at the end of the  
4 meeting I think will get us past the point we were  
5 yesterday. With regard to the design of the concept paper  
6 and its treatment by class, I would invite comments by the  
7 committee, not on the legal basis but on the commonsense  
8 versus noncommonsense approach that was taken on this.

9 I think that would be helpful to the agency  
10 although the legal issue that specifically is raised is a  
11 different one, my one opinion is this seems to be a common

12 sense way to approach the issue, again avoiding the question  
13 as to whether or not that is within the strict legal reading  
14 of the law.

15 Are there other comments on that that the  
16 committee would like to offer?

17 MR. TRISSL: I couldn't agree with you more. The  
18 issue is demonstrably difficult to make correctly without  
19 having these facilities and equipment and training and  
20 procedures all in place. It is not a moleculespecific  
21 problem. It is an issue that spans the entire spectrum of  
22 drugs and, unlike stability, which would be molecule  
23 specific, this is something that applies to anything that is  
24 going to be made as a sterile product.

25 So I see no other way to approach this in any kind

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1 of reasonable manner but as an issue that spans everything.  
2 Unlike, say, the silver nitrate that we put on a list that  
3 you can't compound, this doesn't preclude compounding  
4 anything. It just says that you must have a certain level  
5 of quality assurance to make this in a safe and sane manner.

6 I think it is a perfectly reasonable approach.

7 DR. JUHL: Other comments?

8 DR. PECK: It would appear one has to start

9 somewhere in terms of discussion of drug products that may  
10 be compounded. One approach could be to divide the products  
11 that might be considered to be compounded into certain  
12 groups. It is not necessarily to slot these particular  
13 products into this group, but it does happen, the way they  
14 are delivered. So the approach here would be to consider  
15 the drug delivery system and its complexities.

16 I think what we discussed yesterday, the several  
17 that we discussed, I think, thoroughly, can be well defined  
18 as products and we can approach it from that standpoint.  
19 There are a number of things that were pointed out in terms  
20 of what the committee was going to look at and then we had a  
21 series of questions that we have to respond to.

22 But I think the original paper did divide the  
23 considerations into seven areas of consideration. These  
24 have to be looked at in light of the products and they can  
25 be put into certain categories, and they can be treated as a

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1 group.

2 So we need to, certainly, move on in terms of the  
3 deliberations. One way to move on is to group the  
4 information under consideration into categories. So I think  
5 that is the reason for treating the categories and to try

6 and address the complexities of certain categories of drug  
7 products and their delivery.

8 DR. ALLEN: I have just one comment. Many of the  
9 presentations yesterday were almost classic academic  
10 presentations, you know, that many of us have made. We have  
11 made them in the past primarily from an industrial,  
12 manufacturing standpoint because those are the factors or  
13 considerations in preparing those types of products.

14 But we also have to keep in mind that compounding  
15 for an individual patient is different from manufacturing  
16 for tens of thousands, or hundreds of thousands, of  
17 patients. And I would hope that, of those factors that were  
18 discussed yesterday, that we always keep that in mind, that  
19 we are not after manufacturing a product for hundreds of  
20 thousands of patients but for compounding for individual  
21 patients.

22 That would be one of my main concerns. We looked  
23 so much yesterday at an industrial orientation as compared  
24 to a compounding orientation. Granted, you know, I don't  
25 have any problem with what was done yesterday but I would

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1 hope in the future that we keep that in mind, that they are  
2 two separate things.

3 DR. JUHL: The categories that we considered  
4 yesterday were ones that, apparently, no pharmacists are  
5 doing yet and all that we had available to us was the  
6 industrial model. And all that we had available to us was  
7 the industry model, but I would certainly hope if we get to  
8 categories where pharmacists are doing them, we would be  
9 able to present from both perspectives.

10 DR. SELLERS: Just a follow up. Even if we are  
11 compounding for individual patients, we need to have a  
12 baseline system established so that each individual patient,  
13 their products are compounded in a safe and effective manner  
14 and it needs to be standardized.

15 DR. JUHL: Other comments on the approach?

16 MR. RUSHO: Just another comment to follow up on  
17 Larry's. If I were to teach the sterilization of each and  
18 every individual drug product, first of all, I would never  
19 get through the lectures. You have to lump these as a group  
20 in order to do it. That is the way we teach our students.  
21 It is a rational approach to the problem.

22 DR. JUHL: The curriculum committee thanks you.

23 MR. WELDER: I guess I wasn't aware of the short  
24 time span that was afforded this committee on the agenda. I  
25 got mine when I got here, I guess. But is there a way that

1 these reports could be issued a couple weeks or so before  
2 this meeting so other people can respond and help this  
3 committee?

4 DR. JUHL: I am sympathetic to that portion of the  
5 Academy's comments.

6 MS. AXELRAD: I would like to address that. First  
7 of all, we get it out as quickly as we can. This was  
8 actually put up on the web, I believe, at least two weeks  
9 before the meeting. It was up on the Internet and available  
10 for people to comment on. We put it up on the web at the  
11 same time we sent it out to the committee members.

12 Also, I would like to say, this is only the  
13 beginning of the public process. We have allowed for a  
14 comment period after the meeting where people can submit  
15 comments. We will be taking those comments into account as  
16 well as the deliberations of the advisory committee at this  
17 meeting and preparing a proposed rule on this which will  
18 then be published for public comment with an ample period  
19 for people to comment.

20 There will be other opportunities for us to bring  
21 this and other issues associated with this subject back to  
22 the committee. So I think we are at the very beginning of

23 the public process.

24 DR. JUHL: This thing that we have been calling,  
25 or at least I have been calling, the White Paper is not even

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1 a formal proposal as yet.

2 MS. AXELRAD: That's right. It is not a proposed  
3 rule yet. We wanted to bring it to the committee and hear  
4 from the committee and then we will develop the proposal  
5 which will then, again, be put out for public comment.

6 DR. JUHL: Although that may have been on the web  
7 two weeks in advance, the agenda, I don't believe, was.

8 MS. AXELRAD: The concept paper we

9 DR. ANDERSON: The concept paper, I think, was up  
10 June 20something.

11 MS. AXELRAD: June 20something. It was up a  
12 couple of weeks ago.

13 DR. JUHL: But the agenda wasn't.

14 DR. ANDERSON: The notice for the advisory  
15 committee meeting?

16 DR. JUHL: No; the agenda.

17 MS. AXELRAD: The subjects that were covered were  
18 in the Federal Register notice. I am not exactly Igor, do  
19 you know when the notice was published?

20 DR. CERNEY: I believe it was about three weeks  
21 before the meeting is when the Federal Register notice was  
22 published.

23 DR. JUHL: But the issue was that the agenda  
24 wasn't published and those that would like to comment on a  
25 particular issue that was on a particular day were not made

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1 aware of that. The committee I am assuming we got the  
2 agenda as soon as everybody else which was the day when we  
3 got here. I think that would be helpful to have that that  
4 may not be regulatorily required, but as a courtesy, I think  
5 that if we can do that, it would probably be appreciated.

6 Other comments from the committee?

7 Let me move, then, to Dr. Henri Manasse, Executive  
8 Vice President of the American Society of Health System  
9 Pharmacists. He has asked for ten minutes of our time.

