

MEMORANDUM

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

Date: July 16, 2004

To: Dockets Management Branch (HFA-305)
Food and Drug Administration

From: Ted Sherwood
Program Analyst
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Subject: Docket # 2003N-0341

The attached comments and minutes of meeting should be included in Docket # 2003-0341 (Requirements for Submission of In Vivo Bioequivalence Data).

Attachments (2): GPHA COMMENTS AND QUESTIONS ON THE PROPOSED
RULE ON THE SUBMISSION OF ALL BIOSTUDIES IN
ANDAs

MINUTES OF MEETING OPS/GPHA MEETING ON GPHA'S
COMMENTS AND QUESTIONS ON THE PROPOSED RULE
FOR THE SUBMISSION OF ALL BIOSTUDIES IN ANDAS
HELD JUNE 11, 2004

2003N-0341

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GPhA COMMENTS AND QUESTIONS ON THE PROPOSED

RULE ON THE SUBMISSION OF ALL BIOSTUDIES IN ANDAS

GPhA fully supports the principles behind FDA's request for the submission of all bioequivalence studies conducted in support of an ANDA filing, including failed biostudies. Certainly, the careful evaluation of all bioequivalence studies undertaken, specifically those on the formulation which an applicant intends to market in the United States, may be useful to the Agency's determination of the equivalence of that product to the reference listed drug. GPhA endorses the concept of this regulation.

Nevertheless, there are a number of issues related to how the regulation will be implemented that require clarification.

1. BIOSTUDIES ON SIMILAR FORMULATIONS

One issue relates to the request for biostudy data from formulations similar, but not identical to the submitted formulation. The proposed regulation states (section III.) that "Even in cases where information from additional BE studies is not critical to the Agency's bioequivalence determination for a specific product, the data will provide valuable scientific information that increases our knowledge and understanding of bioequivalence and generic drug development issues." Elsewhere, (section IV. D.) the proposed regulation states that the request for bioequivalence studies includes data for "formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the Agency's determination of bioequivalence" (section IV D). These statements appear to contradict one another. Can studies that are not critical to the Agency's determination of bioequivalence be relevant to the same determination? We believe all studies on the "to be marketed formulation" should be submitted to the Agency. If other formulations are developed or other manufacturing processes are used, and studies are conducted on those products, what relevance do they have toward a determination of the bioequivalence of the "to be marketed formulation"?

Understanding that one goal of the regulation is to increase the Agency's knowledge and understanding of bioequivalence, GPhA is willing and interested to participate in any forum or setting to accomplish that. However, we do not believe that this should be achieved as a part of the regulatory requirements for

generic applications. Rather, the education should be undertaken through a partnership between the Agency, industry, and academia. We would be pleased to host symposia, meetings, and conferences devoted to helping Agency scientists more fully understand the nuances associated with generic drug development and the factors that affect bioavailability.

2. ADDITIONAL BURDEN ON LIMITED FDA RESOURCES

The Division of Bioequivalence has a considerable backlog (226 days was the last reported median estimate from G. Buehler in his presentation at the 2004 GPhA Annual Meeting). Furthermore, despite its best efforts to increase DBE staffing, recent losses from DBE have left staffing levels roughly unchanged over the last approximately 3-1/2 years (7 people added and 6 people lost for a net gain of 1, also from G. Buehler's presentation). Until significant headway can be made in staffing at DBE, it will be especially difficult for DBE to review studies that are not relevant to the "to be marketed" formulation as well as the additional burden of reviewing 'relevant' biostudies based on the proposed rule.

A number of the public comments already received have included concerns about the adverse effect that the new rule will have on the workload at DBE. We share those concerns, and in particular, are concerned about the effect that the new rule will have on approval timelines both for those submissions involving such additional BE studies, as well as for those submissions not involving such additional BE studies.

Furthermore, we have reason to believe that FDA may have underestimated the additional workload resulting from the proposed rule. First, over 300 ANDA submissions were received in the first half of fiscal 2004. This would extrapolate to over 600 for the full year, which is significantly more than the 346 ANDAs per year estimate used in the economic impact calculation in the Federal Register notice. Even 600 may be an underestimate for the year, because many CROs are reporting much higher levels of bookings and activity than for last year, portending an even higher ANDA count for the second half of the fiscal year than for the first half. Second, there are no clear and definitive ways to calculate the percentage of ANDAs which will, under the new rule, need to include the additional BE study reports. However, CROs report that there is a large number of failed BE studies on file at CROs which are often associated with formulations or manufacturing processes that are not proposed in the ANDA. This information suggests that a 10% increase in the number of bio studies submitted in ANDAs may be an underestimate. Finally, we believe that, given the significant ambiguities of the rule as currently worded, many firms will err on the conservative side and submit reports on many biostudies that FDA may not intend to be submitted, so as to preclude being faulted for withholding required reports.

