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FOOD AND DRUG ADMINISTRATION

MUTUAL RECOGNITION AGREEMENT (MRA)
PUBLIC MEETING

Rockville, Maryland
Wednesday, December 8, 1999

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1 PROCEEDINGS

2 (9:04 a.m.)

3 OPENING AND WELCOME

4 MR. GAYLORD: I'd like to give a
5 warm welcome to each of you. My name is
6 Charles Gaylord from the Office of
7 International Programs. On behalf of the
8 Food and Drug Administration I would like to
9 welcome you to today's public meeting. I
10 know some of you have come from a long
11 distance, and some from near. But no matter
12 the distance, we're here to discuss a very
13 important topic.

14 The meeting today will look at the
15 action that has been taken to implement the
16 Sectoral Annex for Pharmaceutical Good
17 Manufacturing Practices (GMP) to the
18 Agreement on Mutual Recognition (MRA) between
19 the United States and the European Community.

20 When the Mutual Recognition
21 Agreement was signed last year, it was a
22 significant milestone that was the

1 culmination of years of hard work by many
2 people both within the EU and the FDA. It
3 was timely when it was signed for several
4 reasons.

5 First, a rapidly changing and
6 increasingly global marketplace regarding the
7 products FDA regulates. Secondly, there was
8 a need to maximize FDA's resources. Third,
9 there was the enactment of the Food and Drug
10 Modernization Act of 1997, which incorporates
11 into the FDA's mission the concept of
12 developing agreements with other countries.

13 The Modernization Act provided a
14 framework for the MRA, and its sweeping
15 provisions endorse many of the things FDA was
16 already doing to keep up with its expanding
17 obligations of protecting the public health.

18 The stated purpose of the
19 Pharmaceutical Annex is to, and I quote,
20 "govern the exchange and normal endorsement
21 of official good manufacturing practices
22 inspection reports after a transition period

1 aimed at determination of the equivalence of
2 the regulatory systems of the Parties."

3 So, as this process unfolds, during
4 this transition period, we have a three year
5 window to accomplish many things. Now, the
6 Agreement became effective on December 7th
7 of 1998.

8 During this transition period, the
9 FDA is participating with its EC member
10 states and the regulatory authorities there,
11 a number of assessment activities with its
12 counterparts, to look at pharmaceutical GMP
13 practices.

14 It includes such things as the
15 conduct of joint training, and the exchange
16 of legal and regulatory information.

17 These activities will enable FDA to
18 assess the equivalence of its counterpart
19 authorities in the EC, and conversely will
20 allow these authorities to assess the
21 equivalence of FDA. Today, as you will note
22 in your agenda, in your packet, presenters

1 will discuss the following items.

2 After the introductory remarks,
3 we'll have an overview of the Pharmaceutical
4 GMP Annex. Secondly, there'll be highlights
5 of the first Joint Sectoral Meeting that was
6 held May 18th and 19th of this year. Then
7 we'll look at equivalence assessment, the
8 development of an alert system, and public
9 transparency of MRA processes.

10 Now, before we get started, I'd
11 like to make a few announcements. In terms
12 of the structure of the meeting itself, after
13 the presentations are given, there'll be a
14 fifteen minute break, followed by
15 presentations from the audience. So, three
16 people from the audience have stated that
17 they would like to give presentations, so
18 we've allotted time for that.

19 After that, there will be two
20 panels convened to answer any questions that
21 you might have. Now, you can ask your
22 questions by way of index cards that will be

1 in your packets.

2 They can be passed to the aisles to
3 you, to your right and left, so that they can
4 be collected and passed to me. Or you can
5 use the floor mikes on either side of the
6 room, and ask the questions directly to the
7 panelists.

8 The questions on the index cards
9 will be read as time allows. We've allowed
10 members of both panels to respond. Now,
11 since the meeting is being transcribed, I
12 would ask that each of you give your name and
13 organizational affiliation, whether you're
14 using the index cards, or asking the
15 questions directly.

16 Now, in terms of housekeeping
17 items. The layout of this building compared
18 to Parklawn is comparatively simple. Right
19 outside the door we have the restrooms
20 immediately across the hall. There is a pay
21 phone that is near the guard's desk to the
22 right of this room.

1 There is also a phone here in the
2 room to my left, and you can dial nine to
3 reach the outside. We have provided coffee
4 and tea for your refreshment. There is a
5 vending room to my left outside of these
6 doors for additional items.

7 Now, to give us our introductory
8 remarks, we have Ms. Holston from the Office
9 of International Consituent Relations. She
10 is the Deputy Commissioner of that office.

11 In that capacity, Ms. Holston
12 provides executive level policy and program
13 direction for FDA's interactions, information
14 exchanges, and liaison activities with a
15 variety of domestic and international
16 external audiences.

17 Ms. Holston is the acting director
18 of FDA Office of International Programs, and
19 as the Deputy Commissioner for International
20 Constituent Relations, her principle goal is
21 threefold.

22 One, is to enhance FDA's working

1 relationships with external organizations.
2 Two, to increase understanding of the
3 agency's operations and objectives.

4 Three, to encourage appropriate
5 collaborations on vital public health issues.
6 She plays a key executive role in directing
7 FDA's relationships with numerous foreign
8 governments and international organizations.
9 It is my pleasure to present Sharon Holston.
10 Sharon?

11 STATEMENT OF MS. HOLSTON

12 MS. HOLSTON: Good morning, and
13 thank you, Charles. First of all, I also
14 want to welcome all of you to this third
15 public meeting on the Mutual Recognition
16 Agreement. We're going to focus on the
17 Pharmaceutical Annex to that agreement.

18 About three years ago when we held
19 one of these public meetings some of you may
20 have been here. But whether you were or not,
21 my title at that time was Deputy Commissioner
22 for External Affairs. I think the fact that

1 it's now International and Constituent
2 Relations is an acknowledgement on the part
3 of FDA that international programs is playing
4 an increasingly more important, more dominant
5 role, in everything we do to protect the
6 public health.

7 So, this meeting on the Mutual
8 Recognition Agreement is also part and parcel
9 of FDA moving aggressively and forcefully
10 onto the global scene.

11 The MRA which is the topic today
12 represents really a quantum leap in that
13 process. That's why we want to share with
14 you the developments that have taken place so
15 far to outline some of our plans, and to
16 invite your comments on issues that are
17 related to the implementation of the
18 Agreement which began exactly one year and
19 one day ago.

20 Why is this MRA so significant?
21 Because after the three year implementation
22 period, it should enable FDA to rely on our

1 counterparts in the European Union to inspect
2 facilities in their countries that
3 manufacture drugs for the United States
4 market.

5 Although FDA will continue to have
6 the final responsibility for the compliance
7 of the imported regulated products, making
8 certain that they do, in fact, comply with US
9 standards, this large scale reliance on
10 foreign regulatory information that is
11 critical for the assurance of the quality of
12 the products that are being exported, this
13 reliance on foreign data is really
14 unprecedented in our history as far as
15 meeting our public health protection mandate.

16 I have to say that it is not a move
17 that we have taken lightly, or without
18 adequate protections. But we did go ahead
19 and do this, after much, much discussion
20 within the Agency, for several very
21 persuasive reasons. Charles mentioned one of
22 them, of course, and that is the FDA

1 Modernization Act of 1997, which in fact
2 absolutely requires the Agency to advance the
3 development of MRA's with the European Union
4 for almost all of the products that we
5 regulate.

6 But the Modernization Act really
7 acknowledged the logic of some developments
8 that have been under way for many years, and
9 have sort of gotten or risen to a climax in
10 the last several years.

11 One of these factors is the ever
12 widening gap between FDA's inspection
13 workload, and the resources that we have to
14 carry it out. Since the start of this
15 decade, imports of FDA regulated products
16 have grown from about one and a half million
17 line entries per year to five and a half
18 million line entries in 1999. That's a 360
19 percent increase.

20 Because we literally haven't had
21 the resources to hire more people to do the
22 job, the number of FDA employees who are

1 actually surveying these imports has remained
2 just about constant, at around 770, or so.

3 In the same decade, our
4 inspectional responsibilities have gone up
5 about thirty-two percent, from about 87,000
6 business establishments to about 115,000
7 business establishments. Most of these are
8 facilities that are using methods and
9 equipment that are a lot more sophisticated,
10 a lot more complex, and therefore more
11 difficult to inspect than was the case a
12 decade ago.

13 Yet, during that same ten year
14 period, we could only increase the number of
15 FDA inspectors by something less than ten
16 percent. So we went from about a thousand to
17 just under 1,100.

18 So just these two factors alone are
19 two of the indicators of what we have to
20 acknowledge are some relentlessly mounting
21 pressures on the Agency. If you'll bear with
22 me, I have just a few more examples.

1 In the last decade, sales of
2 dietary supplements have increased from
3 about \$3 billion a year to \$20 billion a
4 year. Adverse event reports involving human
5 drugs have gone up from 75,000 to 230,000 a
6 year. Bio- medical research expenditures
7 that fuel the development of hundreds of new
8 highly complex regulated products have
9 tripled to \$20 billion.

10 The sales of human drugs, medical
11 devices, and animal drugs between 1993 and
12 this year have gone up somewhere between
13 seventy percent and about eighty-five
14 percent.

15 So you can see that during the last
16 decade, there's been really a prodigious
17 enlargement of our workload.

18 The resources have been relatively
19 stagnant over that same period of time. In
20 constant dollars, the budget has gone up
21 from \$809 million in 1993 to \$915 million in
22 the current fiscal year. But more than a

1 third of that is committed to four specific
2 programs.

3 That's drug reviews, food safety,
4 enforcement of the tobacco rules, and
5 surveillance of mammography facilities.

6 So as a result, the number of
7 employees who handle all of the FDA programs
8 except for drug reviews has actually declined
9 since 1992. This is something that we're
10 seeing across the board.

11 So, we need help. One way of
12 getting it is by utilizing GMP inspectional
13 information that's provided to us by, and
14 this is very important, equivalent regulatory
15 counterparts in the European Union. In
16 return, performing GMP inspections that they
17 need done in this country.

18 When I meet with and speak with my
19 counterparts in Europe, believe me, we're not
20 the only ones that are facing this kind of
21 situation, where the workload is far
22 outstripping the resources that we have to

1 handle it. So we both see significant
2 advantages in having agreements of this sort.

3 But even with all of that, and I
4 know I've given you a lot of numbers about,
5 you know, workload, and resources, and
6 people, and things like that, even with all
7 of that, the legal requirement from FDAMA,
8 the budgetary factors, these are not the
9 only, or even the most important forces that
10 are really driving FDA into partnership with
11 our colleagues in Europe.

12 We're not moving in this direction
13 because we can't afford to do anything else.
14 Far from it. I think the international links
15 that we're forging, and sometimes they feel
16 very unsettling. It feels, you know, umm,
17 we're not really sure if this is something
18 that we should be, you know, sort of running
19 toward.

20 But these links are really an
21 outgrowth of an historical process that I
22 think in the long run is far more compelling

1 than anything that has to do with the budget
2 figures. It's a process for which I think we
3 have to be really grateful.

4 In fact, I'm confident that even if
5 we had all the resources we need, we would
6 still be responding to the growing awareness
7 that public health as a responsibility is an
8 indivisible responsibility.

9 That by reaching out beyond our
10 borders, working with others to raise
11 standards, that we can collectively more
12 effectively accomplish our goals.

13 Certainly more efficiently than we
14 could ever do if we tried to do everything by
15 ourselves. I think this MRA is just an
16 indicator that the Agency is acknowledging
17 the critical role we play as a member of, you
18 know, what is commonly being referred to as
19 the global public health community.

20 We have a major role to play in
21 that community, not only in helping our
22 counterparts with protecting the health of

1 their citizens, but having them help us with
2 the protection of the public health of our
3 citizens. So, we are very grateful that you
4 are here with us today to learn more about
5 the MRA. We thank you for joining us.

6 I had intended to be here for the
7 entire session this morning. But there is an
8 international issue that is forcing me to go
9 back across the street, and talk to some of
10 my buddies in the State Department. So, I'm
11 going to have to run.

12 But again, I hope that you find
13 this session this morning very helpful and
14 informative. We look forward to having a
15 continuing dialogue with you this MRA, and
16 others that undoubtedly will happen in the
17 future. So thank you again.

18 MR. GAYLORD: Sharon, thank you for
19 those introductory remarks. Our next speaker
20 is Joseph Famulare, who is the director of
21 the Division of Manufacturing and Product
22 Quality, and the Center for Drug Evaluation

1 and Research. He is the head of the Project
2 Management Team responsible for helping to
3 implement the MRA.

4 He is also the co-chair of the
5 Joint Sectoral Committee. He will give an
6 overview of the MRA's pharmaceutical GMP
7 annex by describing the framework for
8 achieving mutual recognition of GMP
9 inspections. Joseph?

10 STATEMENT OF MR. FAMULARE

11 MR. FAMULARE: Thank you, Charles.
12 It's a pleasure to be here this morning to
13 share our progress to date on implementing
14 the Mutual Recognition Agreement. Today
15 marks one year and one day since the actual
16 agreement has entered into force, in terms of
17 the United States, as it was published final
18 in the Federal Register, December 7th
19 of 1998.

20 So I would like to give an overview
21 of the Mutual Recognition Agreement. With
22 the help of the members of my team here

1 today, go over the progress we've made in the
2 various areas.

3 (Pause)

4 MR. FAMULARE: Pardon me? Arrow
5 key. Okay, there we go. Technologically in
6 lined; as Sharon mentioned, there's much
7 changing technology that FDA is having to
8 deal with, as you can see right here every
9 day.

10 First of all, I'd like to give a
11 little bit of a background and history on the
12 Agreement itself. Initial discussions of a
13 Mutual Recognition Agreement really began
14 in 1989 as to the practicality of entering
15 into such an Agreement. In actuality, in
16 April of 1994, the actual discussions began,
17 the actual negotiation process.

18 You could see, it took several
19 years of really detailed, and many
20 negotiations, and many issues to be settled
21 in terms of the overall Mutual Recognition
22 Agreement, and particularly with the

1 Pharmaceutical Annex that we're discussing
2 today.

3 Until a tentative Agreement was
4 initialled on June 20th of 1997, and then of
5 course, finally signed by President Clinton
6 over in the UK on May 18th 1998. As I
7 mentioned at the start of my talk, there was
8 then a procedure in order to enter this
9 Agreement into force on both the U. S.
10 side, and the European side.

11 From our standpoint, because of the
12 nature of this agreement, and the fact that
13 it was binding, it was felt by FDA that we
14 needed to go to a rule making process in
15 order to enter into force with this
16 Agreement.