10 Henri, welcome.

11 DR. MANASSE: Good morning. Thank you, Chairman  
12 Juhl and members of the advisory committee. I am pleased to  
13 be here. My name is Dr. Henri R. Manasse and I am the  
14 Executive Vice President and Chief Executive Officer of the  
15 American Society of Health System Pharmacists, formerly  
16 known as the American Society of Hospital Pharmacists.

17 AHSP is the 30thousandmember national  
18 professional and scientific organization that represents  
19 pharmacists who practice in hospitals including outpatient  
20 services as well as health maintenance organizations, long  
21 termcare facilities, homecare agencies and other  
22 components of organized healthcare systems.

23 I am pleased this morning to speak to FDA's  
24 Pharmacy Compounding Advisory Committee about our members'  
25 perspectives on the concept paper that the agency has

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1 developed on drug products that present demonstrable  
2 difficulties for compounding because of reasons of safety or  
3 effectiveness.

4 ASHP will provide FDA with written comments on the  
5 entire concept paper by the 15th of August deadline so I  
6 will limit my comments today to the section of the concept  
7 paper dealing with sterile products.

8 It clearly would not be in the public interest to  
9 ban pharmacist compounding in organized healthcare settings  
10 of sterile products given the decades long experience,  
11 constructive experience, of hospital pharmacists serving  
12 patients by performing this function well.

13 Hospital pharmacists in the United States have

14 been providing centralized intravenous admixture compounding  
15 services since the early 1960s when the concept was  
16 pioneered at the National Institutes of Health Clinical  
17 Center and other leading hospitals throughout the United  
18 States.

19 In general, we think the FDA has come up with a  
20 good approach in dealing with pharmacist compounding of  
21 sterile products by recognizing that one, there are risks  
22 associated with compounding sterile products and, two, that  
23 risk can be managed successfully and effectively if  
24 pharmacists follow appropriate practice standards and  
25 procedures.

21

1 I would like to express ASHP's appreciation of the  
2 FDA's extensive use in the preparation of its concept paper  
3 of ASHP practice standards and guidelines, technical  
4 assistance bulletins and other research on this subject that  
5 has appeared over the years in the American Journal of  
6 Health System Pharmacists, previously known as the American  
7 Journal of Hospital Pharmacy.

8 ASHP has demonstrated its serious commitment to  
9 keeping all its practice standards and guidelines up to date  
10 and reflective of current scientific knowledge and

11 professional practice. I pledge to you that that commitment  
12 will continue.

13 Now, on to some concerns. Our first concern has  
14 to do with FDA's intentions relating to Section 503A,  
15 subpart (f), of the Food, Drug and Cosmetic Act, which  
16 states that, "the term 'compounding' does not include  
17 mixing, reconstituting or other such acts that are performed  
18 in accordance with directions contained in approved labeling  
19 provided by the product's manufacturer and other  
20 manufacturer directions consistent with that labeling," and  
21 I close quote from the law.

22 We believe that FDA's concept paper has not  
23 clearly differentiated between the actions noted in Section  
24 503A, subpart (f), of the Act, and the commonly accepted  
25 professional understanding of compounding of sterile

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1 preparations.

2 For example, in discussing the complexity of  
3 preparing sterile products, the agency says, on Page 7 of  
4 the concept paper, "Each time a pharmacist removes a sterile  
5 product from its original container or reconstitutes," and  
6 I underscore the word reconstitutes, "a sterile product, a  
7 risk of compromising the sterility of the product exists."

8           The use of the word reconstitutes in this context  
9 implies to us that the FDA intends to regulate  
10 reconstitution according to manufacturers' instructions as  
11 well as compounding. We believe that a determination that  
12 reconstitution consistent with product labeling as  
13 demonstrably difficult would be contrary to the intent of  
14 503A, subsection (f) of the Act. ASHP requests that FDA  
15 correct this erroneous implication by using a different term  
16 or completely deleting any reference to reconstitution.

17           We are pleased that the FDA is advocating that  
18 professional practice quality assurance standards must be  
19 applied to sterile product compounding. ASHP agrees with  
20 that philosophy as reflected in our long history of  
21 developing applicable practice standards and fostering the  
22 application of those standards in various articles published  
23 in our peerreviewed professional practice journal and, as  
24 well, in our educational program and training conferences  
25 and various specific training seminars on this subject.

23

1           However, if the FDA is suggesting that only the  
2 standards in Chapter 1206 of the United States Pharmacopeia,  
3 when applied to the compounding of any sterile drug product,  
4 would reasonably assure the potency, purity and quality of

5 the drug product, we must object.

6 As you know, just last month, ASHP issued and  
7 published its guidelines on quality assurance for pharmacy  
8 prepared sterile products which updates a document  
9 originally created in 1993. ASHP believes that the FDA  
10 should strongly encourage state boards of pharmacy to base  
11 their oversight of sterile drug compounding on both  
12 both Chapter 1206 of the United States Pharmacopeia  
13 currently in the process of revision and our newly revised  
14 guideline for the compounding of all sterile products as  
15 well as new scientific knowledge that may not have yet found  
16 its way into these documents.

17 ASHP believes it is appropriate for the FDA to  
18 suggest to state boards of pharmacy the standards they  
19 should apply in the oversight of sterile compounding. This  
20 will foster the establishment of a national quality  
21 assurance standard for compounding sterile drug products in  
22 all pharmacy practice settings.

23 The use of both the USP Chapter and ASHP's  
24 guidelines as well as the latest scientific knowledge in the  
25 literature would provide the assurance the FDA is seeking

1 for the safety and effectiveness of these products.

2           There is little practical difference in content  
3 between the ASHP and USP documents. We recognize this.  
4 However, in a 1996 article by Laura Thoma comparing Chapter  
5 1206 of the USP and ASHP's document, it was noted that ASHP  
6 and the USP documents both contain much useful information  
7 and each has a unique perspective and contains some  
8 information not covered by the other.

9           This was due to the fact that the original USP  
10 chapter was limited to home healthcare practice settings  
11 while the ASHP document applied to pharmacy services in  
12 various and broad practice settings.

13           The ASHP guideline also refers to Chapter 1206 for  
14 specific methods such as environmental monitoring, sterile  
15 process validation and endproduct sterility testing. The  
16 ASHP guideline provides useful shelf time and temperature  
17 criteria for risk level determination and the use of  
18 barriers and isolators and autocompounders.

19           The author of the comparison concluded, and I  
20 quote, "It is recommended that both documents be read for  
21 further information and that professional judgment be used  
22 in applying these guidelines to individual practice  
23 settings."

24           The role of enforcing the application of specific

25 quality assurance standards in pharmacy practice is one that

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1 is well established in law and in practice for state boards  
2 of pharmacy. ASHP believes that the FDA has a role to play  
3 in insuring that state boards fulfill this responsibility by  
4 encouraging that the standards in both Chapter 1206 and  
5 ASP's guidelines are followed.

6 We strongly recommend that the FDA delegate to  
7 state boards of pharmacy the responsibility for overseeing  
8 pharmacists' adherence to those standards rather than assume  
9 this responsibility directly.