3. EVALUATION OF DATA FROM MULTIPLE STUDIES

The proposed rule does not address how conflicting results from two or more biostudies will be assessed, assuming that each study's conduct is deemed to be acceptable and equally valid. For example, will some meta-analysis on pooled data from all valid studies be done? It is important for generic firms to have some yardstick by which to determine, at the time of submission, whether the additional studies will jeopardize the approvability of the submission.

4. SUPAC QUESTIONS AND ISSUES

There are circumstances under which it may be impossible to determine whether a particular older formulation on which a biostudy had been conducted falls within the scope of a SUPAC level 2 change from the approved/submitted formulation. For example: (1) if the older formulation has only single point dissolution data, precluding an f2 comparison; or (2) if multiple dissolution conditions were used, some of which yield f2 factors greater than 50 and some less than 50. In such cases, how is an applicant to decide whether or not a biostudy on an older formulation needs to be submitted?

SUPAC requires biostudies to support formulation changes outside level 1 for narrow therapeutic index (NTI) drugs. Does this mean that biostudies on any formulations differing by more than SUPAC level 1 for NTI drugs will not need to be submitted under the new rule?

Not all dosage forms and routes of administration are covered by SUPAC. For those that are not, e.g., transdermal patches, inhaled products, etc., how will the "sameness" of formulations be assessed, for purposes of determining whether biostudies on prior formulations need to be submitted?

For a modified release oral product, does a change in manufacturing site alone (which automatically qualifies as a SUPAC level 3 change) render the products at the original and new sites sufficiently dissimilar so as to be outside the purview of this rule, even though the formulations and manufacturing processes could be otherwise identical?

If a BE study is required to support a post-approval formulation change, then the two formulations necessarily differ by more than SUPAC level 2. The new rule requires submission of biostudies on "the same formulation for which the supplement is being submitted", so the formulation originally approved will necessarily differ from the new formulation by more than SUPAC level 2, and therefore, previously unsubmitted biostudies on the original formulation need not be submitted. Please confirm that this is the Agency's intended interpretation. If it is not, then what will the requirement then be – to submit all biostudies on both the originally approved formulation and the new formulation?

5. STUDIES NOT GERMANE TO BIOEQUIVALENCE ASSESSMENT

The proposed rule describes a requirement to submit bioequivalence studies. Is there any need to submit prior studies that are not directly relevant to the assessment of BE by the current criteria? Suppose the current BE requirement for a particular product specifies a pharmacokinetic study on the parent drug in plasma, would the following types of studies have to be submitted: a pharmacokinetic study on the metabolite only, a pharmacokinetic study in urine, a pharmacodynamic study, a clinical endpoint BE study or other clinical study, a sensitization or irritation study for transdermal patches, etc.?

If a pharmacokinetic study is conducted using something other than the particular reference listed drug that is the target of the ANDA submission, is such a study subject to the new rule and required to be submitted? Examples include studies conducted against a foreign reference product, another generic product, an oral solution/suspension, a different Reference Listed Drug (RLD) with the same ingredients/strength, etc. Clearly, biostudies conducted against non-RLD strengths of the target reference drug would be relevant and submittable.

6. CONTENT AND FORMAT OF BIOSTUDY SUMMARY REPORTS

The format and content of the summary reports needs to be defined. Particular consideration needs to be paid to the following situations: (1) old biostudies analyzed on the original (not log-transformed) scale, and for which significant statistical analysis would need to be done to present the data per current methods (ANOVA on log-transformed data) and criteria (confidence intervals); (2) biostudies conducted by third parties for which the applicant has no right of reference and for which any sort of traditional summary report might be impossible.