17 Therefore, during 1998, we
18 published a proposed rule, took in comments,
19 then on, as I said in the beginning of my
20 talk, we published this Agreement, in terms
21 of the FDA actually, both the Pharmaceutical
22 and the Medical Device Annex on December 7th

1 of 1998 under 21 CFR Part XXVI which actually
2 entered the Agreement into force. This
3 actually for the US marks the beginning, the
4 first year of the three year transition
5 period.

6 What does mutual recognition
7 actually mean? It means accepting the other
8 party's conformity assessment procedures.
9 This is not a harmonization process, and I'll
10 bring that up again. Sharon already
11 emphasized how this is about equivalence.

12 This is a concept which was
13 established by the World Trade Organization,
14 as Sharon very well went through in her
15 introductory remarks, there are realities as
16 to why we got into this Mutual Recognition
17 Agreement, particularly in terms of
18 diminishing inspection resources, and our
19 need to really cover the pharmaceutical
20 industry and, in the case of medical devices,
21 a need to cover the industry globally, as
22 we're in a global economy.

1 So therefore, this overall Mutual
2 Recognition Agreement came into effect in
3 force with specific Sectoral Annexes. Some
4 of those Annexes, just to make folks aware,
5 you know are things really not related to
6 food and drug, such as recreational craft,
7 electrical communications, and so forth.

8 I guess maybe it'd be more
9 interesting to be the co-chair on the
10 recreational craft. But unfortunately it's
11 not under the purview of the Food and Drug
12 Administration. But those are some of the
13 many product areas that are part of this
14 overall umbrella of Mutual Recognition
15 Agreement.

16 Focusing again on the
17 Pharmaceutical Annex, one of the main
18 features is that it emphasizes our finding
19 equivalence with the fifteen member states.
20 Each one of those member states will be dealt
21 with individually in terms of recognizing
22 their equivalence.

1 The important part of this
2 Agreement is, really I guess the ultimate
3 goal, is that it will lead to the exchange
4 and endorsement of inspection reports.

5 Once we go through this
6 equivalency assessment process, we will be
7 able to receive an inspection report from our
8 European counterparts that we have found
9 equivalent, and be able to normally endorse,
10 to quote the Agreement itself, that
11 inspection report, to use it as if it were
12 our own report. But again, as Sharon pointed
13 out in her introductory remarks, the actual
14 compliance decision will be up to the FDA.

15 Again emphasizing strongly that
16 this Agreement is really based on the
17 equivalence of regulatory systems. Meaning
18 that the regulatory system in the authority
19 that we're evaluating should be able to
20 provide the same level of public health
21 protection as our own system, of GMP's and
22 regulatory enforcement, the overall system.

1 Not that they be the same as a harmonization
2 situation might be, but equivalent.

3 This Annex of the Agreement, the
4 Pharmaceutical Annex, is managed by a Joint
5 Sectoral Committee, with representatives from
6 both the EC and the European Union -- I'm
7 sorry, and the US side, FDA side. I am the
8 co-chair for the United States FDA.

9 My counterpart, my colleague in the
10 European Community is Steve Fairchild, who
11 acts as a coordinator from the European
12 Medicines Evaluation Agency, under the
13 auspices, of course, from the European
14 Commission itself, under Emma Cook, in
15 Director General Three.

16 I won't get into all the details of
17 how the European Commission works at this
18 juncture. But I'll just tell you that from
19 their side, you have Steve Fairchild
20 coordinating with the European's Medicine
21 Evaluation Agency, and representatives from
22 various member states on the Committee from

1 the European Commission side.

2 From our side, of course, the Joint
3 Sectoral Committee consists of what we call
4 our Project Management Team, the
5 Representatives from each center that will
6 make up, and ORA, that will make up the
7 members of this team, which include myself,
8 Brian Hasselbalch from CDER, Ray Mars from
9 ORA, Judy Gushee from CVM, and Merton Smith
10 from the Office of International Affairs.

11 So, all these various factors are
12 working together within the Agency to be
13 part of this committee, internally, the
14 Project Management Team. They in turn report
15 to senior managers at the Commissioner's
16 level, ORA, and all the Center levels, which
17 comprises the Steering Committee internally.

18 As I said, one of the main features
19 of this Annex was in terms of the Agreement
20 was reached that we would have a transition
21 period of three years in order to do this
22 important equivalency determination.

1 As I've said, we're one year into
2 that now, where we will assess the
3 equivalence of each of the regulatory
4 authorities, and the overall European
5 Commission itself, which has set the
6 directives and guidelines for each member
7 state in this area.

8 Other tasks that we're put upon to
9 do within this transition period is to
10 determine what essential information belongs
11 in this inspection report and format, because
12 this is the key document that's going to be
13 exchanged between member states and the FDA.

14 We're also going to develop a two
15 way alert system during this period. You'll
16 hear more details on the progress of these
17 things from the various Project Management
18 Team members as they come up.

19 Then at the end of this three year
20 transition period, there will be a
21 determination of equivalence by the Joint
22 Sectoral Committee. There will be one vote

1 from each side, from both the US and the EC
2 side, to determine whether a particular
3 authority is equivalence.

4 These will only be positive
5 determinations. If, in other words, if both
6 sides agree that an authority is equivalent,
7 that authority will be listed as equivalent.
8 If another authority isn't there yet, that
9 vote may agree upon that, but there won't be
10 anything published or put forward about that.
11 It still remains to see that that authority
12 may be found equivalent.

13 Again going over the basics of the
14 Annex itself, you can see what products are
15 covered. Basically it's human, animal drugs,
16 vaccines, therapeutic biologics, and active
17 pharmaceutical ingredients. The main
18 exceptions here would be obviously human
19 blood and plasma products, veterinary
20 biologicals, tissues and organs, medical
21 gases, radio pharmaceuticals, investigational
22 new drugs, and biological in-vitro diagnostic

1 devices.

2 This is to remind everybody of the
3 member states that are part of the European
4 Union, these are the authorities that are on
5 the table for being evaluated in the European
6 Union. You could also keep in the back of
7 your mind that, of course, the European Union
8 has plans in the future to extend to other
9 authorities. But for now, this is who we are
10 dealing with.

11 Just to focus on the inspection
12 report format, we would expect to have
13 reports in an agreed upon format between both
14 the EC member states, and the US FDA where
15 each authority can normally endorse, except
16 the conclusions from these inspection
17 reports. Of course, as Sharon said earlier,
18 there are protections built into the process.

19 Those exceptions, in terms of
20 inspection reports, of course would be if we
21 found material inconsistencies in the report,
22 inadequacies, quality defects, for example,

1 in products that were identified in post
2 market surveillance, or specific evidence of
3 concern on consumer safety.

4 So, if there is any level of
5 concern to the public health, product
6 defects, or the reports themselves are
7 inadequate, there are recourses within the
8 Annex of actions that could be taken. Up to,
9 you know, which includes up to going out and
10 having, for example, the authority, let's say
11 the FDA go and do the inspection themselves,
12 to satisfy themselves that product being
13 imported is of acceptable quality.

14 Another important feature of the
15 Pharmaceutical Annex is that there is to be
16 an exchange of information, a type of a
17 collaboration effort between both the
18 European Commission and the US FDA. For
19 example, when there are proposals to
20 introduce new controls, or to change
21 regulations or inspection procedures, we will
22 collaborate with each other in doing these.

1 There'll be an added step in
2 collaborating on new GMP's regulations.
3 Because it would certainly have an effect on
4 the equivalence that, let's say, would have
5 been established. It will also serve, again,
6 to have more input from both US and EU side
7 on these guidance or regulation documents as
8 they develop.

9 Article Nineteen of the Annex
10 speaks about the exchange of quality
11 information, information that each other has
12 on product reports, or corrective actions,
13 such as from our standpoint, drug product
14 defect reports, the sharing of recall
15 information, information about import
16 consignments that have been rejected, and any
17 regulatory and enforcement problems.

18 So there'll be, for example as now,
19 each authority may look at this to see if
20 there's an overall industry problem. As
21 industry is global, well now, we'll start
22 looking at this, at industry problems

1 globally with our European counterparts. So
2 this is an important feature in the Annex.

3 Then of course, there will be a two
4 way rapid alert system, as part of the
5 Agreement under Article Twenty, which will
6 call for early alerts when information
7 becomes known that necessitates additional
8 controls or product removal.

9 Some of the implications of this
10 Annex that we need to think of as we go
11 through this meeting today are that we're
12 into this Agreement to make more efficient
13 and targeted use of diminishing inspection
14 resources.

15 By having regulatory authorities
16 collaborating, as I said in my earlier slide,
17 we might expect faster action against
18 adulterated products. Especially, you know,
19 as we deal in an international arena now.

20 As we collaborate this could, you
21 know, have a dual effect of maybe being a
22 supporter or barrier for regulatory change.

1 When I say support for regulatory change, you
2 will have the collaboration of all of the
3 international community as we go through
4 these changes.

5 The reason I use the term barrier
6 is that as you bring more parties to the
7 table, it may become more complicated to
8 bring these changes into effect.

9 As each side looks at each other,
10 the equivalence assessment process may
11 actually result in improvements, as we put
12 ourselves under the microscope, as the US is
13 going to be evaluated by our colleagues in
14 the EU, and as we evaluate our European
15 colleagues.

16 This is to give you a high level
17 view of our overall implementation plan.
18 Early in the process of the transition
19 period, we began the development of the two
20 way rapid alert system. Focusing right now
21 on recalls. We started that, as I say, in
22 February of 1999. We're continuing to

1 develop that with our European counterparts.

2 We're now engaging in the process
3 of working -- in the early stages of working
4 on what will be a common report format. What
5 would satisfy both authorities in terms of
6 the exchange of an EIR. That process is
7 ongoing now.

8 Of course, we've begun the actual
9 equivalency assessment process, which
10 includes not only joint inspections, which
11 will come up in more detail in later
12 presentations, and is always of interest to
13 industry. When will those happen, and how
14 will those be?

15 But remember, this is the overall
16 evaluation of each authority's regulatory
17 system. Do you have enough investigators?
18 Are they trained? Do you have enforcement
19 follow-up, in addition to the actual on- site
20 inspections?

21 Of course, the big beginning part
22 of this process is to actually look at the

1 laws and regulations from each member state,
2 and for the EU to look at our laws and
3 regulations. You'll get more detail about
4 how that process is going in our next
5 presentation.

6 Remember that the transition period
7 ends in December of 2001, at which time there
8 should be a, as I say, a meeting of the Joint
9 Sectoral Committee to decide what authorities
10 are found equivalent. Then for those
11 authorities found equivalent, and as part of
12 the equivalency assessment process, it's not
13 only authorities, but it's also process. For
14 example, solid oral dosage form sterile
15 drugs.

16 Those authorities and processes
17 within authorities that are found equivalent,
18 for example, by FDA, will be declared in a
19 Federal Register announcement. Then we
20 could, beginning and entering into the
21 operational phase with those particular
22 authorities.

1 Just one overall remark on the
2 implementation plan. This is a plan. It
3 depends, like any other plan, on factors
4 beyond our control as we enter into it. One
5 of those being our ability to have resources
6 to implement the plan against all other work
7 that FDA has. Second, our ability to
8 interact with our European authorities in
9 order to implement the plan in terms of their
10 needs, resources, and so forth, to do this.

11 With that, I'll conclude these
12 brief remarks and the beginning part of our
13 session to go on to our other folks. Of
14 course, there'll be the opportunity to ask
15 questions later on in the session. Thank you
16 very much.

17 MR. GAYLORD: Joseph, we'd like to
18 thank you for that overview of the
19 Pharmaceutical GMP Annex. One of the things
20 that Joseph mentioned was the Joint Sectoral
21 Committee.

22 Our next speaker, Raymond Mars, is

1 the Special Assistant to the Director of
2 Division of Emergency and Investigational
3 Operations, and the Office of Regulatory
4 Affairs. He's going to report on the first
5 Joint Sectoral Committee meeting that was
6 held last May 18th and 19th of this year.
7 So, Ray?

8 STATEMENT OF MR. MARS

9 MR. MARS: Good morning, everybody.
10 Why did you turn the lights out when I came
11 up here? I did shave this morning. No,
12 they're fine.

13 Anyway, as Charles said, we had the
14 first meeting with the Europeans May 18th
15 and 19th. It was here in Rockville, right
16 next door at the Parklawn Building. There
17 were twelve representatives present from the
18 EU, and I'll just go through some of the
19 basics of the meeting with you so you had
20 some understanding of what we were doing.

21 There were two people there from
22 the Directorate General Three. I think that

1 name is being changed right now. They're
2 undergoing some reorganization process. But
3 that is the group within the EU governmental
4 bureaucratic structure that's overseeing the
5 implementation of the MRA.

6 There were two people from the
7 EMEA, European Agency for the Evaluation of
8 Medical Products. As Joseph said, that is
9 our counterpart group to the Project
10 Management Team that is helping to organize
11 implementation of the MRA for the Europeans.

12 There are also representatives
13 there from Denmark, France, Germany, Ireland,
14 and the UK. Some countries were obviously
15 not there, since there are fifteen member
16 states in the EU.

17 FDA had twelve participants, so we
18 outnumbered them. We felt good. There were
19 about six or so additional presenters besides
20 the twelve participants. We had three
21 representatives from the Center for Drugs,
22 two representatives from the Center for

1 Biologics, two from Office of International
2 and Constituent Relations. They just changed
3 the name. I have trouble catching up. It
4 used to be Office of International Affairs.

5 One representative each from Center
6 for Veterinary Medicine, and ORA. Three
7 representatives from our Chief Counsel's
8 Office. Chief Counsel weighed in heavily, as
9 you can see, as they sometimes tend to do.

10 Three centers were represented
11 because, as Joseph said, the MRA covers
12 pharmaceuticals that are human, veterinary,
13 as well as biological. So that was the
14 make-up of the meeting generally.

15 We had an agenda. These are some
16 of the topic items that were on the agenda in
17 terms of reference, which I'm going to
18 discuss in some detail here in a minute. We
19 talked about communication. There was a
20 discussion about confidentiality, which was a
21 big issue. A two-way alert system, which
22 deals with the recalls, and sharing emergency

1 information that Sylvia Henry is going to
2 talk to you about in a few minute.

3 Working programs, the equivalence
4 assessment program, and Brian Hasselbalch is
5 going to talk to you about that. That's the
6 approach that we were going to take, as well
7 as they were going to take, to conduct this
8 equivalence assessment. Then we came up with
9 some action items. So it was a good meeting.
10 We had an agenda, and action items, and that
11 kind of thing.