10 ASHP has solicited comments from our members  
11 throughout the country on the FDA's concept paper which will  
12 be incorporated into a written commentary that we will  
13 submit to the agency next month. Some of the comments we  
14 have already received, however, testify to the many lives  
15 that have been saved thanks to the dedication, skill and  
16 professional judgment to pharmacists who have compounded  
17 sterile products that otherwise may not have been available.

18 The important drug products that provide  
19 significant public health benefits and appropriate patient  
20 care should not be considered demonstrably difficult to  
21 compound. We look forward to the continued opportunity to

22 advise the agency on this important publichealth and  
23 pharmacypractice issue.

24 Thank you for the opportunity to present and I  
25 would be pleased to respond to any questions.

26

1 DR. JUHL: Thank you, Henri. If I could have you  
2 just stand by for a second, our next speaker is going to  
3 require a computer hookup. I wonder if we could endeavor to  
4 do that while we are having some discussion.

5 Let me take the questions that Henri raised and  
6 see if we can address them here. The reconstitution effort  
7 would appear to be a use of words that we weren't precise  
8 in; is that accurate?

9 DR. ANDERSON: No; that's right. We could clarify  
10 that. It doesn't apply to reconstitutions within the  
11 labeling. It is just compounds.

12 DR. JUHL: So anything that the pharmacist is  
13 instructed to do within the approved FDA labeling

14 DR. ANDERSON: The way the law states; right.

15 DR. JUHL: Is not compounding, legally speaking.

16 DR. ANDERSON: Right.

17 DR. JUHL: The question of guidelines. You have  
18 obviously made good use and the ASHP guidelines are

19 certainly respected and useful to pharmacists. Given the  
20 Congressional instruction to work with USP and the history  
21 of USP as being a legally recognized body for other things,  
22 I guess it was quite reasonable and logical that you would  
23 choose to use the USP Chapter rather than the ASHP  
24 guidelines, even though, as Henri points out, they are very  
25 similar.

27

1 Are there views on the committee about the two  
2 guideline approach that has been suggested as opposed to the  
3 singular guideline approach? Loyd?

4 DR. ALLEN: If I could make a request. You know,  
5 the new Sterile Products Compounding Committee of USP has  
6 just been named. The Chapter 1206 is under constant  
7 revision, as you are aware. What I would like to request,  
8 if possible, would be any of the components with the ASHP  
9 guidelines that are not in 1206.

10 I am sure those are going to be looked at and  
11 quite possible or probably incorporated into 1206. I guess  
12 what I am asking is if it would be possible to get some type  
13 of summary of the information that is in your guidelines  
14 that is not in 1206 and that can be presented to the  
15 committee that will probably have its first meeting around

16 the 1st of September or so.

17 Is that reasonable?

18 DR. MANASSE: Yes; I think that is quite  
19 reasonable. In fact, ASHP does have a standing committee  
20 that relates to USP. We can ask for that summarization from  
21 our documents and then transfer that to dialogue with the  
22 USP. Very reasonable.

23 DR. JUHL: Other comments or recommendations of  
24 the agency on the use of guidelines? Elizabeth?

25 DR. McBURNEY: In your paper that you presented,

28

1 that we got your written comments, you said there is little  
2 practical difference in the content between ASHP and the USP  
3 documents. Are you aware of any conflicting or discordant  
4 information between those two documents?

5 DR. MANASSE: I am not aware of that directly  
6 right now, but we will do a careful review and will include  
7 that in our written commentary.

8 DR. JUHL: Sara?

9 DR. SELLERS: Are you advocating, then, that these  
10 remain guidelines and not requirements?

11 DR. JUHL: The 1206 or the ASHP?

12 DR. SELLERS: Or the combination of both.

13 DR. MANASSE: My impression is that the  
14 suggestions of FDA staff is that Chapter 1206 essentially be  
15 considered as requirements. ASHP's documents are  
16 guidelines, a technical assistance paper. We don't have the  
17 authority of law, if you will.

18 We obviously feel, as I said, that perhaps the  
19 translation of ASHP guidelines into state law, particularly  
20 that govern the compounding of sterile products, is a  
21 reasonable direction.

22 DR. JUHL: Have you reviewed your guidelines in  
23 relationship to the NABP proposed section of the Ideal  
24 Pharmacy Practice

25 DR. MANASSE: In the model acts? That is

29

1 currently in process.

2 DR. JUHL: Other questions on the guidelines? I  
3 think the last issue that Henri had raised is the agency  
4 delegating to the state boards the authority to overview  
5 this. I think that has already happened, although it was  
6 probably delegated by the Constitution and not by the FDA,  
7 so the agency and the state boards would like to work  
8 together on this, but the practice of pharmacy is governed  
9 by the states.

10 MS. AXELRAD: I think that the interrelationship  
11 between the states and federal government is addressed in  
12 the compounding provisions. We will be working with the  
13 states, with the states having the principal responsibility  
14 in terms of enforcing all of the provisions. But we will be  
15 working together, basically, on that.

16 DR. MANASSE: Our underlying recommendation here  
17 is to reinforce the fact that all practice acts should have  
18 the model language. That is presently not the case and,  
19 perhaps, this committee, in its work and its recommendation,  
20 could move that along.

21 DR. JUHL: Other comments for Henri? Thank you.

22 DR. MANASSE: Thanks for the opportunity.

23 DR. JUHL: Our last scheduled speaker on the open  
24 public hearing is Gregg Jones, Inspector for the State of  
25 Florida.

30

1 MR. JONES: Good morning. I apologize if I seem a  
2 little disorganized this morning. I returned from vacation  
3 on Wednesday and learned that I was going to be here, so I  
4 have put this together pretty hastily.

5 [Slide.]

6 My name is Gregg Jones. I am a pharmaceutical

7 program manager with the State of Florida Department of  
8 Health. I work in the regulation of drugs, devices and  
9 cosmetics. I have been an inspector for fifteen years this  
10 week. In our responsibilities, we monitor the manufacture  
11 and distribution of drugs, devices and cosmetics in Florida.

12 The purpose of my visit today is to share with the  
13 committee some of our findings in Florida on compounding. I  
14 am not here to discuss the safety, efficacy of products or  
15 the legal issues but just to give the committee an  
16 inspector's perspective of what we see when we go into  
17 certain compounding situations.

18 We have seen the compounding of respiratory  
19 therapy medications, in particular, bronchodilator drugs, as  
20 the main thrust of all of the compounding that we have had  
21 in Florida and I am going to spend the first part of the  
22 presentation talking about the large amount of compounding  
23 that occurs in that area and some of the problems that we  
24 see.

25 [Slide.]

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1 I would like to give you a little bit of  
2 historical perspective on our dealing with compounding. The  
3 best place to start is here with respiratorytherapy

4 medications. In the mid 1980s, Medicare covered nebulizer  
5 devices for inhalation of medication. They did not cover  
6 the medication that went into the device.

7 A resourceful home medical equipment dealer in  
8 Florida convinced Medicare that, to be truly effective, they  
9 needed to cover the medication. So Medicare began covering  
10 albuterol sulfate, among many other respiratory therapy  
11 drugs. Medicare does cover many medications used in the  
12 home under Medicare, Part B, despite the common  
13 misunderstanding today that Medicare doesn't cover any  
14 prescription drugs.