7. BIOSTUDIES CONDUCTED OTHER THAN BY OR FOR THE APPLICANT

The proposed rule requires submission of all biostudies “conducted by or otherwise obtained by the applicant”. How much burden, if any, rests on the applicant to search out such information (e.g., conduct literature searches)? How can an applicant possibly provide FDA with a report on a study conducted by a third party (e.g., competitor), even if the applicant were aware of the existence of such a study. We suggest that the wording of the rule be changed to read “conducted by or for the applicant” to eliminate any such onerous and, perhaps, unintended burdens on generic firms.

Many ANDAs have undergone a change in ownership, so that the current ANDA holder is not the same firm that sponsored the biostudies. In such cases, if the new ANDA holder files a supplement that would trigger submission of all prior biostudies per the new rule, it may be difficult for the new ANDA holder to obtain information on pilot biostudies or dissolution profile testing conducted by the previous owner. How much burden then rests on the new ANDA holder to try to collect such old information from the previous owner?

8. WHAT EVENT DETERMINES WHEN A BIOSTUDY IS CONDUCTED?

For purposes of deciding whether a biostudy needs to be submitted, what event (e.g., administration of first dose, issuance of final report, or some other event) determines the date upon which the study was deemed to have been conducted?

9. NON-CLINICAL AND *IN VITRO* STUDIES

While not commonly done, it is possible that there may be some pilot pharmacokinetic studies done in animals. Would such studies potentially need to be submitted per the new rule?

Although the title of the Federal Register notice suggests that the new rule would apply only to *in vivo* studies, the proposed change in CFR language does not specify *in vivo* studies. Because 21 CFR currently does describe “*in vitro* bioequivalence studies”, would such studies also need to be submitted? *In vitro* studies that could potentially fall in this category could be dissolution profiles upon which biowaivers are based, and *in vitro* tests for nasal sprays as described in the draft guidance on nasal sprays. In this sense, does the filing of a new “*in vitro* bioequivalence study” then trigger the requirement to file all such prior “*in vitro* BE studies” which could potentially involve huge amounts of experimental dissolution data?

10. PUBLIC DISCLOSURE OF SUBMITTED STUDIES VIA FOI?

One of the comments received from Hyman, Phelps, & McNamara raises the question and associated concerns about whether the reports of the additional studies that will be submitted under the new rule will be disclosable via FOI, and if so, how might such FOIable information be used in practice. We share the same question and concerns.

11. SAMPLE RETENTION

Pilot biostudies are not currently subject to any test and reference product sample retention requirements as long as they are not relied upon for approval. If a report from such a pilot biostudy must now be submitted per the new rule on submission of all biostudies, will the pilot biostudy now be subject to sample retention requirements? If the new rule were, in effect to impose sample retention requirements on pilot biostudies, this would put an undue burden on the industry.

12. IMPLEMENTATION TIMELINES

We believe that it is critical for the Agency to issue at least a draft version of the promised guidance on the submission of additional bioequivalence studies no later than the time that the final rule is issued, so that firms know how the rule is to be implemented. Failure to do so would impose an significant and unnecessary burden on both the industry and the Agency for at least two reasons. First, publication of such an ambiguous final rule without a corresponding guidance would result in numerous inquiries from generic firms to the Agency, both by phone and in writing, to seek clarification of the rule. Second, in the absence of clear guidance from the Agency, many generic firms would likely submit every conceivable study that they had, just to be sure that they could not possibly be criticized by the Agency for not submitting a required study. This would result in the submission of many studies that the Agency never intended to be submitted. Both of these significant and unnecessary burdens could be prevented if the Agency issues its promised guidance in a timely fashion.

MINUTES OF MEETING
OPS/GPHA MEETING ON GPHA'S COMMENTS AND QUESTIONS ON THE
PROPOSED RULE FOR THE SUBMISSION OF ALL BIOSTUDIES IN
ANDAS HELD JUNE 11, 2004

OPS Attendees: Dave Read, Gary Buehler, Dale Conner, Lizzie Sanchez, Helen Winkle,
Ted Sherwood

GPhA Representatives: Siobhan Barr (MDSPS), Greg DeRosa (TEVA),
Gordon Johnston (GPhA), Russ Rackley (Mylan), Charles DiLiberti (Barr)

Preliminary remarks from the Office of Pharmaceutical Science (OPS):

OPS explained that the notes from this meeting and background document will be placed in the Food and Drug Administration (FDA) Docket.

This was acceptable to the Generic Pharmaceutical Association (GPhA).