12 The terms of reference, I think
13 this probably was one of the biggest
14 accomplishments we had in the meeting. The
15 terms of reference really are a document that
16 supplement the MRA. It's intended to clarify
17 the role of the Joint Sectoral Committee, and
18 give us more specifics about how we're
19 supposed to go about this implementation
20 process. The MRA has a number of things in
21 there that said they're supposed to happen,
22 but very little detail.

1 So we developed this terms of
2 reference document that talks about
3 responsibilities, the different parties
4 involved, the composition of the Joint
5 Sectoral Committee. As Joe mentioned, the
6 MRA talks about the Joint Sectoral Committee
7 really being two people with two boats, one
8 on the US side, and one on the European side.
9 Two people were not going to get this done.
10 So there's obviously a necessity to expand
11 the committee, which we did.

12 We talked about participants in the
13 Joint Sectoral Committee. We had a long
14 discussion about this, and agreed mutually
15 that wanted to exclude external parties. We
16 identified some of those as being industry,
17 trade associations, the press.

18 The focus here was trying to make
19 sure we had a fairly tightly knit group that
20 felt free to communicate openly with each
21 other. We thought that's the keystone of
22 trying to move this agreement forward.

1 Sometimes some things may come up that might
2 be embarrassing to the other party.

3 We wanted to limit the restraint on
4 the communication, so that we openly conveyed
5 information, and both sides could make a good
6 assessment, good judgment about assessments
7 we thought that was necessary to limit
8 participants in the group.

9 We also defined a number of things,
10 work groups as an example. Joseph talked
11 about the safety alert, the recall procedure
12 that's being developed. That's being done by
13 a work group. We have a separate work group
14 set up to look at the common inspection
15 formats.

16 So these are additional groups that
17 are actually going to come up with the things
18 that we're going to implement to move the
19 agreement forward.

20 We identified observers. That
21 really was to help, I think, foster broad
22 participation by the member state folks when

1 we go overseas, to meet, have a Joint
2 Sectoral Committee. Countries who may not
3 have a specific part at the meeting could
4 have observers. It's limited to regulatory
5 authorities as an example, from the member
6 states.

7 Also experts could attend the
8 meetings. These would be people from
9 regulatory authorities. Generally they
10 participate, are active in the work groups.

11 Specific responsibilities for the
12 Joint Sectoral Committee were identified, one
13 of the first being communication with the
14 Joint Committee. The Joint Committee is the
15 overall group that is managing the whole
16 mutual recognition agreement. So they're
17 going to deal with telecommunications,
18 recreational craft, as well as
19 pharmaceuticals and medical devices.
20 Communication with that group would be an
21 important part of the Joint Sectoral
22 Committee.

1 Recognizing we would coordinate
2 activities and monitor implementation of
3 different steps and phases of the MRA, the
4 Joint Sectoral Committee would be responsible
5 for exchanging key information. One of the
6 things that we've accomplished to date is
7 developing a bibliography of laws and
8 regulations as an example that was exchanged
9 through the Joint Sectoral Committee.

10 Develop a two-way alert system, and
11 ensure operation. The ensure operation part
12 here is a monitoring function. The Joint
13 Sectoral Committee will be responsible for
14 making sure that once an agreement is
15 reached, about how we're going to do that,
16 that it runs smoothly. Making documentation
17 available. We use each other as a conduit
18 for obtaining information about other
19 countries laws, and regulations, and
20 procedures. Agreeing on an inspection report
21 format, which we're working on now.

22 Clarify the composition of the JSC.

1 We set up procedures for meetings. We
2 decided that we would meet at least annually,
3 and we would alternate the site between the
4 US, and the European Community. The first
5 meeting was held here, so the next meeting
6 will be held in Europe somewhere, probably in
7 May. Somewhere along there. It'll be about
8 a year from the last one.

9 We set a procedure for adoption of
10 documents, setting this up as a consensual
11 procedure, wanting agreement on what we did
12 agree to. We agreed to communication to
13 external parties as an example, at the end of
14 the first JSC meeting, we did prepare a
15 public document, a public press release,
16 which I think some of you have. There were
17 some on the chair in the back, and we can
18 certainly make available to you.

19 Other things we did during the
20 meeting. Confidentiality, as I said, was a
21 big issue. Very sensitive to the Europeans,
22 more so than us. I think we've dealt with it

1 long enough. We're a little bit more used to
2 it.

3 But the European folks reviewed
4 European laws. Member state practices vary.
5 They're not the same. Only a few have what
6 would be equivalent to our Freedom of
7 Information Law. We learned that public
8 access to information in Europe is frequently
9 not a right that is enjoyed by US citizens.

10 Frequently there is no publication
11 of recall information there. FDA, as you
12 know, publishes recall information. The
13 enforcement report is available on the Web
14 site, and that kind of thing. The press also
15 helps us out with those on occasion.

16 There was a lot of concern about
17 releasability of information. We could see
18 exchanging sensitive documents and we're
19 still discussing exactly how we're going to
20 deal with some of those things.

21 For our side we reviewed US laws
22 and regulations. We talked about the Freedom

1 of Information Act, which most of you know,
2 controls release of documents that FDA
3 generates, such as inspection reports. Those
4 of you from inspected firms know that your
5 reports are releasable after some purging.

6 We talked about the Privacy Act,
7 which deals more with individual personal
8 privacy. Names, social security numbers,
9 things like that. We explained Congressional
10 oversight, which is different for us than it
11 is for them. Already the pharmaceutical MRA
12 I think has been the subject of two very
13 pointed GAO probes about what we're doing,
14 how we're going to implement this.

15 Frequently the Europeans do not
16 have that kind of oversight. So that's a
17 difference. We also had folks explain our
18 regulations that protect commercial
19 confidential information, trade secret
20 information, and deliberative documents.

21 Other meeting highlights, we
22 exchanged contact information for both sides.

1 We set up a monthly phone call that occurs
2 between Joseph and generally Steve Fairchild,
3 to keep lines of communication open. We set
4 up a procedure to establish counterpart
5 contacts between the US and the Europeans as
6 these work groups are set up. As an example,
7 on the report writing format there is a
8 designated US contact for that, as well as a
9 European, so that we can share progress and
10 process on that, and help us move forward in
11 that area.

12 We agreed to exchange information
13 on investigational training, and invite other
14 parties to those. In the past year we've
15 been able to invite two, up to two
16 representatives per training course from the
17 EU to attend training that we give to our FDA
18 investigators.

19 Actually this week I think is the
20 second week of a basic pharmaceutical
21 inspection training course that we're having
22 in Baltimore, and there are two people from

1 the EU that have attended that.

2 So that again, an effort to try and
3 understand each other's system better, learn
4 from each other, and hopefully move us
5 forward in the equivalence process.

6 Also made presentations about our
7 alert system and recall systems, and they
8 did, too. We discussed the equivalence
9 process. So, that's kind of a summary of
10 what happened. Again, I think developing the
11 terms of reference took some time, and I
12 think was a good accomplishment. We raised
13 the issue of confidentiality, which we're
14 going to have to deal with, and is going to
15 be a sticky one.

16 I think set up some good procedures
17 for communication with the other side, with
18 the EMEA, our partners in moving this thing
19 forward. So, thank you.

20 MR. GAYLORD: Thank you, Raymond,
21 for those meeting highlights. We now would
22 like to give our attention to Brian

1 Hasselbalch, who is our next speaker. He's a
2 compliance officer in the Division of
3 Manufacturing and Product Quality in the
4 Center for Drugs.

5 He will give an overview of the
6 evaluation of the pharmaceutical GMP
7 regulatory systems among EU member states, by
8 talking about equivalence assessment.

9 Brian.

10 STATEMENT OF MR. HASSELBACH

11 MR. HASSELBALCH: Thank you,
12 Charles. Good morning. My presentation in
13 the area of equivalence assessments will
14 begin with, if you can stand it, another
15 detailed, a more detailed overview of the MRA
16 conditions regarding this aspect of the
17 agreement. Then I'll discuss how we plan to
18 perform the assessments of the EU member
19 states. Finally, I'll update you on where we
20 are in this effort.

21 The MRA pharmaceutical GMP's Annex
22 defines equivalence as follows: "Systems are

1 sufficiently comparable to assure that the
2 process of inspection and the ensuing
3 inspection reports will provide adequate
4 information to determine whether respective
5 statutory and regulatory requirements of the
6 authorities have been fulfilled. Equivalence
7 does not require that the respective
8 regulatory systems have identical
9 procedures."

10 Now, the key element to this
11 definition of equivalence that I want to
12 highlight is that it applies to systems, and
13 not just GMP requirements and regulations.

14 To date there are twenty-one EU
15 systems in place for regulating
16 pharmaceutical GMP's for the various products
17 covered by this agreement. Our long term
18 goal is to assess them all, in addition to
19 the EU directives.

20 The Annex establishes the parts of
21 a regulatory system that can be assessed in
22 deciding on equivalence. There are seven

1 major areas of assessment, according to the
2 Annex.

3 These are, legal regulatory
4 authority and structures, standards of
5 conduct, avoidance of conflicts of interest,
6 administration of the regulatory authority,
7 execution of enforcement activities,
8 effective use of surveillance systems,
9 conduct of inspections, and certain very
10 specific issues concerning pre-marketing
11 approval inspections.

12 As you can see from criterion one,
13 which I've posted here, and two, the major
14 areas of assessment are often further defined
15 by sub-categories, which I won't describe
16 here. But simply put, virtually every aspect
17 of a regulatory system can be assessed under
18 this MRA.

19 The MRA also establishes that the
20 final determinations of equivalence are a
21 joint effort, and this has already been
22 discussed. I would like to point out that

1 this process is expected to be, I think, less
2 deliberative and more determinative.

3 The Agreement also allows for
4 determinations of equivalence by certain
5 process and product types, which the
6 Agreement leaves to the discretion of either
7 party. Finally, the MRA requires that a
8 finding of non-equivalence be documented to,
9 and reported to, the appropriate regulatory
10 authority.

11 As to our approach, we intend to be
12 objective, deliberative, and comprehensive.
13 To accomplish this, we've developed a written
14 plan to effect the assessments and the other
15 features of the Agreement. Joe has already
16 summarized the major elements of that plan.
17 I'll add to the details that concerns
18 equivalence assessments.

19 As I mentioned earlier, the
20 Agreement permits assessments and
21 determinations to distinguish by product and
22 even process types. Which means that it's

1 possible for us to find an authority
2 equivalent for conducting tableting
3 inspections, let's say, but not equivalent
4 for conducting aseptic processing
5 inspections.

6 In projecting our workload and
7 resource needs, we identified seven product
8 and process types: solid oral products,
9 non-sterile products, vaccines and biological
10 products, medicated feeds, sterile products,
11 and API's.

12 Of course, we'll cover all products
13 and process types during our equivalence
14 assessment and documentation reviews. But
15 we'll key in on selected process and product
16 types during the on-site inspection audit
17 phase.

18 Since we can't evaluate all fifteen
19 member states at the same time, we'll have to
20 choose a priority. The priority will
21 consider such factors as the volume of
22 imports, the number of inspections FDA now

1 performs in that member state jurisdiction,
2 and the number of manufacturing sites we have
3 registered or licensed in that jurisdiction.

4 Our aim to this priority is to
5 assess the member states in an order which
6 will give us the greatest possible reduction
7 and total number of inspections performed if
8 that member state is found equivalent.

9 We will assess the member states in
10 a staggered sequence, such that before we
11 complete the assess of the first member
12 state, we'll have begun the assessment of the
13 second member state, and so on. There will
14 also be three phases to the assessment, which
15 you see here on the screen.

16 The paper review will be the first
17 phase, and consist of comparative evaluation
18 of the documentation about a regulatory
19 system, again, covering the criteria
20 established in the Agreement. The paper
21 review findings will inform the second phase,
22 which will be an on-site system verification

1 audit.

2 Both the paper assessment findings
3 and the on-site system audit findings will
4 inform the third and final phase of our
5 assessment, inspection audits. I might add
6 that we also intend as part of the assessment
7 in the three year transition period to
8 exchange establishment inspection reports. A
9 purpose of that would be to not only build
10 mutual confidence, but to test our system for
11 exchanging that information, which of course,
12 is the currency, the end goal to this whole
13 process.

14 As to the organizational approach
15 to the assessments, we are making use of
16 technical and program specialists from the
17 involved centers, the Office of Regulatory
18 Affairs, and the Office of the Commissioner,
19 and other FDA offices. These specialists
20 will work together on teams on a part-time
21 schedule.

22 Finally, our approach has features

1 that promote our accountability to our
2 public, and to the EU authorities we are
3 assessing. We will communicate to each
4 member state any concerns and questions we
5 have as the assessment proceeds. We'll
6 establish an administrative record of our
7 assessments and our final determinations.
8 We'll publish the list of equivalent
9 authorities in the Federal Register at the
10 end of the transition period.

11 Before I discuss the progress we've
12 made to date, I wanted to share this work
13 load chart with you to give you a general
14 understanding of how the various phases of
15 the process fit into our decision making on
16 equivalence. I think you have in your packet
17 a photocopy of the real size of this. It's
18 kind of hard to see, I know, from the back.

19 If I could just point out very
20 quickly, there are basically two phases. The
21 transition period, the end of transition, or
22 operational period. As I've mentioned, the

1 paper assessments is the first phase.
2 On-site audits, which I've combined here to
3 indicate both the system audits, as well as
4 the inspection audits, are the second and
5 third phases.

6 At this point we are right here.
7 We have, and are receiving, and I'll go over
8 this a little bit later, EU MS documentation
9 that's under review. Of course, that'll
10 require additional clarification. As we get
11 that, we will at some point generate a report
12 on our findings of that comparative
13 evaluation.

14 Those findings will contribute to a
15 targeted audit procedure for each member
16 state authority, which will also, as I
17 mentioned, inform the FDA inspection audit.
18 Reports will be generated from that. They
19 will contribute to -- eventually all this
20 will contribute to an Agency decision record
21 on our assessment, and on a finding of
22 equivalence or non-equivalence.

1 Of course, as has already been
2 mentioned, the equivalence is a joint
3 determination to be made at the end of the
4 three year transition period.

5 Now I'll discuss our progress to
6 date. This summer a working group comprised
7 of representatives from the involved FDA
8 centers, ORA, the Office of Chief Counsel,
9 and led by the Office of International
10 Affairs, developed a comprehensive
11 bibliography about FDA's regulatory system
12 for pharmaceutical GMP's.

13 The purpose of this information was
14 two-fold. One, we wanted to initiate the
15 process of equivalence assessment, and
16 provide the EU with the information about our
17 system, for their assessment. Two, we wanted
18 to set an example of the kinds of information
19 we want to have detailing their system, and
20 how we want that information to be organized.