15 The patients, prior to using these unit dose  
16 medications, would be dispensed a concentrated bottle of  
17 albuterol sulfate, take this medication home, drop it into  
18 the nebulizer using sterile normal saline and administer the  
19 medication. The manufacturers, Schering being one of the  
20 first, came up with the unit dose medication that you see on  
21 the screen in a 3 cc vial with the most common dose in the  
22 0.083 percent.

23 At this point, this became better patient  
24 compliance and Medicare's reimbursement rate for this  
25 product was somewhere in the range of \$1 per cc that is \$3

1 per vial, roughly given three times a day for roughly \$300  
2 a month.

3 This was a large amount to pay for these  
4 medications but this was based on the brandname price.  
5 What we were seeing in Florida was an escalation in the use  
6 of these products because durable medical equipment dealers  
7 were allowed to bill Medicare as opposed to a pharmacy  
8 billing Medicare, or a pharmacy billing for drugs which is  
9 the traditional way that occurs.

10 Occurring on a parallel track in the mid 80's was  
11 a sort of a reintroduction to compounding, in general,  
12 basically brought about by a company in Texas that was  
13 reintroducing pharmacists to techniques used in compounding  
14 and making certain chemicals available to them for that  
15 purpose.

16 This is not the compounding that we were seeing  
17 escalating at that point. What happened, on a parallel  
18 track to that, is that the respiratory therapy medications,  
19 pharmacists in Miami learned that they could take the  
20 concentrated solution and place it in the 3 cc vials and  
21 continue to bill Medicare, but they started using the  
22 concentrated solution.

23 Soon after this, about 1989, they had access to

24 albuterol powders. They started acquiring these from  
25 various sources and started to compound what you see on the

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1 screen, which is a product made from a powder that has been  
2 imported.

3 [Slide.]

4 These are just a few of the many different  
5 products that we have seen. There is no consistency in the  
6 production of some of these products. They have no lot  
7 numbers. Many of them have no expiration dates. They have  
8 no indication of the strength and no indication of the  
9 quantity.

10 [Slide.]

11 This picture was taken about ten years ago in  
12 Orlando in the back of a regular community pharmacy. It is  
13 rather difficult to see, but this is behind the traditional  
14 pharmacy. This is the storage area for storage of supplies.  
15 These are the 3 cc vials. This is the area where the mixing  
16 of the albuterol solution is occurring and the filling of  
17 the vials and the capping, and this is where the solution is  
18 stored after it is mixed.

19 [Slide.]

20 This picture was taken very recently at a pharmacy

21 where they continue to fill the 3 cc vials out in the open.  
22 This is in the shipping area of the pharmacy. This  
23 particular pharmacy is making a large volume of respiratory  
24 medications for pediatric patients using combinations, half  
25 strengths of albuterol and other medications as well as

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1 antibiotics.

2 [Slide.]

3 This particular pharmacy, about a year and a half  
4 ago, was making 30,000 to 40,000 of these unitdose vials  
5 per day, all under compounding regulations. These people  
6 sitting at the desk are placing a 30day supply of these  
7 vials into boxes and are labeling.

8 [Slide.]

9 This is the stock shelf where the products are  
10 maintained after they have been produced by the pharmacy and  
11 then pulled from here for shipping to the patient.

12 [Slide.]

13 Typically, we were seeing, a couple of years ago,  
14 that the preservative used for these is benzalkonium  
15 chloride.

16 [Slide.]

17 These are just a few of the containers that we

18 have encountered that are used to store the product once it  
19 is produced. This is a commercial container, but we often  
20 see various types of plastic jugs used to hold the products.

21 [Slide.]

22 Sterile water for irrigation or injection is often  
23 what is used to dilute the powder. The powders can come  
24 from wide, wide varieties of sources. Some pharmacies  
25 import directly through chemical importers. Some buy from

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1 some of the major chemical distributors.

2 [Slide.]

3 This picture was taken at a pharmacy in Miami.  
4 These are bulk solutions of albuterol sulfate that have been  
5 prepared, ready for bottling. As you can see, it is just  
6 kept in the refrigerator with the other items such as their  
7 lunch.

8 [Slide.]

9 This picture was taken in the bathroom of a  
10 pharmacy where stacks of the containerclosure systems were  
11 kept.

12 [Slide.]

13 This particular photo was taken in Miami where the  
14 finished product has been stored in the bathroom. These are

15 the finished vials of albuterol sulfate.

16 [Slide.]

17 Because of the tremendous amount of profit in  
18 compounding these products, various home medical equipment  
19 companies developed brochures, they developed sales forces  
20 and sales promotional material which would be detailed to  
21 doctors. Here you can see an example of what would be given  
22 to the representative.

23 A good prescription is written for compounded  
24 inhalation solution. A bad prescription would indicate the  
25 name of the product. Here, the products, as you can see, it

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1 is stated they could be shipped directly. Here, they are  
2 not saying they are going to dispense the namebrand product  
3 but that they would have to go through the extra step of  
4 contacting the physician to change the order.

5 [Slide.]

6 What you are looking at here is the back of a  
7 pharmacy. All of these containers have n-acetylcysteine in  
8 them, one product. I would like to share with you some of  
9 the information that has been obtained in the past couple of  
10 years on this particular product.

11 Within the past couple of years, the number one

12 billed product by pharmacies for home respiratory care has  
13 become ipratropium bromide. But the acetylcysteine, up  
14 until about a year ago, was the numberone billed product.  
15 In Dade County, the county where Miami is located, there  
16 were ten pharmacies that were billing in excess of  
17 \$5 million a year for the one product.

18 100 percent of that was compounded. The tenth  
19 pharmacy on that list was billing Medicare for more  
20 compounded nacetylcysteine than all of the rest of the  
21 pharmacies in the country combined. So this gives you some  
22 idea of the amount of volume of these products that are  
23 being produced.

24 [Slide.]

25 We did some analysis with other agencies on some

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1 of the products, and I believe that, out of ten samples that  
2 were tested, only one met the potency standards. This  
3 particular one, and it is very difficult to read but it  
4 failed the assay test with 0.092 percent acetylcysteine  
5 found which is less than 1 percent of the declared amount of  
6 acetylcysteine.

7 [Slide.]

8 This, again, is a document to show you how

9 commercialized this has become. This particular company was  
10 promoting to pharmacies and to homemedical equipment  
11 companies that if you use manufactured respiratory  
12 medications, "We can assist you to establish your own  
13 compounding pharmacy. We give you the necessary marketing  
14 information and you will be able to compound the 3 cc vial,"  
15 that I showed you a picture of, "of albuterol 0.083 percent  
16 for 12 cents a unit dose."

17 Remember, at that time, the time this was taken,  
18 the reimbursement rate was something around \$3 per vial, so  
19 you see the huge incentive for making this yourself.

20 [Slide.]

21 I would like to move on to just some of the  
22 general findings involving sterile products that we have  
23 seen in Florida, quite a few products for use in impotency  
24 and injection of prostaglandin products and combination  
25 products. I would like to pass around I have some examples

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1 of this and some of these others. I would like to pass them  
2 around and let the committee take a look at these, and then  
3 I will collect them over here at the end.