Background from GPhA:

GPhA fully supports the principles behind FDA's request for the submission of all bioequivalence studies conducted in support of an ANDA filing, including failed biostudies. Certainly, the careful evaluation of all bioequivalence studies, specifically those conducted on the formulation that an applicant intends to market in the United States, may be useful to the Agency's determination of the equivalence of that product to the reference listed drug. GPhA endorses the concept of this regulation.

Nevertheless, there are a number of issues related to how the regulation will be implemented that require clarification.

Questions from GPhA:

1. BIOSTUDIES ON SIMILAR FORMULATIONS

One issue relates to the request for biostudy data from formulations similar, but not identical to the submitted formulation. The proposed regulation states (section III.) that "Even in cases where information from additional BE studies is not critical to the Agency's bioequivalence determination for a specific product, the data will provide valuable scientific information that increases our knowledge and understanding of bioequivalence and generic drug development issues." Elsewhere, (section IV. D.) the proposed regulation states that the request for bioequivalence studies includes data for "formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are

similar enough to be relevant to the Agency's determination of bioequivalence" (section IV D). These statements appear to contradict one another. Can studies that are not critical to the Agency's determination of bioequivalence be relevant to the same determination? We believe all studies on the "to be marketed formulation" should be submitted to the Agency. If other formulations are developed or other manufacturing processes are used, and studies are conducted on those products, what relevance do they have toward a determination of the bioequivalence of the "to be marketed formulation"?

Understanding that one goal of the regulation is to increase the Agency's knowledge and understanding of bioequivalence, GPhA is willing and interested to participate in any forum or setting to accomplish that. However, we do not believe that this should be achieved as a part of the regulatory requirements for generic applications. Rather, the education should be undertaken through a partnership between the Agency, industry, and academia. We would be pleased to host symposia, meetings, and conferences devoted to helping Agency scientists more fully understand the nuances associated with generic drug development and the factors that affect bioavailability.

Discussion Points:

- *The template that the Division of Bioequivalence (DOB), Office of Generic Drugs (OGD), OPS, uses to conduct its assessment of bioequivalence (BE) will be made publicly available. This template will illustrate what the DOB reviewers are looking at from the studies.*
- *It is important for the applicant to provide an explanation about why the results of the study are not relevant (i.e., the technical flaw, underpowered) along with a summary of the failed study.*
- *DOB will use the data to obtain a better understanding of the products and related pivotal studies. DOB will also benefit from a better general understanding of the drug development process.*
- *All studies are currently required in the review of new drug applications (NDAs).*
- *DOB will try to ask only for relevant data.*
- *OPS will consider holding a small workshop in support of the rule.*
- *OPS will clarify what failed studies it should receive, determine and establish a threshold for submission of studies, and define "similar."*

2. ADDITIONAL BURDEN ON LIMITED FDA RESOURCES

The Division of Bioequivalence has a considerable backlog (226 days was the last reported median estimate from G. Buehler in his presentation at the 2004 GPhA Annual Meeting). Furthermore, despite its best efforts to increase DBE staffing, recent losses from DBE have left staffing levels roughly unchanged over the last approximately 3-1/2 years (7 people added and 6 people lost for a net gain of 1, also from G. Buehler's presentation). Until significant headway can be made in staffing at DBE, it will be especially difficult for DBE to review studies that are not relevant to the "to be marketed" formulation as well as the additional burden of reviewing 'relevant' biostudies based on the proposed rule.

A number of the public comments already received have included concerns about the adverse effect that the new rule will have on the workload at DBE. We share those concerns, and in particular, are concerned about the effect that the new rule will have on approval timelines both for those submissions involving such additional BE studies, as well as for those submissions not involving such additional BE studies.

Furthermore, we have reason to believe that FDA may have underestimated the additional workload resulting from the proposed rule. First, over 300 ANDA submissions were received in the first half of fiscal 2004. This would extrapolate to over 600 for the full year, which is significantly more than the 346 ANDAs per year estimate used in the economic impact calculation in the Federal Register notice. Even 600 may be an underestimate for the year, because many CROs are reporting much higher levels of bookings and activity than for last year, portending an even higher ANDA count for the second half of the fiscal year than for the first half. Second, there are no clear and definitive ways to calculate the percentage of ANDAs which will, under the new rule, need to include the additional BE study reports. However, CROs report that there is a large number of failed BE studies on file at CROs which are often associated with formulations or manufacturing processes that are not proposed in the ANDA. This information suggests that a 10% increase in the number of bio studies submitted in ANDAs may be an underestimate. Finally, we believe that, given the significant ambiguities of the rule as currently worded, many firms will err on the conservative side and submit reports on many biostudies that FDA may not intend to be submitted, so as to preclude being faulted for withholding required reports.