21 Along with the bibliography, we
22 sent hard copies of each referenced document.

1 I've lugged them here from my office to show
2 you the kind of volume we're talking about.
3 The information we've provided also serves as
4 benchmarking information about our system
5 against which we will evaluate their systems.

6 The cover letter for this
7 information requested each authority to
8 provide us with comparable information
9 organized according to the criterion in the
10 Annex. Most have responded with
11 documentation, although some have yet to
12 respond. This letter, as well as our
13 attached bibliography, can be found at our
14 Web site.

15 You can see how we organized our
16 bibliography, in the slide I have on the
17 screen now, in response to the first
18 criterion as shown here, appropriate
19 statutory mandate and jurisdiction. For
20 example, under 1-A, we identified relevant
21 sections of the Food, Drug and Cosmetic Act.
22 We've provided, although you can't see them

1 here on the screen, we've provided the URL's
2 or the Web site addresses, for each
3 reference, as available.

4 The total length of this
5 bibliography is sixty pages. Again, it is
6 posted at our Web site, complete with
7 hyper-link text. By the way, if you take
8 time to review this bibliography, and find
9 that -- or think that there are omissions or
10 mistakes, please don't hesitate to call them
11 to our attention.

12 To continue then, currently we are
13 reviewing the EU directives concerning
14 pharmaceutical products. We began this
15 review approximately one month ago. We also
16 recently initiated a review of the EU
17 standards of conduct. Recently we commented
18 to the -- for the record to the EU on their
19 recent draft proposal for establishing new
20 standards of conduct. Those comments were
21 not meant, though, to be in lieu of our
22 assessment process. It's still under way.

1 I'll close my presentation by
2 sharing with you another flow chart
3 describing the basic work process for our
4 documentation review of the information we
5 have received from the member states. This
6 was drafted for the purpose of guiding our
7 work group participants.

8 Once the evaluation -- well, let me
9 point out again here, we've requested the
10 documentation that's being provided now. We
11 are currently evaluating one part of all the
12 documentation we'll eventually have
13 evaluated, the EU Directives. Once we get to
14 the point of needing clarification about that
15 information, as I'm sure we will, we will
16 make a request to the appropriate EU office
17 or member state authority, await a response.

18 Continue on until at some point,
19 our review work group is satisfied that they
20 have seen all the information that they need
21 to see, and that they have a complete
22 understanding of the documents provided, and

1 the system they're evaluating.

2 Once they're satisfied, they will
3 report their findings to the Project
4 Management Team. Then they'll move on to
5 developing an on-site auditing procedure.
6 Then they'll move on to the next member
7 state.

8 If the evaluation is for some
9 reason considered unsatisfactory, either
10 because of a lack of adequate response by the
11 member state, or because the information
12 suggests a serious flaw with the system, as
13 it compares with our system, in terms of
14 equivalence.

15 Then the PMT will help coordinate a
16 response or reaction by the member state.
17 Of course, if -- that may take some time to
18 generate. In which case, the Project
19 Management Team will move on to the next
20 member state assessment.

21 Finally, I'd like to remind
22 everyone of the existence of an open public

1 docket for the purpose of sharing MRA related
2 information. That docket number
3 is 98-S-1064. I thank you for your interest
4 and attention, and I look forward to your
5 questions and comments later in the meeting.

6 MR. GAYLORD: Thank you, Brian. We
7 can see some of the intricacies involved with
8 determining equivalence for the member
9 states.

10 Now I'd like to give our attention
11 to Sylvia Henry, who is a consumer safety
12 officer in the Office of Compliance and
13 Biologics Quality in the Center for Biologics
14 Evaluation and Research, CBER. CBER is
15 represented on the PMT and the JSC by her.
16 So she's that representative for both bodies.
17 She's going to speak to us today about the
18 development of a two way alert system to
19 ensure the rapid exchange of information
20 between FDA and the EU. Sylvia?

21 STATEMENT OF MS. HENRY

22 MS. HENRY: Thank you, Charles, for

1 that introduction. It's a pleasure for me to
2 be here today to speak on the two way alert
3 system. The purpose of the alert system is
4 to share information in a timely and
5 effective manner in order to alert the
6 public.

7 Under the alert system, we will be
8 notified of defective products which are
9 potentially life threatening, or could cause
10 an injury to health. It is our hope that
11 this information will be shared jointly
12 amongst the US and the EU member states, so
13 that corrective actions can be carried out in
14 a timely and effective manner.

15 This information was discussed
16 briefly by Joseph in his overview of the MRA,
17 but bears repeating for clarification of the
18 products which are included, and are not
19 included in the Pharmaceutical Annex of the
20 MRA. For the human medicinal products, this
21 includes prescription and non-prescription
22 products.

1 For human biologicals, this
2 includes vaccines and immunologicals, but
3 excludes blood and blood related products.
4 For veterinary pharmaceuticals, this includes
5 prescription and non-prescription drugs, with
6 the exclusion of veterinary immunologicals.
7 For pre-mixes, this includes the preparation
8 of medicated feeds for the EC, and type A
9 medicated feeds for the US.

10 Lastly for intermediates, this
11 would include active pharmaceutical
12 ingredients, or bulk pharmaceuticals for the
13 US, and starting materials for the EC.

14 For the elements of the alert
15 system, there were criteria that were listed
16 and were taken into consideration for the
17 development of the project. The first being
18 documentation. We took into consideration
19 the definitions for crises and emergencies,
20 standing operating procedures, mechanisms for
21 health hazard evaluations, classifications,
22 language, and the transmission of

1 information.

2 For the crisis management system,
3 this would involve the analysis and
4 communication mechanisms, and establishing
5 contact points, and subsequent reporting
6 mechanisms. For enforcement procedures, this
7 would include follow-up mechanisms, and
8 corrective action procedures.

9 Under quality assurance, this would
10 include surveillance and monitoring of the
11 implementation of the corrective actions
12 taken.

13 Lastly, for the contact points, the
14 EU and the US FDA have established contact
15 points which are identified for each of the
16 three centers being CBER, CDER, and CVM.

17 The last point on the previous
18 slide mentioned the establishment of contact
19 points. Both sides have agreed to designated
20 contact points. This will ensure that the
21 information that we're sharing will be sent
22 to the correct office. The items that are

1 listed are included in that process.

2 The alert system itself is being
3 developed into separate components. The
4 first being the recall procedure, which is a
5 joint development to capture vital
6 information that could be considered
7 hazardous to public health. Contact points
8 have been identified in each of the three
9 centers to handle this information. So
10 again, the information that we intend to
11 share will include quality defects, recalls,
12 counterfeiting, and other quality problems.
13 For example, situations such as stability
14 failure, and potency.

15 For the mode of communication, in
16 order to expedite the receipt of information,
17 and the delivery of information, we agreed to
18 share information using one or both of the
19 following methods: either by FAX transmission
20 or electronic mail.

21 As with any large project with a
22 magnitude such as this for the MRA, there are

1 concerns. As being the person who worked
2 directly with the working group, who put
3 together the alert system, specifically the
4 recall SOP, there were several concerns that
5 came out in discussion during our meetings.

6 The first being language. The
7 concern was receiving documents in fifteen
8 languages, probably from fifteen member
9 states. The second being, if the documents
10 did come in in fifteen different languages,
11 they would have to be translated. So our
12 concern was, how would this affect the
13 urgency and the handling of critical
14 information? Because the information that
15 we're receiving under the alert system is
16 critical?

17 The third would be the maintenance
18 of records. The problems that could occur if
19 the Agency had to take an action. We wanted
20 assurances that the records are being
21 maintained, and are easily accessible.

22 Last, we wanted assurances that the

1 firm could take enforcement actions, if
2 needed. Examples would be recalls, seizures,
3 and injunctions. For this, I didn't want to
4 concentrate on the negatives, which are
5 concerns, but should be addressed,
6 nonetheless. The group made major
7 accomplishments as far as the alert system is
8 concerned.

9 The Agency's progress to date has
10 been accomplished through the hard work and
11 the dedication of the working group, with
12 individuals from each of the centers who are
13 considered experts in the areas identified
14 for the alert system.

15 A major accomplishment was the
16 development of the recall S-O-P, which is
17 currently being reviewed by the EU member
18 states, and comments are pending to the
19 Agency. While listening to my co-workers,
20 and listening to some of the things that they
21 were talking about in their presentations,
22 one of the major items I kept hearing was

1 communication, and the need to establish and
2 maintain communication with our EU
3 counterparts.

4 I am pleased to say that in
5 developing the alert system, we have
6 maintained regular contact with our
7 counterparts in the EU, and with the alert
8 system in general, specifically the recall
9 S-O-P, we hope to complete the initial phase
10 of the alert system with the appropriate
11 speed, to benefit and protect both the US and
12 EU consumers.

13 With that said, that concludes my
14 presentation on the two way alert system.

15 MR. GAYLORD: Thank you, Sylvia for
16 giving us an overview of the two-way alert
17 system. Our final presentation this morning
18 is going to be given by Merton Smith, the
19 Associate Director for International
20 Agreements in the Office of International
21 Programs. He's going to address public
22 transparency of MRA processes. That is, the

1 information disclosure requirements regarding
2 non-public documents. Merton?

3 STATEMENT OF MR. SMITH

4 MR. SMITH: Thank you, Charles. I
5 too am pleased to be here this morning. I
6 want to mention that my title up until
7 recently was Associate Director for
8 International Agreements. International
9 agreements are so important at FDA that in
10 the re-organization of the international
11 programs, we have created a new staff with
12 several people, that are involved in
13 international agreements now.

14 Transparency, and the importance of
15 transparency. When we were setting up the
16 agenda for this meeting, we right away
17 recognized that this should be a topic for
18 discussion. I think everyone else on the
19 Project Management Team selected a topic, and
20 sort of by default, this became my topic.

21 I know, looking at the audience, I
22 know that many of you are very well versed in

1 the requirements of the F-O-I act. Really,
2 what we're talking about this morning is not
3 only some of the exemptions under the F-O-I
4 act, establishing non-public information.
5 But more importantly, we're talking about a
6 more esoteric, or sort of arcane area of FDA
7 law involving the exchange of non-public
8 information with foreign governments, foreign
9 regulatory counterparts.

10 As you have heard from several
11 speakers, if this M-R-A Pharmaceutical Annex
12 works out well, we will be normally endorsing
13 inspection reports received from equivalent
14 E-C member state authorities. So conceiv-
15 ably, scores of FDA inspections that are
16 currently done by FDA could, during the
17 operational period of this agreement, then be
18 done by EC member states.

19 For this reason, FDA believes that
20 it is critically important to make the
21 information that is the basis for equivalence
22 determinations as available to the public as

1 possible. Indeed, the credibility of the MRA
2 process requires this.

3 Recently, the FDA was invited to a
4 meeting in Paris, basically to explain our
5 regulatory system. In particular, the
6 Europeans wanted to know how we maintain such
7 good credibility with the wide variety of
8 interested parties that follow FDA
9 activities. Remember, this meeting came on
10 the heels of two important controversies in
11 Europe, the BSE, or mad cow episode, and the
12 dioxins in animal feed problem.

13 During this meeting in Paris, FDA
14 officials emphasized one key principle that
15 underlies FDA's public credibility. Namely
16 the fact that FDA takes very deliberate
17 efforts to openly communicate with all of its
18 stake holders and that important benefits
19 flow from the resulting feedback.

20 There are, however, necessary
21 limitations on public openness that are
22 reflected in several pieces of Congressional

1 legislation. I mentioned the Freedom of
2 Information Act, also the Privacy Act, some
3 other laws, including the Food, Drug and
4 Cosmetic Act, the Economic Espionage Act, and
5 the Trade Secrets Act.

6 Transparency must be achieved in
7 accordance with these statutes, as well as
8 the regulations that implement their
9 statutes. So I want to spend a few minutes
10 talking about FDA's disclosure rules, and the
11 policies that underlie those rules.

12 In the next five minutes or so, I
13 will go over FDA's general disclosure policy
14 with -- and discuss and describe some of the
15 important provisions of the Freedom of
16 Information Act that exempt certain types of
17 information from disclosure. Then I'll focus
18 again on how FDA is able to, and in some
19 cases how FDA is not able to, exchange
20 non-public information with foreign
21 government officials.

22 It is FDA's policy that it will

1 make the fullest possible disclosure of its
2 records to the public. Such disclosures,
3 however, must be balanced against privacy
4 rights of individuals, balanced against the
5 property rights of persons, such as trade
6 secret information that resides at FDA,
7 confidential commercial information that is
8 property, that belongs to others, that
9 resides at FDA.

10 Also we need to balance disclosure
11 against FDA's need to promote frank internal
12 policy deliberations. Then, finally, we need
13 to balance FDA's disclosure against its need
14 to pursue regulatory activities without
15 disruption.

16 Finally, FDA must disclose records
17 except where disclosure is specifically
18 exempted. Now let's look more closely at
19 where the law permits or requires exceptions
20 to full disclosure.

21 This slide lists the important
22 exemptions for FDA under the Freedom of

1 Information Act. The so-called B-1 exemption
2 recognizes non-disclosure in the interests of
3 national security. This includes national
4 defense, and foreign affairs. While FDA
5 normally has not relied on this exemption to
6 a great extent, obviously in the area of the
7 MRA, and international agreements,
8 international relations, there is a distinct
9 possibility that we could rely on this in
10 certain instances.

11 The B-4 exemption recognizes
12 non-disclosure of public -- or, of trade
13 secret information, including confidential
14 commercial information, and confidential
15 financial information. B-5 exemption
16 recognizes non-disclosure of internal
17 government memos and drafts. B-5 is rather
18 circumscribed for FDA, and for other
19 government agencies through some policies
20 that have emanated from the Department of
21 Justice, as well as some clarifications in
22 FDA's regulations.

1 B-6 recognizes non-disclosure of
2 information the release of which would be a
3 clear invasion of an individual's privacy.
4 B-7 recognizes non-disclosure of records that
5 the release of which would interfere with law
6 enforcement proceedings, or deprive a person
7 of the right to a fair trial.

8 Now let's look at how FDA can share
9 non- public information with a foreign
10 government without triggering the requirement
11 to share with the rest of the world. These
12 requirements are part of FDA's regulation,
13 namely Section 20.89 of our CFR, Title 21.

14 This slide summarizes 20.89. Here
15 I've listed a number of purposes for being
16 able to share non-public information with
17 foreign governments, namely, exemptions
18 should be made to facilitate cooperative law
19 enforcement and regulatory efforts, to pursue
20 harmonization of regulatory requirements, and
21 to implement international agreements.