4 We have also seen, in some pharmacies, the  
5 preparation of preservativefree morphine sulfate. This was

6 for intrathecal administration. Pretty commonly, we see the  
7 production of morphine sulfate for use in pumps. It is  
8 still occurring, primarily used in hospice situations.

9 We very seldom see any type of testing, potency  
10 testing, sterility, pyrogenicity testing, and very rarely  
11 any stability testing.

12 [Slide.]

13 This is an example of a pharmacy that is making  
14 products for the treatment of impotency. These are the  
15 vials where the solutions have been prepared using powders  
16 that you see some of them down here. These are the finished  
17 syringes that are going to be shipped out to patients.

18 [Slide.]

19 I have some examples of those in here.

20 [Slide.]

21 Pharmacies don't enjoy the privilege of knowing  
22 when inspectors are coming and, unfortunately, we walked in  
23 right after the Christmas party. But this focus on this  
24 area here is where a community pharmacy was preparing some  
25 impotency injection using papaverine and prostaglandin in

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1 this particular environment.

2 [Slide.]

3 This is where they were storing their empty vials,  
4 in the food section.

5 [Slide.]

6 This picture didn't copy very well, but I wanted  
7 to demonstrate for you a real typical procedure that we have  
8 observed for the production of prostaglandin. This is a  
9 vial of spectrum prostaglandin E1 for research purposes.

10 This is a bottle of grain alcohol from the ABC store.  
11 Typically, what will be done is some alcohol will be drawn,  
12 injected into the vial here to dilute the prostaglandin.

13 An amount of sterile water will be added to the  
14 graduate cylinder here, mixed with the powder solution,  
15 drawn into a syringe and then transferred through a  
16 0.2 micron filter to another syringe and then injected back  
17 into an evacuated vial.

18 [Slide.]

19 This is another pharmacy where we encountered the  
20 same alcohol, type alcohol, being used.

21 [Slide.]

22 The first picture I showed you, this is a hood,  
23 here. Next to it in this compounding room is a bulk  
24 container. I think this is a 50 kilogram barrel of  
25 sulfadiazine used to compound some veterinary products.

1 [Slide.]

2 This is the area of that room on that very  
3 opposite end where a number of various products are being  
4 compounded. You can see the condition of that compounding  
5 area.

6 [Slide.]

7 This procedure indicates the production of  
8 preservativefree morphine sulfate, which Medicare, by the  
9 way, does cover and pays a lot more for this particular  
10 product than they do the nonpreservativefree. This is a  
11 small boat that is used to weigh out the morphine sulfate.  
12 It is diluted with preservativefree water and then mixed  
13 and transferred through 2.2 micron filters to the syringe  
14 which is used in the intrathecal pump.

15 [Slide.]

16 Not all of the places that we visit are quite as  
17 unclean as the other picture that I have showed you, and we  
18 don't often take pictures of the good things we see in  
19 compounding. But I don't want to imply from these pictures  
20 that everywhere we go, we see nothing but problems in  
21 compounding because we do see some very advanced systems.

22 This particular room you are looking at is a clean

23 room in a regular community pharmacy that is doing some IV  
24 compounding. They are JCAHO inspected using JCAHO standards  
25 for this clean room. They have hepafilterpositive airflow

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1 coming into this room. They have another laminarflow hood  
2 where the work is done.

3 They do take some swabs and do some culturing of  
4 this area on a periodic basis, so I don't mean to imply that  
5 everywhere we go, we encounter a problem because there are  
6 some pharmacists that are going to extremes to insure a  
7 quality product.

8 [Slide.]

9 This is the pump that I was mentioning to you  
10 before which is used in the morphine injection.

11 [Slide.]

12 In this particular pharmacy, they were making  
13 pellets for implantation under the skin. These are the  
14 machines that are used to press the pellet.

15 [Slide.]

16 This is an autoclave which is used to sterilize  
17 the product.

18 [Slide.]

19 This is the finished product here, a pellet which

20 is inserted under the skin for hormonereplacement therapy.

21 That is my thumbnail, so you get an idea of the size of

22 these. This tape is a temperaturesensitive tape which

23 changes colors when the autoclave reaches a certain

24 temperature, which is when the product is removed.

25 [Slide.]

42

1 This is the dispensing of that product, Estradiol,

2 25I can't tell if that is milligram or microgram pellet

3 which is sent to the doctor and then inserted by the

4 physician.

5 [Slide.]

6 As far as the active pharmaceutical ingredients,

7 we have seen all types of products being used, some

8 imported, this one imported from the Czech Republic, this

9 one from an unlicensed distributor in I believe it is

10 Minnesota, and this one, another unlicensed company. This

11 is actually for a research chemical, prostaglandin, from

12 Spectrum Chemical.

13 [Slide.]

14 This product, phentolamine, which is one of the

15 ingredients used in impotency treatments. The common

16 product, prostaglandin used, but it is also being used in

17 combination with papaverine and phentolamine for bimixes and  
18 trimixes. The phentolamine, which is the brand name,  
19 Regitine, as used primarily in emergencyroom situations, is  
20 not readily available and it is inaccessible to pharmacists.  
21 They have had to obtain this product from various sources  
22 and compound it. They virtually cannot get their hands on  
23 the Regitine.

24       We went into a pharmacy in a Central Florida town  
25 and told them that they are using this phentolamine which is

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1 labeled for research purposes only, they had no certificates  
2 of analysis on it.

3       The next week, we went to another pharmacy in that  
4 general vicinity, and you see what was on the bottom of that  
5 same type of label. They have removed this information.

6       [Slide.]

7       I want to briefly touchI know my time is upbut  
8 on a couple of issues that you will be addressing in the  
9 future which is sustainedrelease products. These are bags  
10 full of methylphenidate and a diluent. They are filling  
11 these bags with hydroxymethylcellulose, I believe. These  
12 are methylphenidate tablets. These will be ground up and  
13 put into capsules as sustainedrelease capsules in various

14 strengths, depending on what the doctor needs.

15       Some of these vary from 1.5 milligrams to 35  
16 milligrams per cap. This particular unique dose was  
17 13.75 milligrams.

18       [Slide.]

19       This is the common sustained-release chemical that  
20 is used.

21       [Slide.]

22       These are morphine sulfate which is used in this  
23 extensively in hospice situations which are commercially  
24 available strengths that are being made.

25       [Slide.]

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1       This particular group of controlled substances was  
2 taken this picture was taken in a pharmacy where over  
3 80 percent of all their medications they were dispensing to  
4 hospices were compounded.

5       I think that concludes it. I am sorry, Mr.  
6 Chairman, for running over my time.

7       DR. JUHL: Thank you for the information. Let me  
8 ask the obvious question. Do you have the regulatory and  
9 legislative power that you need to shut places like this  
10 down?

11 MR. JONES: The office that I work in regulates  
12 manufacture and distribution of these products. Our board  
13 of pharmacy regulates the practice of the profession of  
14 pharmacy which includes compounding. Every state differs in  
15 how they regulate it but, traditionally, all of the  
16 compounding activities have fallen under the purview of the  
17 boards of pharmacy.

18 When we find products that I showed you that were  
19 grossly under their potency, we have taken action on those.  
20 When we see chemicals that may indicate that they are not  
21 for human use, we take action on some of those. But, in  
22 general, there have been very few actions taken on the  
23 actual controls used in compounding products.