22 The last point on this slide notes

1 that to permit such sharing of non-public
2 information with a foreign regulatory agency,
3 FDA will usually need to enter into a written
4 agreement, or receive a written statement
5 from the recipient government, stating that
6 it has the authority to protect the
7 non-public information and, also, that it
8 makes an affirmative commitment to protect
9 that information.

10 Now let's look at some of the
11 detail of what FDA has to do in order to
12 share various categories of non-public
13 information with foreign governments, and
14 then not trigger the Uniform Access to
15 Records Requirement that I mentioned.

16 First, for law enforcement records
17 that are open or ongoing, there's no
18 requirement for FDA to receive a statement
19 from the foreign government that it will --
20 that it has the authority, and will protect
21 this information. However, FDA does transmit
22 this kind of information to foreign

1 regulators with a cautionary letter that
2 advises those regulators of the need to keep
3 this information; -- to non-disclose this
4 information.

5 For records containing confidential
6 commercial information, FDA needs a statement
7 that the foreign government has the authority
8 to not disclose the information, and also a
9 commitment that they will not disclose it.

10 Furthermore, FDA often needs the
11 consent of the submitter of the confidential
12 commercial information. Although if we feel
13 that it's in the interest of public health to
14 share this information, we may not need that
15 consent, for confidential commercial
16 information.

17 I wanted to note to this audience,
18 and when we go to the question and answer
19 period, FDA is really looking for a reaction
20 to the problem that we have of having to deal
21 with getting consent, particularly from the
22 industry, to share confidential commercial

1 information, as well as trade secret
2 information, with foreign governments.

3 Rather than do this on a case by
4 case basis for every piece of information
5 that we have to share under this agreement
6 and other agreements, we're looking for ideas
7 from the audience about whether we could have
8 some sort of blanket agreement with an
9 industry that has this kind of information
10 that we want, or that we may have to share
11 with under these agreements.

12 So, if you could give us some
13 feedback, either during the question or
14 answer period, or send written comments to
15 the docket that Brian mentioned, we would
16 appreciate it. We're looking for ways to
17 make this exchange more practical for FDA,
18 without jeopardizing industry's rights,
19 property rights.

20 Finally, for records containing
21 confidential commercial information that are
22 shared with visiting foreign scientists on

1 FDA premises, we have to get, we want to get,
2 and we have to get a signed statement from
3 the visiting scientist that they commit to
4 not disclosing this information. Also, we
5 need to get a statement saying that they have
6 no conflicting financial interest in the
7 information.

8 For records containing trade
9 secrets that are shared with foreign
10 governments, in this case, FDA requires a
11 statement of authority and commitment, but
12 also needs the property owner's consent.
13 Again, we're looking for ways to avoid having
14 to get that consent on a case by case basis.
15 So, any ideas that particularly members of
16 the industry have in how we could do this
17 would be appreciated.

18 For records containing trade
19 secrets that are shared with the visiting
20 scientists on FDA's premises, FDA requires
21 again, a signed statement committing that
22 they will not share this information. We

1 don't allow them to take this information
2 away from FDA, obviously. But they have to
3 sign a statement saying that they commit not
4 to share it, not to disclose it and they also
5 commit that there is no conflicting financial
6 interest that they have.

7 For records containing
8 pre-decisional information that is shared
9 with foreign governments, FDA requires a
10 statement from the foreign government that
11 they have authority to not disclose this
12 information, and also a statement that they
13 commit not to disclose the information.

14 Although in 1998 FDA published a
15 proposal that would eliminate this
16 requirement for pre-decisional information.
17 we are about ready to publish the final rule.
18 So there's a chance that this requirement
19 could be eliminated.

20 However, FDA, for pre-decisional
21 information, we do have internal FDA
22 procedures that assure that there's no

1 improper pre-decisional information that
2 would be shared with foreign governments.

3 Finally, for records containing
4 personal privacy information, again, FDA
5 generally requires a statement of authority
6 and commitment, as I've mentioned before, for
7 other types of information. But we also
8 require, generally, that the individual give
9 their consent to disclose this information.

10 In conclusion, while FDA strives to
11 be as completely transparent as possible,
12 there are certain limitations that reflect
13 legitimate public policies. Namely the
14 protection of public rights, or property
15 rights. The protection of privacy rights.

16 A need by FDA not to chill the
17 documentation of spontaneous internal Agency
18 deliberations. Or not to chill or circumvent
19 regulatory -- FDA's regulatory pursuits. As
20 I explained, that generally if FDA shares any
21 non-public information with a foreign
22 government, it must share it with the general

1 public. This is, again, under 20.21. It's
2 called the Uniform Access Rule.

3 But if we follow procedures
4 outlined in 20.89, where we have certain
5 safeguards, FDA can share non-public
6 information with foreign governments without
7 triggering this Uniform Access to Records
8 Requirement. Every day as part of FDA
9 increasingly frequent international
10 cooperative efforts with foreign counterpart
11 regulatory agencies, the FDA finds it
12 increasingly necessary to exchange non-public
13 information with its foreign regulatory
14 colleagues.

15 I look forward to any questions
16 that you might have about this. I note that
17 we have some experts from our General
18 Counsel's Office, and other offices that deal
19 with Freedom of Information. The exchange of
20 information with foreign government
21 counterparts really doesn't fall under
22 Freedom of Information. But obviously from

1 what I've said, there are implications for
2 Freedom of Information.

3 Thank you very much.

4 MR. GAYLORD: Well Merton, we'd
5 like to thank you as well, and each of the
6 presenters this morning for providing us with
7 that information.

8 At this point, we'd like to take a
9 fifteen minute break, and come back to the
10 second part of the meeting. As Sharon
11 mentioned at the outset, this is a dialogue.
12 So, when we come back, we'll have
13 presentations from the audience, followed by
14 the Q and A part, which I know that you are
15 waiting for.

16 We like your input, and look
17 forward to those parts. So, we're going to
18 re-convene at twelve minutes of by this clock
19 here.

20 (Recess)

21 MR. GAYLORD: As I had indicated at
22 the outset of the meeting, there were three

1 who were going to be in attendance today who
2 said that they would like to give
3 presentations. I saw two of the people on
4 the sign-in sheet. I'd like to know if
5 Ms. Doris Haire or Ms. Sybil Shainwald is here,
6 from the National Women's Health Alliance?
7 They were one of the presenters. Are either
8 one of them here today? I know Doris. I
9 didn't see her.

10 So, well, they may have stepped
11 out. I'd also like to acknowledge the
12 problem with parking that some of you may
13 have faced. Most people when they called
14 said that they were going to take the subway,
15 but I know a fair number drove. So, some had
16 to go out to feed the meters, or to move
17 their cars. I apologize for the tight
18 parking space situation here. It's something
19 that as FDA'ers we've endured for a while.
20 We hope that you were able to get your cars
21 to safe haven. We have the parking lot, but
22 it fills up pretty quickly, the pay parking

1 lot.

2 One thing, too. After the
3 presentations, we will have the question and
4 answer period. as I mentioned before, you
5 can write your questions down on the index
6 cards that are in the packet. We have
7 people that will collect those. So, if you
8 can pass those down. whoever on the end of
9 each of the rows, if you would just hold
10 those up.

11 Erik Henrikson, or Nancy, or others
12 that have volunteered, said that they would
13 pick those up, we will relate those.

14 Well, to give our first
15 presentation, we have with us from the
16 Consumer Health Care Products Association,
17 Mr. William Bradley, who is the vice
18 president for technical affairs. So, let's
19 give our attention to Mr. Bradley as he gives
20 our first presentation.

21 STATEMENT OF MR. BRADLEY

22 MR. BRADLEY: Thank you, Charles.

1 Originally, these comments were going to be
2 given by Dr. Frank Sena, who is chairman of
3 our Manufacturing Controls Committee. But he
4 was called to jury duty. Therefore could not
5 be here. So, I'm going to be presenting
6 these comments for him.

7 My name is Bill Bradley. I am Vice
8 President for Technical Affairs for the
9 Consumer Health Care Products Association,
10 CHPA, which was formerly the Non-
11 Prescription Drug Manufacturer's Association,
12 which more of you are probably familiar with
13 at this time.

14 CHPA is a national trade
15 association that has been representing the
16 manufacturers and distributors of
17 non-prescription or over the counter OTC drug
18 products for over a hundred years.

19 I would like to take this
20 opportunity to state that CHPA strongly
21 supports the MRA effort, and the proposed
22 rule, with its potential to improve patient

1 access to safe and effective technologies,
2 reduce unnecessary regulatory redundancies,
3 enhance the access of United States and EC
4 companies to each other's markets, provide
5 significant savings to both companies and
6 regulators, and set the stage for further
7 regulatory cooperation and harmonization.

8 CHPA believes that the proposed
9 rule and the MRA allow for incorporation of
10 the best regulatory attributes of both
11 parties. CHPA supports the FDA view that
12 equivalence of GMP reports, and other
13 conformity assessment reports and evaluations
14 between the FDA and EC member state
15 authorities and CAB's can be relied on to
16 help ensure the safety, quality, and
17 effectiveness of products exported to the
18 United States while also reducing the
19 regulatory burden on manufacturers.

20 CHPA hopes that the MRA and the
21 pending regulation also permit FDA to
22 re-direct some of its inspectional resources

1 from countries whose systems are found
2 equivalent to or higher than risk priorities
3 not covered under the MRA. I'm sorry, that
4 we hope they can re-direct some of it to risk
5 priorities not covered under the MRA.

6 The Agency may thus better target
7 its limited foreign inspection and other
8 resources devoted to imports and other
9 regulatory concerns. Thus, FDA will be able
10 to leverage its resources by relying on
11 information from its counterpart regulatory
12 authorities in foreign countries that have
13 demonstrated equivalence.

14 CHPA anticipates that under the MRA
15 and the proposed regulation, as equivalence
16 is achieved between regulatory systems of EC
17 member state authorities or conformity
18 assessment bodies, and FDA, there will be
19 reduced need for importing countries to
20 engage in resource intensive foreign
21 inspection, sampling, and examination of
22 products being considered for entry from

1 countries with equivalent systems.

2 This can assist in speedier
3 approvals of safe and effective products, and
4 in more comprehensive and effective
5 surveillance of GMP's and quality systems.
6 We support the transition period, with its
7 emphasis on collaborative confidence building
8 activities between FDA and EC member state
9 authorities, and CAB's which should result in
10 harmonization of requirements at a high level
11 of consumer protection, thus enhancing
12 regulatory controls.

13 CHPA also urges FDA to consider and
14 ensure the continuance of the US system for
15 the approval, manufacture and compliance
16 programs associated with OTC medicines. Few
17 countries within the EC maintain a class of
18 quality drug products equivalent to the US
19 OTC industry. Hence, the compliance approach
20 within the EC should be to treat OTC as
21 Rx-products.

22 A clear example of the difference

1 in compliance evaluation in the US is the
2 longstanding FDA exemption from expiration
3 dating for non-dosage limitation OTC's for
4 which the manufacturer has greater than three
5 years satisfactory stability support. This
6 type of exemption does not exist in the EC.

7 CHPA is also concerned that the
8 language of the proposed rule published on
9 April 10, 1998, refers almost exclusively to
10 marketing authorizations, licenses, et
11 cetera, which are terms usually applied to
12 our ex-products or, in the EC, registered
13 pharmaceuticals, and may not be associated
14 with OTC products.

15 Finally, CHPA would also add its
16 encouragement to the efforts proposed by FDA
17 during the transitional period, designed to
18 build joint confidence between the parties
19 through seminars, workshops, joint training
20 exercises, and observed inspections.

21 Furthermore, CHPA offers its
22 membership to assist in this effort in any

1 reasonable way that FDA may judge
2 appropriate. Examples of such assistance
3 could be hosted joint plant tours, or
4 participation, or contributing faculty to
5 inspectorate training, or workshops.

6 Thank you for the time and
7 opportunity to present these comments.

8 MR. GAYLORD: Thank you,
9 Mr. Bradley, for presenting those comments
10 for us today. Now I'd like to give our
11 attention to Ms. Mary Bottari, of "Public
12 Citizen". she is the director of their
13 Harmony project, Harmonization project. She
14 is fresh back from Seattle, and so is still
15 recovering from that. But it is a pleasure
16 to have you with us Ms. Bottari?

17 STATEMENT OF MS. BOTTARI

18 MS. BOTTARI: Thank you very much.
19 I am the director of "Public Citizen's"
20 Harmonization Project. what the
21 Harmonization Project does is we track
22 international harmonization activities in all

1 federal agencies, and we try and examine the
2 harmonization impact upon consumers.

3 We are also part of the Steering
4 Committee of the Trans-Atlantic Consumer
5 Dialogue, and so have been following this MRA
6 with great interest, and was very interested
7 in the presentations here today.

8 We are basically a little
9 uncomfortable with this mutual recognition
10 agreement for a wide variety of reasons. But
11 I'll make my comments brief. It's very
12 concerning that the MRA was discussed as
13 early as 1989. Yet prior to it being signed,
14 there was very little public notice, public
15 involvement, in the MRA process.

16 We are also concerned that the MRA
17 will be privatizing what are normally public
18 health functions of the US government. We
19 are concerned that EU manufacturers can pick
20 and choose amongst CABs and that as a 1996
21 GAO report made clear, that the notified
22 bodies in Europe operate under much less

1 comprehensive conflict of interest standards
2 than our FDA officials do here.

3 "Public Citizen" has a wide variety
4 of interests in these types of issues. But
5 most importantly to us are the impact of
6 these trade negotiations on four of our most
7 treasured laws: the Freedom of Information
8 Act, Administrative Procedures Act, the
9 Government and Sunshine Law, and the Federal
10 Advisory Committee Act, which require
11 balanced advisory committees in the
12 government.

13 There's been a lot of discussion
14 here about transparency and confidentiality.
15 These continue to be controversial topics in
16 negotiation of the MRA. For those of you in
17 the room that think the FDA is persnickety
18 about this stuff, they're not half as
19 persnickety as we are.

20 We want to ensure that all
21 government documents that are currently
22 available to consumers will remain available

1 to consumers during the implementation of
2 this MRA. That means all inspection reports,
3 all recall alerts, and a variety of other
4 documents that will be generated.

5 When we hear from Merton Smith that
6 the FDA could possibly invoke a national
7 security exemption to the FOIA, that alarms
8 us. It's hard to imagine what the national
9 security implications are of this type of
10 pharmaceutical agreement.

11 We're also uncomfortable with the
12 notion of equivalency. The notion was
13 created in the World Trade Organization as
14 sort of a wishy washy notion that doesn't
15 mean that you have to harmonize specific
16 standards. That you can take whole sets of
17 regulatory, perhaps very disparate regulatory
18 rules, and just sort of declare them
19 equivalent.

20 US federal agencies have been
21 reaching different equivalency agreements.
22 They haven't been defining their terms. They

1 haven't been defining what criteria they use
2 to reach equivalency. The FDA is doing a
3 slightly better job than other agencies by
4 defining different criteria they would use in
5 reaching equivalency determinations.

6 But we would hope that when you get
7 to the point where you are going to make an
8 equivalency decision, that you will post that
9 as a proposed rule. That you will list every
10 single criteria examined, and the performance
11 of the other nation state on those criteria.

12 Of course, we would hope that the
13 FDA is going to be maintaining or improving
14 the current level of public health and safety
15 achieved under our US laws. We would ask
16 that once an equivalency decision is reached,
17 that there is a mechanism for an ongoing
18 review of the equivalency decision. That
19 after three years or five years, there is
20 again, public record of rule making on the
21 equivalency decision, to make sure that it's
22 working for US consumers.

1 Lastly, the FDA has often stated
2 that its resources to engage in these kinds
3 of activities are stretched thin. We would
4 hope that the FDA would be able to secure the
5 resources needed to make sure they pursue all
6 these international trade activities in the
7 most appropriate manner guarding US public
8 health. Thank you.

9 AUDIENCE QUESTIONS

10 MR. GAYLORD: I'd like to thank
11 you, Ms. Bottari. We appreciate that input.
12 We're glad that at least one consumer group
13 was here. We know that many were in Seattle.
14 So we appreciate your being here today.

15 I'd like to ask again if the
16 National Women's Health Alliance is here.
17 It's one of the consumer groups, and they
18 wanted to present, as well. If not? Then we
19 will proceed to the convening of the panel,
20 so that we can have the Q and A discussion.

21 We'd like to have our attention
22 directed again to the project management

1 team, that will comprise one panel. In
2 addition, we have representatives from each
3 of the organizations, the centers and other
4 offices that have been involved in the
5 implementation, as well as the negotiation of
6 this particular agreement.

7 So, for the second panel, we have
8 two directors from the Office of
9 International Programs. We have Walter
10 Batts, who is the Director of the
11 International Relations Staff. I'd like you
12 to come forward. We've had your name,
13 plaquard for you there. I know that Linda
14 Horton was here earlier. She will be back
15 very shortly, okay, and will join us. She's
16 the director of the International Agreements
17 and Trade Staff.

18 As Merton mentioned to you, there
19 is an organizational change within the Office
20 of International Affairs. There are now
21 going to be sub-offices under the Office of
22 International Programs. So, Linda Horton and

1 Walter Batts are two of the directors of the
2 four staffs.

3 In addition we have, in our
4 audience, we have representatives from the
5 Centers. The Center for Biologics, we have
6 Dr. Elaine Esber. I see her in the audience.
7 We have, from the Center for Drugs, we have
8 Stephanie Gray. I saw, she is here. Also,
9 we have from the Office of General Counsel,
10 we have Miss Leigh Hayes. We have Katherine
11 Cooper, who is a recent addition to the
12 Project Management Team. So, I would like to
13 welcome each of them.

14 At this point we are going to throw
15 open this part of the meeting to you in terms
16 of questions that you might have. We ask
17 that you use the microphones that are on each
18 of the outer aisles. Again, if you would
19 give your name and organizational
20 affiliation, we would appreciate it. Again,
21 if you have any questions that you've put on
22 the index cards, you can pass those to the

1 outer aisles, and they will be collected and
2 forwarded.

3 So, who would like to go first.

4 Yes, please?

5 MR. FREY: I'm Ed Frey, and I'm
6 with the EA, which is an international
7 association pharmaceutical scientists. I
8 noted what Joe Famulare said, that the MRA is
9 not a harmonization process. I appreciate
10 that. It's about equivalence determination.

11 But it seems as if it will not
12 fulfill its promise without -- without
13 attention being given to harmonization of the
14 requirements that underlie the very purpose
15 of inspections. The situation the way it is
16 now, companies who operate in various regions
17 of the world face different requirements for
18 sterile filtration, different environmental
19 monitoring requirements for new technologies.

20 Example, barrier systems for
21 aseptic processing. Different rules for
22 media fills. The implementation of Part 11,

1 the new FDA rules for electronic
2 identification, electronic signatures.
3 Possibly even the very definition of GMP
4 itself.

5 There is a player that has not been
6 mentioned, the Pharmaceutical Inspection
7 Convention/Cooperation Scheme, which is
8 producing GMP requirements that appear to be
9 adopted by the European Union authorities
10 without a public participation process. I
11 wonder if the panel has given any thought to
12 the impact of this. What is the thought
13 about the importance of harmonizing, so
14 that the inspections really do report on the
15 same things, and apply the same requirements
16 worldwide.

17 MR. GAYLORD: Joseph?

18 MR. FAMULARE: Your question is
19 loaded with many aspects in determining
20 equivalence. First of all, I'll start out
21 with the whole concept of harmonization.

22 While harmonization is not at the

1 core of this Agreement, its equivalence, as
2 we well emphasized, the fact that regulatory
3 authorities now as part of this process are
4 coming into collaboration and working
5 together, there are certainly holes.

6 There's certainly no prohibition
7 against certain harmonizations taking place.
8 I think it's just a natural outcome of the
9 process.

10 So certainly, as we look at
11 evaluating each other's standards, there may
12 be differences in standards, whether it be
13 for aseptic filling, media fills, or laminar
14 flow hoods, and so forth. These other
15 technical areas where there may be
16 differences, it remains to be seen as a
17 result of our equivalency assessment process
18 if we can live with those differences.

19 Or whether, for example, an
20 authority or an area is found not equivalent,
21 if they're found so -- to be disparate and
22 harmonization in those areas, or some meeting

1 of the minds will occur.

2 So these are things that are yet to
3 play out in terms of how those things will be
4 evaluated. Just bear in mind that what holds
5 it does hold, that some things that are not
6 exactly the same will be deemed equivalent
7 and maybe some things will be deemed so
8 different that they cannot be equivalent.
9 That may move both sides towards some sort of
10 "harmonization" on those efforts.

11 The other point you brought up was,
12 for example, Part 11 was one other point you
13 brought up. We have a rule in place here.
14 The Europeans have their ways of dealing with
15 the electronic records and signatures and
16 again, just like the GMP's or other
17 directives, guidances, and so forth, whether
18 they emanate through rule making processes in
19 each authority at the EC level.

20 Or if something is adopted as a
21 result of PIC influence, we will have to look
22 at and evaluate if it's equivalent to our own

1 process. Our process, of course, any
2 guidance, or directive, or regulation that
3 comes forward, we have standard procedures
4 for sharing that with the public.

5 Whether the European authorities
6 are bringing into place directives or
7 guidances that aren't going through that
8 process, whether it be through PIC, or some
9 other means, we will look at that against our
10 own. We are looking at our laws, directives
11 and regulations as bench marks, to compare to
12 theirs.

13 Remember that we're looking at
14 their overall system for evaluation. So it
15 looks at how they put together their laws,
16 regulations, how they enforce them, and so
17 forth. So, these things will be encountered
18 as we go through our equivalency assessment
19 process.

20 They may slow things down. They
21 may cause problems. They may cause bumps in
22 the road as we go along. These are things

1 that we have to consider, and important
2 factors, as you pointed out in your question.

3 MR. GAYLORD: Would any of the
4 other panelists like to address that
5 question?

6 Okay. I'm going to read one of the
7 questions that was just passed forward. It's
8 a three part question. Raymond had mentioned
9 about GAO had at least two pointed inquiries
10 that they directed to FDA.

11 So the first part concerns GAO. It
12 says, GAO has expressed concern about FDA's
13 MRA implementation. What are GAO's current
14 concerns? What GAO concerns have been
15 addressed? What are the potential impacts of
16 GAO's ongoing concerns on the implementation
17 time table?

18 So, who would like to address that?
19 For those who give responses, if you would
20 give your name, so that that can be recorded
21 for the transcription process. Raymond?

22 MR. MARS: Is anyone from GAO here?

1 You get an answer, so I don't know. I'll
2 have to be careful.

3 I've been in this process for about
4 a year. What I've seen really are two
5 focused probes. From my perspective, the
6 probes are focused at the procedures we're
7 going to use to assess equivalence. They're
8 also interested in a plan, and time table,
9 and things like that.

10 I think FDA has assuaged that
11 concern pretty well. We have a very detailed
12 plan for progressing and taking specific
13 steps to move forward. We've given you a
14 summary of that.

15 The other part of it has to do with
16 the actual criteria we are going to use to
17 make those equivalence assessments, as well
18 as some concern about the order in which
19 we're going to deal with the countries. Our
20 responses to GAO have basically been that, in
21 stepping through the plan, as we've developed
22 it, that we will develop criteria that we'll

1 use to assess each of the fifteen member
2 states, and all of the regulatory systems.

3 It will be a common approach. It's
4 going to be kind of an iterative process that
5 we anticipate is going to be completed with
6 the first assessment of the first member
7 state. Brian laid out some of the criteria
8 we're going to use to determine who we're
9 going to do first.

10 But you know, that's basically
11 where I've seen them questioning us. The
12 other issue has been resources. Have we got
13 the resources to do it? Do we have the
14 expertise to do it? Some of that I think
15 we've answered. We do, FDA does in some
16 other areas domestically, within the state
17 program, milk program and some others, we do
18 make equivalence assessment of other
19 regulatory systems.

20 So it's not an area totally new to
21 us, although doing it overseas certainly is.
22 So it's been, the specifics of the

1 implementation program, resources, that kind
2 of thing.

3 MR. GAYLORD: All right. What
4 about potential, in terms of the -- Brian?

5 MR. HASSELBALCH: Brian
6 Hasselbalch. If I could just add to that.
7 That was a very good summary of GAO's
8 concerns. The two outstanding in their most
9 recent report were the order of member
10 states, and the lack of values assigned to
11 equivalence criteria. Such that, could we
12 consider a particular element to a system so
13 critical that, absent it, we'd find them not
14 equivalent at the outset, and so on?

15 So of a system of critical major
16 and minors. You're very familiar with the
17 sampling plans. As Ray mentioned, we
18 understand the need for that kind of an
19 approach. That is the approach we will take.
20 But we didn't have answers for GAO in
21 accordance with their time line or table for
22 needing answers.

1 But I think we satisfied them that
2 that is how we are thinking. We'll develop a
3 more detailed procedure for that in the
4 future. As well as the establishment of the
5 order of member states.

6 So I think GAO's concerns were
7 largely a result of a difference of opinion
8 on the timing for that information, rather
9 than the need for it.

10 MR. GAYLORD: Sylvia?

11 MS. HENRY: There was also some
12 concern from GAO regarding the Gant chart
13 that was provided. The Gant chart is a line
14 by line listing of the activities which are
15 involved in the MRA process itself. we
16 provided answers to the questions that came
17 up from GAO on that.

18 MR. GAYLORD: Okay. All right.
19 We're going to ask one other question from
20 this, and then we'll go to Dr. Wood.

21 The Canadian authorities issued an
22 SOP describing processes or procedures they

1 will use for joint inspections. Will the FDA
2 give industry similar guidance on US - EU
3 accompanied inspections?

4 Secondly, can industry assume the
5 process for the US - EU MRA will be similar
6 to that described in the Canadian SOP?

7 Raymond?

8 MR. MARS: Ray Mars. When we get
9 to the point of doing on site inspection
10 equivalence determinations, I think what we
11 foresee is accompanying the member state
12 inspector, after reviewing their procedures,
13 and policies, and that kind of thing, and
14 observing what they do.

15 We will develop measures that
16 identify probably critical things that we
17 think need to be done on an inspection. But
18 I think it's going to be very similar to what
19 we're doing now with the Device Certification
20 Program.

21 Basically, we're along to observe
22 how the other person does what it is they're

1 doing. then to make a judgment of that, to
2 determine whether or not they're doing an
3 equivalent job in terms of inspection.
4 Again, it's not going to have to be identical
5 to the way we do it. But some equivalency of
6 critical areas.

7 MR. FAMULARE: I might just add on,
8 I think the concern there on the question is
9 the -- will industry know what's going on?
10 We've discussed on both sides, from our side
11 and from the European side, that we would try
12 and keep industry appraised of our plans on
13 how we're going to go about these joint
14 inspections.

15 Because there's been concern
16 raised. Well, will it be a, you know, one
17 topping the other type thing? No. We want
18 to make sure that the folks that do these
19 assessments are trained in the assessments on
20 our side, and the Europeans on their side, in
21 terms of doing an inspection in a normal
22 manner that could be observed by the other

1 side.

2 MR. GAYLORD: Would anybody like to
3 address that? Okay. Dr. Wood, please.

4 MR. WOOD: I'm Richard Wood. I'm
5 the director of Animal Concerns Trust. We're
6 a consumer group that works on food animal
7 issues. I have a question that you've really
8 touched on, I think, but I want to see where
9 it fits on the flow chart.

10 The regulation states that the FDA
11 will make available in a public document the
12 complete administrative file that constitutes
13 the basis for the FDA's equivalence
14 determination. So Dr. Brian Hasselbalch, you
15 laid out the flow chart. Where in that flow
16 chart might we expect that report to come,
17 then?

18 Would it come out as one
19 assessment, equivalency assessment is
20 completed, and then we'll see a report? Or
21 what might we anticipate as we look at this?

22 MR. HASSELBALCH: Brian

1 Hasselbalch. The timing of that, as I
2 indicated, albeit not clearly, would happen
3 at the end of the transition period, that is,
4 at the end of the three year period. We
5 don't intend to issue reports of our finding
6 of equivalence or non-equivalence until the
7 very end.

8 MR. WOOD: So even though in the
9 flow chart, under the transition period,
10 where it indicates there's FDA assessment
11 findings compiled in the report, and so on,
12 that would not be -- those kinds of -- that
13 public report would -- at that point, then,
14 would have to wait until the end, is that
15 right?

16 MR. HASSELBALCH: Right. That
17 information at that point wouldn't be
18 publicized. Again, those are findings of
19 assessments, many pieces to the overall
20 assessment that get compiled, and put into an
21 Agency decision making record, which would be
22 the decision point on equivalence or

1 non-equivalence. Or no finding can be made
2 because of a lack of information.

3 MR. WOOD: Just so that I'm clear,
4 and I apologize for belaboring this a moment.
5 But then the only point at which the public
6 will be able to really see the full status of
7 these assessment findings will be after the
8 assessment has been made then, is that
9 correct?