24 DR. JUHL: But many of the products that you  
25 showed us were essentially copies of commercially available

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1 products, the products for inhalation and so on.

2 MR. JONES: I would say the majority of those  
3 products have been just copies of the commercially available  
4 product. Under Florida law, and I don't know how the other  
5 states handle this, but if a doctor orders a product that is  
6 essentially similar to a commercially available product and  
7 the patient is aware of it, then the pharmacy may compound

8 it.

9           What we have seen, in the Miami situation, is that  
10 they will order, in the case of the acetylcysteine it is  
11 available, I believe, in 4 ml and 10 ml quantities,  
12 commercially, in unit dose, they will order 5 cc's. By  
13 ordering the 5 cc volume, the pharmacy then will compound  
14 and dispense that amount as opposed to combining  
15 commercially available quantities.

16           That is very, very typical. Efforts have been  
17 under way by various offices in Miami to educate the  
18 physicians because the physician typically will write  
19 whatever the patient tells them that they have been taking  
20 before and not know what volumes are available commercially.

21           They will write 5 cc's not knowing it is not  
22 available. Many of the actions taken on the acetylcysteine  
23 in interviews with the doctors indicated they were not aware  
24 that the product was actually compounded from a powder.

25           DR. JUHL: Federal law now prohibits producing,

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1 essentially, copies of commercially available products and  
2 they speak to the issue of changing just a little tincture to  
3 make it different. Has that been, at the practical level, a  
4 useful piece of legislation for enforcement or is it people

5 don't know about it, or what I am asking is is there  
6 anything we can do to be helpful here?

7 MR. JONES: I don't think it has slowed down any  
8 of the practices that we have seen involving the respiratory  
9 drugs; no.

10 DR. JUHL: Other questions? RoseEllen?

11 MS. HOPE: Could you give me some indication as to  
12 how frequently a pharmacy in the State of Florida would  
13 expect to be inspected?

14 MR. JONES: I believe pharmacies are required to  
15 be inspected annually in Florida.

16 MS. HOPE: Okay, because some states, now, it is  
17 only about every three years. I am thinking in terms of how  
18 long it would take to uncover something like this that was a  
19 developing problem in some states.

20 MR. JONES: In Florida, they are inspected  
21 annually.

22 DR. JUHL: There appear to be enough inhalation  
23 products billed to serve the entire country. Can I assume  
24 that many of the products that are being produced and billed  
25 are not actually going to patients but just being billed on

1 a fraudulent basis?

2 MR. JONES: I think there is a tremendous amount  
3 of fraud involved there. I am not sure they are not going  
4 to the patients. They may be going to the patients and not  
5 being used, I think is what some of the findings are.

6 DR. McBURNEY: Mr. Jones, thank you very much for  
7 coming from Florida on such short notice. We appreciate  
8 your presentation. One of my concerns with the data that  
9 you presented could you give us a little perspective as to  
10 what numbers we are talking about here in regard to  
11 compounding pharmacies. We have seen some overwhelming  
12 examples of abuse and inappropriateness.

13 Is this the norm, or is this a small percentage of  
14 the compounding pharmacies, to kind of put it in perspective  
15 for us?

16 MR. JONES: Most of the photos that I have showed  
17 you were taken in an effort to go out and look at some of  
18 the areas such as injectables and some of the respiratory  
19 situations that we knew posed some public health hazards.  
20 But what I can address, as far as volume, is the respiratory  
21 element. I talked with a person yesterday who works in this  
22 routinely and I think we can safely say that there are  
23 hundreds of pharmacies in Miami, alone, Dade County, that  
24 are compounding respiratory meds daily.

25 DR. McBURNEY: Of those hundreds that are

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1 compounding, could you make a reasonable or an educated  
2 guess as to the number that are doing it properly versus  
3 improperly?

4 MR. JONES: Most of the smaller pharmacies that  
5 are doing that are not following any type of controls in  
6 producing them.

7 DR. McBURNEY: The other question; I was not clear  
8 from the presentation you stated that Medicare paid the  
9 durable goods companies for these medications.

10 MR. JONES: Yes.

11 DR. McBURNEY: Are these pharmacies subsidiaries  
12 of the durable goods companies or are they freestanding  
13 pharmacies?

14 MR. JONES: Medicare changed their policy in, I  
15 believe, it was 1996. Now they will only allow a pharmacy  
16 to bill for those medications, so they no longer will allow  
17 the homehealth company to bill for them. That policy has  
18 increased the number of small pharmacies that are now  
19 billing and producing those products.

20 DR. McBURNEY: If I understood you correctly, the  
21 issue of sterility, that would fall under the board of

22 pharmacy to enforce, not under your agency.

23 MR. JONES: Right; compounding is included in the  
24 definition of the practice of the profession of pharmacy.

25 DR. McBURNEY: I see. Thank you.

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1 DR. JUHL: Realizing that you are only one state,  
2 but could you give us an idea of the interest of the state  
3 board of pharmacy to deal with this kind of issue or are  
4 they understaffed, underresourced and it is not high on the  
5 priority list?

6 MR. JONES: I don't feel really qualified to speak  
7 for the board since we work in an entirely separate section.

8 DR. JUHL: How responsive is the board when you  
9 provide them with reports of these kinds of activities?

10 MR. JONES: The actions that we have taken, we  
11 have taken independently under the Drug, Device and Cosmetic  
12 Act under misbranding provisions. I am not sure what the  
13 board's actions have been on other violations.

14 DR. JUHL: When you find things that are, in your  
15 mind, things that pharmacists shouldn't be doing that the  
16 board should have called to their attention, is the board  
17 responsive to these kinds of things?

18 MR. JONES: I believe so; yes.

19 DR. JUHL: Thank you.

20 DR. SELLERS: I can state, just from reading the  
21 disciplinary actions from the state boards that you rarely  
22 ever I have never seen a disciplinary action taken.

23 DR. JUHL: Bill?

24 MR. RUSHO: Just a couple of questions. On your  
25 slide where you showed the prostaglandin being prepared, you

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1 said that they injected alcohol into the vial. Are you  
2 saying that these pharmacies do not have analytical balances  
3 necessary to weigh out that material?

4 MR. JONES: That is a good question. Some do  
5 weigh it out with some sophisticated balances. This  
6 particular example that I showed you, the company has the  
7 stated amount of micrograms on the vial that comes from  
8 Spectrum. What they will do is produce the concentrated  
9 solution in the the impotency drugs have disappeared. This  
10 would have a concentrated amount of the solution, and then  
11 this would be drawn off.

12 I have seen a sample of this sent to an analytical  
13 laboratory to actually determine the exact concentration  
14 because when you are talking about 10 micrograms as a dose,  
15 and you may have 100,000 micrograms in this concentrated

16 solution, they need to make sure that, as they dilute it,  
17 they get you can't just assume that when you start to  
18 dilute this 100,000 micrograms, you are going to end up with  
19 anything close to your target, 10 micrograms or 15.

20 So they will do one case only, I have seen  
21 this concentrated solution analyzed as a starting point on  
22 how to determine the exact concentration.