10 MR. HASSELBALCH: That is correct.

11 MR. GAYLORD: Yes? Please?

12 MS. WEXLER: I'm Jill Wexler, with
13 Pharmaceutical Executive magazine. As I
14 understood from Dr. Hasselbalch's remarks,
15 the current procedure is that you're looking
16 at certain member states first, and others
17 later. that you also may look, focus your
18 equivalence assessments on certain kinds of
19 products or processes.

20 Is this procedure, the modus
21 operandi agreed on by the EU? My impression
22 was initially that they were looking for sort

1 of an all or nothing Agreement.

2 MR. HASSELBALCH: The product
3 process distinction is of course, agreed
4 upon. That is enshrined in the Agreement.
5 You're correct, the EU is concerned that we
6 finish all member states, all systems, in the
7 three year transition period established in
8 the Agreement.

9 The Agreement of course, also has
10 language which allows either party to make as
11 diligent an effort as possible, given their
12 existing resources, to complete the effort.
13 It doesn't actually require that, the
14 assessments, the language of the Agreement,
15 to our read, my read, doesn't require that
16 assessments be necessarily finished at the
17 end of the three years.

18 But the EU did indicate to us in
19 our last meeting that they felt if we
20 couldn't finish them all by the end of the
21 three years, to a determination, then we'd
22 have to extend the transition period,

1 effectively. Move it beyond three years.
2 thus, delay any benefits that we might
3 otherwise get from a finding of equivalence.

4 Which would be an exchange of
5 inspection report for normal endorsement. A
6 cessation of inspections for those equivalent
7 authorities, and so on. So, we're still
8 discussing that. We have a difference of
9 opinion on how the Agreement obligates either
10 party in that regard.

11 MR. FAMULARE: That's why I
12 emphasized in my presentation that although
13 we have a plan over this next three years,
14 that plan is subject to the availability of
15 resources, and other factors beyond our
16 control, in getting done with the member
17 states by the end of the three year
18 transition period.

19 MR. GAYLORD: All right. As I
20 mentioned, there's a three part question, and
21 I'll ask the third part of this question
22 that's stated on the first card I received.

1 It says, does FDA see piecemeal
2 implementation as possible or likely? Now,
3 there's a definition of piecemeal here, and I
4 cannot make out a portion of it. But it
5 says, piecemeal means a member state could be
6 found equivalent for tablets, not for
7 something dealing with production.

8 Then it says, is piecemeal
9 absolutely out of the question? So, the
10 author of this question, if you'd like to
11 elaborate further before this is passed to
12 the panel? Yes? Please?

13 MR. McMILLAN: -- aspect of their
14 production, their equivalent. There is
15 equivalence in other parts -- we can proceed.

16 MR. GAYLORD: All right. your name
17 and organizational affiliation?

18 MR. McMILLAN: Steve McMillan --
19 American Pharmaceutical --

20 MR. GAYLORD: Okay. Mr. McMillan.
21 Thank you. We'd like to address that
22 question.

1 MR. HASSELBALCH: I'll address it.
2 Brian Hasselbalch again. Yes, we would
3 proceed. In fact, that is my understanding
4 of the negotiation process. The development
5 of the language of the Agreement was that
6 that particular element of the Agreement was
7 put in for the most part to allow us to move
8 forward to a potential finding of
9 equivalence, even though many member states
10 couldn't or don't regulate active
11 pharmaceutical ingredient production.

12 But of course, it includes not just
13 API's but all product and process types, any
14 product and process types. So, it's a
15 feature of the Agreement that allows us to
16 carve away from, or carve out, problem areas,
17 or areas of major disagreement, so that we
18 can move forward to a finding of equivalence
19 for other areas where equivalence exists.

20 MR. McMILLAN: (Inaudible)

21 MR. HASSELBALCH: I'm sorry? It's
22 possible. Until we actually get further into

1 the reviews, you know? My guess, yes. It's
2 very likely. Certainly for API's, at this
3 point. If I were to --

4 MR. FAMULARE: Joe Famulare. I
5 might just add to that also, from the
6 European perspective. They also looked at
7 that feature, because they realize that not
8 every of the fifteen member states for
9 example, may have expertise in every area of
10 production.

11 There may be authorities that don't
12 even have facilities that produce sterile
13 products. So that's another encumbrance
14 that's overcome by this parsing out of
15 processes.

16 So there's two ways of looking at
17 it. One, a process may exist in a member
18 state authority that is not found equivalent
19 after our review.

20 The other way of looking at it is
21 that a particular -- when we give an
22 authority, when we say an authority is found

1 equivalent, if they don't even have the
2 capability or expertise in that area, we
3 certainly wouldn't say that they're
4 equivalent in small volume parenteral
5 production.

6 Then three years later a plant
7 opens up, and we've never assessed them for
8 that particular technical aspect.

9 So that allows a number of
10 flexibilities. That's why that's worked into
11 the Agreement.

12 MR. GAYLORD: Anyone else? Merton?

13 MR. SMITH: Merton Smith. I'd like
14 to just clarify that if we do this piecemeal
15 at all, you don't necessarily infer that
16 where we have not determined equivalence that
17 there's a problem with their system. It may
18 be a problem with getting the information
19 about their system, or some other problem.

20 Not necessarily that we're finding
21 them non-equivalent, and trying to work on
22 that. That's the delay. So, I just wanted

1 to --

2 MR. GAYLORD: Okay. Anyone else
3 from the audience would like to ask a
4 question? Would you please use the
5 microphone? So, whenever you have questions,
6 please, if you'd go to the microphones, we'd
7 appreciate it.

8 MR. HOLMES: Malcolm Holmes. I
9 chair the Working Party for the EFPI
10 Committee on MRA's, the European Federation
11 of Pharmaceutical Industries, and also work
12 with Glaxo-Wellcome.

13 I'd just like to take up on the
14 issue of API's, which is something I see
15 where perhaps there could be non-equivalence
16 stated, because the legislation isn't in
17 place in much of Europe to actually cover
18 API's at this stage.

19 I wanted to know what the process
20 would be for including those API's post the
21 transition phase. Because many countries
22 will actually have legislation in place

1 probably towards the end of the three year
2 transition period.

3 MR. HASSELBALCH: Brian
4 Hasselbalch. The specific details of
5 post-transition operational period management
6 of the Annex, joint management of the Annex,
7 haven't been decided.

8 But we have talked basically that
9 the equivalence assessments would of course,
10 make a finding, or the assessments would
11 arrive at a finding of equivalence, or
12 non-equivalence, or lack of information. It
13 would be stated and reported to the EU, as
14 well as the involved or affected member
15 state.

16 It would be up to them at that
17 point, then, to re-initiate our review of
18 their system, or one or more aspects.
19 Whatever the glitch is, we'd re-visit it. It
20 would be prompted by, I guess in short, the
21 member state making a request, or providing
22 us with the information that remains

1 outstanding. So that we could continue on
2 the review in that area.

3 MR. HOLMES: There is a mechanism
4 which would allow this to take place post the
5 completion of the transition phase.

6 MR. HASSELBALCH: The Annex doesn't
7 describe such a mechanism.

8 MR. HOLMES: I know.

9 MR. HASSELBALCH: But we intend
10 there to be such a procedure, or an allowance
11 for that. In other words, we don't intend
12 that, just because somebody's found
13 non-equivalent, or that we have a lack of
14 information to make a finding of equivalence
15 or non- equivalence, that that's the end of
16 it for that member state, or that authority.

17 We intend that there's a way for an
18 authority to resurrect the review with the
19 FDA. We hope that that would work in
20 reverse, also.

21 MR. FAMULARE: Joe Famulare. If I
22 could just add, we really don't find somebody

1 non-equivalent. If we really come to a point
2 where we cannot find equivalence, we report
3 back to that authority, and the EC. As Brian
4 said, "These are the problems."

5 Then, it's up to that authority to
6 come back. Of course, with the hope that any
7 authority would be able to answer those
8 problems, questions, or come up to the -- or
9 find the ability to come up technically, or
10 whatever the problem might be, to then come
11 to a finding of equivalence.

12 That's why we said at the end of
13 the transition period, we will list those
14 authorities which are found equivalent. The
15 other authorities that you don't hear about,
16 either we didn't get to yet. Or we've
17 reached that point where we had to report
18 back, we are not finding equivalence because.

19 MR. HOLMES: I think this might
20 well be a point, though, where there will be
21 an early recognition from all parties that
22 because legislation isn't in place, then

1 equivalence can't be there. Therefore, just
2 looking at the way forward for that process,
3 when the Europeans are working towards
4 putting legislation in place, perhaps the
5 same legislation via ICH.

6 MR. FAMULARE: Well, of course,
7 when we've already broached that subject,
8 even in terms of what products will be
9 included in alert system exchange. Whether
10 or not API's can be included in the exchange
11 if there isn't legislation in place in member
12 states for API. So it's an issue we're
13 already broaching.

14 MR. HOLMES: Thank you.

15 MR. MARS: This is Ray Mars. If I
16 could add to that just a little bit. I think
17 I was reading into your question whether or
18 not there would be a continuation of an
19 assessment beyond the transition period. I
20 think even the MRA talks about re-evaluating
21 radio pharmaceuticals, and some other
22 products that are excluded during the three

1 years.

2 So, I think the anticipation is
3 there that the assessment process will
4 continue, even once we get into the, quote
5 "operational" phase.

6 MR. GAYLORD: Mr. McVicar?

7 MR. McVICAR: Thank you. My name is
8 William McVicar. I do a publication on
9 recalls, regulations, and so forth.

10 I'm particularly concerned about
11 Freedom of Information, not only for my own
12 purposes, but also many government agencies
13 routinely release information such as consent
14 decrees, court decisions, such as from the
15 Justice Department. Even FDA releases
16 recalls, talk papers.

17 Now, my question is, not even
18 getting to Freedom of Information, which is
19 going to be very difficult, but these routine
20 things which the public has come to expect.
21 Are we going to move in the direction of
22 Europe, where these things are not discussed,

1 not released?

2 Or are they going to have to move
3 in the direction where some things adverse
4 are routinely released?

5 MS. HENRY: I'll speak directly on
6 the alert system itself. That was one of the
7 concerns in developing the working system and
8 the fact that, in the US, we're very
9 concerned with alerting our public of
10 potential dangers to health.

11 For the recall information that
12 will be released, it's the same information
13 that's seen in the FDA enforcement report.
14 It includes things such as the firm's name,
15 the reason for the recall, the consignee,
16 whether or not we've received contact back
17 from the consignee. Any follow up
18 mechanisms, and corrective action.

19 But as far as the alert system is
20 concerned, we are working jointly to make
21 sure that all information will still remain
22 available to the US consumers.

1 MR. McVICAR: Is that all
2 information concerned with foreign firms?

3 MS. HENRY: That will be the
4 exchange of all information related to recall
5 that the FDA is made aware of, the
6 classifications being Class One and Class
7 Two.

8 MR. McVICAR: That FDA is made
9 aware of.

10 MS. HENRY: Right. FDA expects to
11 be made aware of, in a timely manner, Class
12 One and Class Two recall notifications.
13 Class Three notification actions are not as
14 severe. They do not cause an injury to
15 health. They don't cause potential death.

16 So that information will be
17 received, but it won't be received in a
18 timely manner, as what we would receive with
19 Recall Classification One and Two.

20 MR. McVICAR: I want to commend
21 FDA. This is a very difficult assignment.
22 Lots of luck.

1 MR. GAYLORD: Joseph?

2 MR. FAMULARE: I just

3 wanted to add to your overall concerns, in
4 terms of FDA releasability of information.

5 We've already stated when we published our
6 rule that we intend to treat EIR's that we
7 receive, and normally endorse as we would our
8 own, in terms of Freedom of Information.

9 We're looking with that view
10 overall on all documents that FDA maintains,
11 that are obtained, to the degree our laws
12 allow releasability now, in general, we will
13 continue to handle those documents in the
14 same manner. In terms of, if we use them to
15 make a regulatory decision, then the public
16 is entitled to them as if FDA generated the
17 documents on their own.

18 MR. GAYLORD: Any other panelists like
19 to address that? Linda?

20 MS. HORTON: About inspection
21 reports. There also is a sensitive issue of
22 FDA's assessment of a foreign country's
23 regulatory system. At the point where FDA

1 makes a finding of equivalence, there will be
2 made public a summary of the basis, as we
3 promised in our rule making.

4 During the preliminary stages,
5 however, I think people can understand
6 there's a great deal of sensitivity about
7 looking at other country's systems.
8 Particularly when there still is some work to
9 be done. So there is -- there is that issue
10 that we're working on with the Europeans,
11 because it would inhibit candor and in the
12 deliberative process if there were premature
13 disclosure of information of that nature.

14 But we're committed to a
15 transparent process, and the implementation
16 of the MRA.

17 MR. GAYLORD: Merton?

18 MR. SMITH: Merton Smith. I'd like
19 also to add that the issue of transparency,
20 as I said in my remarks, we found our
21 transparency at FDA to be valuable in
22 protecting the public health. The feedback

1 that we get from interested parties is
2 critical in that.

3 As part of the equivalence
4 assessment of each member state, we've stated
5 that the criteria for doing that assessment
6 will include the transparency of the member
7 state system. So we will be assessing the
8 equivalence of their transparency within the
9 member states. So we'll have to -- obviously
10 there's no way to avoid these issues at all,
11 not that we want to.

12 MR. GAYLORD: Mr. Frey, before we
13 take your next question, I'd like to read one
14 from the index cards. This is from Mary
15 Bottari of Public Citizen.

16 "Will the FDA notice any
17 equivalency decision as a proposed rule and
18 allow public comment on a country by country
19 basis"?

20 MR. FAMULARE: If I could take on
21 that question. Our intention is to put the
22 notification of equivalency in the Federal

1 Register, but not as a proposed rule.
2 Realize that the docket is open at all time,
3 the docket number that has been mentioned
4 already, for us to obtain any comments from
5 the general public, industry at large, et
6 cetera. Any interested parties, of any
7 information they may have bearing on the
8 equivalency of any particular member state,
9 or the overall process.

10 So that process is open for public
11 input. As Linda Horton said, at the end of
12 the process where we find an authority
13 equivalent, we intend to make our record open
14 as to what the basis was for finding that
15 equivalence.

16 MR. GAYLORD: Linda?

17 MS. HORTON: If I might add,
18 nothing in this MRA changed any FDA
19 requirement. Furthermore, we were adamant
20 about our need to go through notice and
21 comment rule making on the MRA itself, it
22 probably was not strictly required. But we

1 felt that this was such a significant public
2 policy that to be on the safe side, we should
3 do rule making on the MRA itself. There is
4 not a need to go through an individual
5 country by country rule making for each
6 individual European country, as we continue
7 the implementation of the MRA.