23 MR. RUSHO: What I was trying to get at was we  
24 talked about some of the difficulties in compounding here at  
25 this meeting. One of the things that we were interested in

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1 was the proper equipment in order to do to compounding.  
2 That is why I was asking you about the analytical balance.

3 MR. JONES: Many of the ones that were making this  
4 would start with a given amount of prostaglandin and dilute  
5 that and base their further dilutions on the assumption that  
6 that was the exact amount that was weighed in the vial and  
7 not do any weighing of the product.

8 MR. RUSHO: Have you seen these products being  
9 dispensed as generic equivalents?

10 MR. JONES: In Florida, the product is written for  
11 albuterol, for instance. That is the common way it is  
12 written. The pharmacist can substitute a generic. We don't

13 regulate and we don't see these prescriptions so I can't  
14 really accurately say we have seen it. But, the majority of  
15 the cases we have worked, when something is written  
16 albuterol sulfate, 0.083 percent, dispense a month's supply,  
17 they will dispense the compounded whether the doctor has  
18 indicated to dispense compounded product or not.

19 MR. RUSHO: So they are using it as a generic  
20 equivalent, then, without bioequivalency and bioavailability  
21 testing and everything the generic houses have to go  
22 through.

23 MR. JONES: Yes.

24 MR. RUSHO: What about the calculations of the  
25 drug dosage. I noticed one of the cartons said

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1 0.083 albuterol sulfate expressed as albuterol. Have you  
2 noticed any problems with the pharmacist calculating that,  
3 in accounting for the salt form of the drug and waters of  
4 hydration of such?

5 MR. JONES: No; we didn't look at anything as  
6 detailed as that.

7 MR. RUSHO: Okay. Thank you.

8 DR. JUHL: Joan?

9 MR. LaFOLLETTE: Could you comment on the scope of

10 the manufacturing? Are you actually seeing manufacturing  
11 going on whereas as an industry we are approved for certain  
12 batch sizes, or are you seeing things being compounded per  
13 patient and per prescription?

14 MR. JONES: Well, in some of the surveys that we  
15 did, we did see a lot of compounding done, one prescription,  
16 one product would be made. But most of the pharmacies will  
17 compound a certain supply based on what they think they are  
18 going to dispense. When you look at a bottle of 100  
19 sustained release capsules, they may go through those in a  
20 week. So they will make 100.

21 But, to extrapolate that, if you are dispensing  
22 50,000 units a week, they make 50,000. So I am not sure  
23 what your question is, whether we have seen manufacturing.  
24 It depends on the size of the pharmacy. Some of them are  
25 rather large and do compound large amounts of those

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1 medications.

2 MR. LaFOLLETTE: I am getting at that the industry  
3 has to abide by GMP regulations, and a lot of regulations.  
4 If you start to see the scope of what I would call  
5 manufacturing, from my view, especially of the inhalations  
6 on a large scale, it doesn't appear that all of these

7 pharmaciessome may, but it doesn't appear that they would  
8 abiding by all the regulations that we have to to insure  
9 that the public is receiving a safe and efficacious product.

10 Along with the testing and the data that we have  
11 to do, I don't see it demonstrated that theycompounding  
12 pharmacy on the scale that some of the abuse that you are  
13 showing where it is not demonstrated to me. It makes me  
14 very nervous.

15 DR. JUHL: Other comments? Larry?

16 MR. TRISSL: Perhaps you would have no knowledge  
17 of this, but I will ask anyway. The examples you have all  
18 shown are presumably retain pharmacies. Does this practice  
19 of compounding basically copies of the commercial drugs  
20 extend to hospitals in Florida as well? Have you seen  
21 examples of that on any kind of scale that is approaching  
22 this?

23 MR. JONES: No; we haven't.

24 MR. TRISSL: Have you looked?

25 MR. JONES: We haven't looked.

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1 MR. TRISSL: I am just checking. Thank you.

2 DR. JUHL: Jane?

3 MS. AXELRAD: I would just like to ask one

4 question. All of the pharmacies that you have shown, are  
5 they still operating or have they been shut down?

6 MR. JONES: Many of those pictures you saw, the  
7 pharmacies are no longer operating.

8 MS. AXELRAD: That would have been the action that  
9 you would have taken or

10 MR. JONES: Among actions by other agencies  
11 including Medicare.

12 DR. ALLEN: With the recent, I guess, enforceable  
13 regulations of the USP and the activities of the committee  
14 here, is there anything that you are aware of that we are  
15 not addressing that would help take care of this problem  
16 that you have seen?

17 MR. JONES: I think you are headed in the right  
18 direction in addressing these various areas. Without going  
19 into pharmacies more often and actually seeing what the  
20 current practices are, I couldn't really say that there is  
21 anything additional that you need to be doing because I  
22 understand, just from listening this morning, that there are  
23 various legal arguments that are going to persist in the  
24 direction that you are heading now.

25 I think the primary problems that we have had have

1 been in respiratory therapy and then the sterility of the  
2 products that are injections. Those are some of the areas  
3 that we have seen some of the major concerns.

4       Anything would be better, I think, than what we  
5 have now.

6       DR. JUHL: Elizabeth?

7       DR. McBURNEY: Mr. Jones, could I not infer from  
8 your comments that the reason that you are seeing it mostly  
9 in respiratory is because Medicare is covering the cost of  
10 those medications?

11       MR. JONES: I think so; yes.

12       DR. JUHL: Other comments from the committee? If  
13 not, I appreciate your coming here. It is not information  
14 that I, as a pharmacist, like to see but it does, I think,  
15 speak to the issues that we here as a committee have to deal  
16 with. One of the definitions of a profession is that it is  
17 selfpolicing. Pharmacy has not done a good job of  
18 establishing standards for compounding, translating those  
19 standards into regulations and enforcing them.

20       That does a disservice to the many pharmacists who  
21 do compounding on a patientspecific basis and do good  
22 deeds. This, certainly, is a black eye for us and we  
23 appreciate finding out how the real world works.

24 Thank you.

25 MS. GUZZO: I'm Susan Guzzo. If I may, I would

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1 like to offer this up to the committee. You raised the  
2 point this is a television commercial that aired where  
3 pharmacy compounders are soliciting patients who are on  
4 inhalers to convert to unit dose vials because they can have  
5 their medication reimbursed through Part B. It is a public  
6 commercial that aired on television, and I will leave it  
7 with whomever you think should have it for viewing.

8 DR. JUHL: Thank you.

9 I am going to continue the open public hearing and  
10 my next step, now, is to ask if there others who would with  
11 to address the committee.

12 MS. CAPPS: I find this very disturbing and I  
13 would like to request a copy of the powerpoint presentation  
14 so that we could show it to our pharmacists because I think  
15 many of our members would be very disturbed by it as well.  
16 That is the best way to make it known out there and, like  
17 you say, to begin the selfpolicing aspect of this and even  
18 invite Mr. Jones to come to one of our meetings and make  
19 this presentation would be very valuable.

20 So I would like to offer that.

21 DR. JUHL: Thank you. Are there others who would  
22 like to briefly address the committee? Larry?

23 DR. SASICH: Larry Sasich, pharmacist, Public  
24 Citizens Health Research Group. I do really appreciate Mr.  
25 Jones coming. I have seen this presentation before and each

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1 time that I see it, I become more outraged than the time  
2 before and absolutely at the loss for words.

3 I think one of the issues that this committee has  
4 to think about, and it shouldn't have to think about, is  
5 there is no longer any affective regulatory route for  
6 preventing or protecting the public from these kinds of  
7 activities. That was eliminated with FDAMA.

8 If you stop and think, as I have done for the last  
9 thirty years, as to one situation, one publichealth  
10 problem, or one egregious act or series of acts that has  
11 been controlled by the selfregulation either of an industry  
12 or a profession doesn't work, it simply doesn't work.

13 As I said yesterday, this committee has very few  
14 tools and the agency has very few tools to operate within to  
15 be able to protect the public health, until, I hope, that  
16 FDAMA goes back to Capitol Hill and that it is either  
17 totally repealed or there is a serious rewrite of what is in

18 this piece of really, really, bad legislation.

19       One of the things that I think you can do in terms  
20 of sterile products that would make it very easy and plain  
21 for state board of pharmacy inspectors some of whom are  
22 probably not even pharmacists to be able to police this  
23 particular situation is to place sterile products or  
24 products that should be sterile that are prepared from  
25 nonsterile bulk drug substances absolutely on the list of

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1 drugs that are demonstrably difficult to compound.

2       What we saw today from Mr. Jones' presentation and  
3 the egregious quackery that Jana Nestlerode was subjected to  
4 yesterday from injectable DMPS would be prevented. I think  
5 what I would like to see you discuss is that possibility of  
6 placing those types of compounds on the demonstrably  
7 difficult to prepare list unless they are done in an  
8 organized healthcare facility; i.e., a pharmacy that meets  
9 some type of professional standards.

10       I know you are going to have to work out whether  
11 these should be requirements or guidelines and, perhaps,  
12 differences or similarities between the USP and the ASHP  
13 approaches.

14       But that is the only thing that I can see in the

15 short term to protect a large number of citizens from what  
16 you surely have to admit is a very clear publichealth  
17 problem. 50 percent of the oralinhalation solutions in the  
18 State of Florida? That is stealing. The representative  
19 from Boehringer Ingleheim was very diplomatic but it is  
20 nothing more than stealing.

21 Thank you very much for your time.

22 DR. JUHL: Thank you. Are there other comments?

23 If you are brief, please.

24 MS. GUZZO: Susan Guzzo from Boehringer Ingleheim.

25 Before joining Boehringer Ingleheim, I was a Florida

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1 attorney as well and I was called in on several occasions to  
2 serve as defense counsel for many of these pharmacists. I  
3 can tell you that, in fact, it is manufacturing. I declined  
4 the opportunity, after reviewing the cases, at least four of  
5 those cases that the HHS was bringing that I was not going  
6 to defend the pharmacist there because they were simply  
7 manufacturing.

8 Thank you very much.

9 DR. JUHL: We have the videotape cued up. It is  
10 only 30 seconds long so we will go ahead and run that for  
11 the committee's information.

12 [Video played for the benefit of the committee.]

13 DR. JUHL: Is that a legal directtoconsumer ad

14 for

15 MS. AXELRAD: I don't know if it is a legal

16 directtoconsumer ad, but I believe it is a generic

17 approved product. Day Laboratories has a generic product I

18 think that has been approved.

19 DR. JUHL: But it is not the manufacturer who is

20 MS. AXELRAD: I don't think it is a compounder.

21 DR. JUHL: Other comments? Larry?

22 MR. TRISSEL: I know it is a difficulty sometimes

23 to differentiate between largerscale compounding and

24 manufacturing, but at the extremes, we can identify easily

25 what is compounding and what is largescale manufacturing.

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1 This would seem to fall into one extreme of those. Does the

2 agency have no regulatory authority over an unapproved

3 manufacturer in this regard?

4 MS. AXELRAD: I think that the whole purpose of

5 the FDAMA provision was to put some structure around our

6 attempts, over the last many, many years to try and

7 distinguish between compounding and manufacturing. The

8 specifics that were put forth in the exemption that it has

9 to be by a licensed pharmacist or physician upon a  
10 prescription for an individual patient and then to define  
11 the limited circumstances in which you could compound in  
12 anticipation of receiving that and the fact that there has  
13 to be this close relationship, and then the other provisions  
14 that deal with copying regularly or inordinate amounts what  
15 are essentially copies of commercially available products,  
16 all of those parameters in the law were trying to help us, I  
17 think, try and distinguish between compounding and  
18 manufacturing.

19 We are going to be addressing a lot of that in our  
20 general regulations, but I think it is always going to be  
21 very difficult to try and draw the line. Some of these  
22 pharmacies that we just saw were making things in large  
23 amounts. There will be issues. Are they essentially copies  
24 of commercially available products if it is 1 or 2 cc  
25 difference in terms of amount.

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1 Are they doing it regularly and in inordinate  
2 amounts? Do they have prescriptions for individual  
3 patients? Is there a real need for a compounded product?  
4 Is there a medically significant difference?

5 So all of those things are things that we would

6 have to look at. Also, as we have been talking about, the  
7 state boards of pharmacy will have principle responsibility  
8 to do something here. I think that it is fair to say that  
9 not all states are as aggressive. Some states are less.  
10 Maybe they have too few resources or are not able to inspect  
11 as often. Maybe they don't have the expertise.

12 But they may not be as aggressive in terms of  
13 enforcing this as other states. In those cases, we will  
14 have to see where we would be stepping in to do something.

15 MR. TRISSL: I think it is unfortunate that Carmen  
16 was not able to make this meeting because the input of the  
17 Boards of Pharmacy would be very welcomed in this. Maybe we  
18 should solicit that apart from this meeting.

19 DR. JUHL: Loyd?

20 DR. ALLEN: In fact, if I could recommend that,  
21 possibly at the next meeting, maybe Carmen could even  
22 provide a report on what activities, educational, et cetera,  
23 that they are doing for the individual state boards for the  
24 enforcement of all of the new things that are going on.

25 MS. AXELRAD: We can certainly try and arrange

1 that. We would love to hear from other states, too, about  
2 what they are seeing and what they are doing. We have tried

3 to conduct a survey of a few states to try and find out what  
4 they are seeing with regard to compounding.

5 We didn't get a very significant response. We  
6 didn't hear from very many states and we also didn't get a  
7 lot of information about their practices. I think Florida,  
8 we have had more about what is being observed in Florida  
9 with regard to compounding pharmacies than any other state.

10 DR. JUHL: Seeing no further comments, we will  
11 close the open public hearing portion of our meeting and  
12 return to the business at hand.

13 Committee Discussion

14 DR. JUHL: We have before us our last question to  
15 consider on sterile products. Let me ask, is there further  
16 discussion before we call the question?

17 MR. RUSHO: I think, from my perspective, that the  
18 document is not something that I could adhere to at this  
19 particular point in time. I think I run a good shop but I  
20 think there are provisions in there, as I expressed  
21 yesterday, that need to be modified.

22 To use the colloquialism, I think they need to  
23 start thinking outside the box. They have taken  
24 manufacturing documents and tried to apply those to a  
25 compounding pharmacy. That doesn't work. As we heard