8 MR. GAYLORD: Mr. Frey, please?

9 MR. FREY: Thank you. Ed Frey,
10 PDA. Just a quick question for Sylvia Henry.
11 I may be jumping ahead too far, but what
12 effect does the information exchanged in the
13 alert system have on the status of NDA and
14 BLA approvals and supplements? Specifically,
15 in order to interrupt or suspend the
16 approvability of supplements and applications
17 pending before FDA, how much information do
18 you have to have from abroad?

19 MS. HENRY: Well, with the alert
20 system itself, and with the mechanisms for
21 the information we expect to exchange, it
22 could impact. Because if we find out, in

1 particular, usually with manufacturing
2 facilities, if there's a problem in one
3 particular area, there may in fact be
4 problems in another.

5 That information could alert other
6 individuals who are responsible for
7 conducting the review of BLA's that problems
8 could exist. It may not delay the process.
9 But it would give the Agency more information
10 to go on.

11 MR. FAMULARE: If I might, this is
12 Joe Famulare. If I might add, one of the
13 things that we're realizing is that we
14 publish all our recall information already.
15 I mean so, it's no, from the European side,
16 it's nothing new, other than maybe some
17 earlier notifications, than when it actually
18 goes into the enforcement report.

19 There are already some existing
20 systems for us to find out from Europe when
21 recalls are published, and so forth. They're
22 not organized for the whole European Union,

1 and organized.

2 So, one of the things that we
3 realized in putting together, particularly
4 this aspect of the alert system, that a lot
5 of this information is already known, but
6 will now be organized, you know, in a more
7 coherent fashion over the whole European
8 Union.

9 So hopefully even today, if such a
10 recall would exist, and it would have an
11 effect on a licensing application, and so
12 forth, that we would already be aware of that
13 information, through some formal and informal
14 means that already exist.

15 MS. HENRY: I just wanted to add
16 one point. Sylvia Henry. The structure of
17 the alert system itself is to make sure the
18 information, as Joseph mentioned, the
19 information that we have in the US is the
20 same information that our EU member states
21 counterparts have.

22 So when -- and when we are alerted

1 of a Recall Classification One, the EU has
2 that same information. So, it's not a
3 delayed process; everything is published.

4 MR. GAYLORD: We now have a legal
5 question, it is as follows, but there is not
6 a name or organizational affiliation.

7 It says, "Under what legal
8 authority can the FDA make the Joint Sectoral
9 Committee closed to the public"?

10 MR. FAMULARE: Closed?

11 MS. HORTON: Closed to the public.

12 MR. GAYLORD: Linda?

13 MS. HORTON: The Joint Sectoral
14 Committee is a traditional bi-lateral
15 government to government meeting. It is not
16 in any way subject to one of the openness
17 provisions of the statute. We have other
18 ways of assuring public transparency. We're
19 very committed to public transparency.
20 That's why we're having this meeting.

21 But the Joint Sectoral Committee
22 itself is a bilateral government to

1 government meeting.

2 MR. GAYLORD: Any other panelists
3 like to address that? Raymond?

4 MR. MARS: I'm not sure where the
5 question was directed. But it was, the
6 meeting as an example we had here in May, I
7 think, you know, we view that as a
8 deliberative process meeting. So, you know,
9 again we're trying to work to get things
10 accomplished.

11 I think at that point, we probably
12 have not invited the public, and I don't
13 imagine we will in the future. We do make
14 the outcomes of those meetings public.
15 That's what happened with the press
16 statement -- so there's an effort made to
17 advise the public of what happens during
18 those meetings. It is posted on the Web
19 site, too. So it's available on the
20 Internet.

21 MR. GAYLORD: All right. Would the
22 individual that authored this particular

1 question, are they here? Would they like to
2 identify themselves? Your name, please? Can
3 you use the microphone, please?

4 MS. RODRIGUEZ: Yeah. My name is
5 Rina Rodriguez. I work for Community
6 Nutrition Institute. Just a quick comment, I
7 guess. From what I'm hearing, it sounds like
8 groups like -- and others really aren't going
9 to know until the decisions have been made.
10 It sounds like everything's closed, and then
11 we'll find out afterwards.

12 I have a problem with that. Does
13 anyone have a comment about that? We'd like
14 to know. The decisions, you know, which
15 countries are being reviewed? Not after the
16 fact, as kind of -- have decided, but a
17 little earlier in the process.

18 MR. GAYLORD: Joseph?

19 MR. FAMULARE: Just to bring up
20 your concern there. It's important to
21 remember that in assessing the equivalence of
22 a particular authority, it is a deliberative

1 process. There will be a lot of very frank,
2 back and forth discussion as to certain laws,
3 regulations, the way inspections are
4 conducted, and so forth, that will be done,
5 but really not finalized at that time.

6 Things will happen to change, the
7 way we think about something, when more
8 information comes forward, and so forth. So,
9 it wouldn't be fair, and it wouldn't chill.
10 It would maybe chill the effect of our doing
11 a very frank and detailed evaluation.

12 Just like, if I could draw a
13 parallel, when we inspect a firm, we're not
14 giving the public a blow by blow of every
15 issue that comes up during an inspection. We
16 wait until the end of the inspection, when
17 things have been settled and then, under FOI,
18 the report can be revealed. Then, there's
19 been proper opportunity on both sides to ask
20 and answer questions.

21 This is just an example of a
22 parallel as to how we do an equivalent

1 assessment of a particular member state
2 authority. We will come in, or the European
3 Union will come here, and we'll ask very
4 direct, frank questions. Look very intently
5 at things. Certain conclusions may be
6 derived very early on, which may not be
7 accurate, once there's been an opportunity to
8 answer them.

9 That's why our Freedom of
10 Information laws allow for such discretion in
11 releasing such information. Wait until all
12 parties have been heard, for things to be
13 released at the end of the process.

14 But we have endeavored and
15 committed to make things as open and publicly
16 transparent as possible, as we said in the
17 rule making process, to publishing the final
18 rule, in terms of having these meetings on an
19 annual basis. In terms of posting what we
20 can post on a Web site and having that open
21 docket to receive information on anything
22 that could affect our process.

1 MR. GAYLORD: Any other panelists
2 like to address that? Our next question is
3 from Mr. Rex Rhein, of Scrip World
4 Pharmaceutical News. It's a two part
5 question.

6 It says, "Only five countries
7 showed up at the May meeting. Are these the
8 ones FDA will look to first in the
9 equivalence determination"? The second part
10 is, "Who were the observers"? Raymond?
11 Brian?

12 MR. HASSELBALCH: They, of course,
13 selected who would attend. I don't know how
14 they did it. But it -- certainly, some of
15 the big ones there. The obvious ones, like
16 UK, Germany, France. Italy I don't believe
17 was represented there, of course, a very big
18 manufacturer of pharmaceutical products, as
19 well as active ingredients, was all there.

20 But there's no relationship between
21 those who attended on behalf of the EU, and
22 which member states will choose earlier than

1 later in the process.

2 MR. GAYLORD: Are there any
3 additional questions that the audience has,
4 that they would like to make at this time?
5 Yes, please? Mr. Holmes?

6 MR. HOLMES: In the document that
7 was published after the May meeting, there
8 was a section in heavy type in the middle of
9 the document which I was led to believe
10 indicated that there were doubts being
11 expressed during the meeting. That the
12 commitment of the FDA to complete the review
13 of all member states during the three year
14 transition period.

15 I've been hearing this morning that
16 there now does appear to be a commitment to
17 complete the process within the three year
18 period. I'd like to know if that could be
19 confirmed. I'd also like to know if you have
20 any start date for the joint inspections
21 which will be undertaken, or the joint
22 visits. Because we expected those to kick

1 off in September '99. They still haven't
2 seen anything happen.

3 MR. FAMULARE: If I could speak to
4 the discussion that was held at the May
5 meeting. We expressed our plan, and how it
6 would be laid out. We made it very clear, as
7 we have had, even before that meeting, in
8 other forms, that we will conduct the
9 equivalency assessments in accordance with
10 our available resources.

11 Does that mean that every authority
12 will be brought to a finding of equivalence?
13 It may or may not and we wanted to make that
14 very clear to our European counterparts.
15 They of course, expressed, as we've said here
16 earlier, that well they felt either all
17 authorities we found equivalent, or we extend
18 the transition period.

19 We reiterated how we did not feel
20 that the Agreement stated that. How there's
21 an Article which addresses resource, you
22 know, limitations, and how we'll make our

1 best faith effort. Are we committed to do
2 our best faith effort to look at each member
3 state over the next three years? Yes. We
4 will commit to do our best faith effort.

5 That depends upon, again, the
6 availability of resources within FDA,
7 commitments from all centers and the field
8 organizations which are represented here by
9 high management. We hope that they'll be
10 able to put forward those resources. But
11 again, we have to realize the realities of
12 FDA's main public health mission, to do its
13 work, its inspections.

14 We have to realize that there are
15 factors that weigh in in doing that process,
16 as resource considerations. In terms of, for
17 example, receiving documentation from all of
18 the member states, as Sylvia broached on in
19 her discussion, these things are now being
20 received in the languages of the member
21 states, and calls upon us to look at more
22 resources to obtain translations. May cause

1 more delay in the process.

2 So that's a very important
3 encumbrance that we're trying to overcome
4 right now. In reviewing the paper
5 submissions, as Brian mentioned, we're in the
6 first phase of the process.

7 If you're looking for when the
8 actual on site audits will begin, we actually
9 didn't anticipate the on site audits to start
10 until those paper processes were done. That
11 will not be until we get into the phase which
12 will obviously bring us into the next year.

13 Again, it depends on the flow of
14 the -- on our ability to get the paper review
15 completed.

16 MR. HASSELBALCH: Brian
17 Hasselbalch. To clarify, the September '99
18 date that you're referring to as to the start
19 date of the inspection audits, is actually a
20 planning date for us to begin the process of
21 preparing for those inspection audits. We
22 never intended they would start September

1 of '99.

2 Nonetheless, we are delayed a
3 little bit in our projection, at least, in
4 meeting our projection as to when we would
5 start. I've learned enough now to know not
6 to give you a month. But perhaps sometime
7 mid-year 2000 we might be in a position to
8 begin inspection audits. Which means by then
9 we'll have to have reviewed at least one
10 member state's documentation. We'll have had
11 to have completed at least one member state's
12 system audit.

13 MR. FAMULARE: With the idea, Joe
14 Famulare again, with the idea that we had
15 sufficient basis to do the on site audit in
16 the paper review that we did. We found
17 sufficient and adequate laws, directives, and
18 so forth.

19 Because obviously if on the paper
20 review we hadn't even broached that, that
21 threshold, we would want to correspond and
22 discuss those problems before we invested the

1 resource into the on site audit.

2 MR. GAYLORD: Are there any
3 additional questions that anyone would like
4 to ask at this time? Certainly we've had a
5 nice cross section of questions, and we
6 appreciate that very much.

7 ADJOURNMENT

8 When we convened the panels, there
9 were two representatives that I neglected to
10 mention, that I'd like to mention now. One
11 is a member of the Project Management Team,
12 and that's Ms. Judith Gushee. She's from the
13 Center for Veterinary Medicine. Also,
14 Dr. Robert Livingston is also from that
15 Center, as well.

16 So, each of those Centers, the
17 Center for Drugs, Biologics, as well as
18 Veterinary Medicine, working with the Office
19 of Regulatory Affairs, and the General
20 Counsel's Office, working in concert, in
21 terms of implementation at this particular
22 time.

1 In addition, both Walter Batts and
2 Linda Horton were involved in negotiation
3 processes of the MRA, Walter on the
4 pharmaceutical GMP side, and Linda on the
5 medical devices side. So there's been a
6 continuum in this Agreement that will
7 continue as time goes on, to bear fruit.

8 So, this morning we've looked at a
9 number of the people that have been involved
10 in helping to negotiate and implement this
11 Mutual Recognition Agreement for
12 Pharmaceutical Good Manufacturing Practices.

13 As the Agency and the EU work
14 together to fulfill the Agreement in its
15 entirety, there are three keys that the
16 Agency would like you to remember. First, a
17 thorough assessment is going to take place.
18 Secondly, the process will take time, as it
19 is resource intensive. Third, a
20 determination about equivalence for each of
21 the member states will occur.

22 I want to thank each one of you for

1 being here, and joining us today, and
2 participating in today's meeting. As Sharon
3 Holston mentioned, this is a third in a
4 series of public meetings that will continue
5 to be held, so that our constituents are
6 informed about this process.

7 But it's more than about informing.
8 It's also, as Sharon mentioned, a dialogue
9 that we engage in. So, it's necessary to
10 have feedback from all of our constituents:
11 industry, consumers, and so forth. Health
12 advocates, whatever the communities that FDA
13 serves, we need your input as we proceed.

14 So therefore, as was mentioned a
15 couple times this morning, we have the open
16 docket, which is 98S- 1064. We welcome and
17 ask that you would submit your comments that
18 you have. I noticed when I talked to some
19 people on the phone, they stated that they
20 would submit detailed comments for the
21 record. That is much appreciated.

22 If you need the address to send

1 that to, please see me, or any of the other
2 Agency officials that are present today. I'd
3 like to thank each of the presenters and the
4 panelists for coming here today. They wanted
5 to share their expertise with you firsthand
6 and the offices that worked with the Office
7 of International Programs in putting the
8 meeting on.

9 The Office of Consumer Affairs,
10 we've worked with Chandra Smith Collier
11 there. We've worked with the Office of
12 Legislative Affairs, Michael Eck was there.
13 Ken Nolan, in the Office of Public Affairs,
14 who was very helpful in contacting industry
15 groups. Barbara Steller in the Center for
16 Devices and Radiological Health. Each of
17 them played a role so that we'd have as many
18 people here as possible.

19 Last but not least, in helping to
20 put the meeting, in their thousand and one
21 details have to be attended to, Erik
22 Henrikson worked tirelessly to help this

1 meeting be possible. So he's in the back,
2 Erik. That is appreciated.

3 Finally, the hard work of the
4 Project Management Team, and Agency
5 officials, as well as their counterparts in
6 the EU is much evident I think from the
7 information that's been presented. As they
8 continue to work together, they will strive
9 to bring the promise of this Agreement to
10 fruition. There are some uncertainties. But
11 the commitment on both sides is to implement
12 this Agreement as quickly and as
13 expeditiously as possible for the good of the
14 public health.

15 So, thank you for attending. For
16 the hand-outs that are here, please help
17 yourselves to them. If there's any follow-up
18 information, please see us, that we can help
19 you with. Thank you.

20 (Whereupon, at 12:00 p. m. , the
21 PROCEEDINGS were adjourned.)

22 * * * * *