Discussion points:

- *DOB acknowledges that it is very busy with the current workload involving traditional studies and that the new rule may affect future workload.*
- *GPhA expressed concern over the "selection reporting target."*
- *DOB is working on the format/criteria for its review of these studies.*
- *A total reanalysis will not be needed nor will the DOB reviewer look at these studies with the same intensity as they do with pivotal studies.*
- *OPS is still discussing issues with the Division of Scientific Investigations (DSI) and Office of Regulatory Affairs (ORA), such as, retention samples, how "relevant" is defined, roles and responsibilities, and threshold criteria for when OGD will call in DSI to conduct an inspection.*
- *In certain situations, DSI may be able to explain why a study failed.*
- *OGD is appreciative of the quality and consistency of DSI and ORA inspections.*

3. EVALUATION OF DATA FROM MULTIPLE STUDIES

The proposed rule does not address how conflicting results from two or more biostudies will be assessed, assuming that each study's conduct is deemed to be acceptable and equally valid. For example, will some meta-analysis on pooled data from all valid studies be done? It is important for generic firms to have some yardstick by which to determine, at the time of submission, whether the additional studies will jeopardize the approvability of the submission.

Discussion Points:

- *The applicants need to provide a rationale on why the study failed. This information will be the beginning point of DOB's review.*
- *Pooling studies will not be covered by this rule or during this meeting.*
- *Industry needs to know if they have a successful product – there is more certainty built into the ANDA process than the NDA process.*
- *GPhA and DOB both estimate that 20% of the non-pilot studies are failed studies.*
- *DOB will only conduct a quick review of pilot studies.*
- *Because one of the most common failures is in the proposed formulation, new formulations are pursued.*

4. SUPAC QUESTIONS AND ISSUES

There are circumstances under which it may be impossible to determine whether a particular older formulation on which a biostudy had been conducted falls within the scope of a SUPAC level 2 change from the approved/submitted formulation. For example: (1) if the older formulation has only single point dissolution data, precluding an f2 comparison; or (2) if multiple dissolution conditions were used, some of which yield f2 factors greater than 50 and some less than 50. In such cases, how is an applicant to decide whether or not a biostudy on an older formulation needs to be submitted?

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Discussion Points:

- *DOB acknowledges that “sameness” needs to be clarified and that use of the Scale-up and Post-approval Changes (SUPAC) principles is confusing (i.e., index of differences).*
- *Development data leads to biostudy determinations and provides product knowledge.*
- *There may be cases where the applicant does not have the old product for a variety of reasons, including transfer of ownership. In these cases, DOB should be consulted first and the applicant should send in as much data as available. DOB will address the possible exclusion of older bio studies.*
- *Site transfers are not covered by SUPAC – a new study would be needed.*
- *DOB will consider how to address non-SUPAC products (i.e. transdermals).*
- *DOB recognizes that there may be cases where it is unclear to the firm if the failed study should be submitted. In these cases, DOB suggests that a study summary be submitted and DOB will ask for additional data, if needed.*
- *DOB will train staff not to review unnecessary data.*

5. STUDIES NOT GERMANE TO BIOEQUIVALENCE ASSESSMENT

The proposed rule describes a requirement to submit bioequivalence studies. Is there any need to submit prior studies that are not directly relevant to the assessment of BE by the current criteria?..Suppose the current BE requirement for a particular product specifies a pharmacokinetic study on the parent drug in plasma, would the following types of studies have to be submitted: a pharmacokinetic study on the metabolite only, a pharmacokinetic study in urine, a pharmacodynamic study, a clinical endpoint BE study or other clinical study, a sensitization or irritation study for transdermal patches, etc.?

If a pharmacokinetic study is conducted using something other than the particular reference listed drug that is the target of the ANDA submission, is such a study subject to the new rule and required to be submitted? Examples include studies conducted against a foreign reference product, another generic product, an oral solution/suspension, a different Reference Listed Drug (RLD) with the same ingredients/strength, etc. Clearly, biostudies conducted against non-RLD strengths of the target reference drug would be relevant and submittable.

Discussion points:

- *DOB cannot answer questions related to this issue as they will be significant to the rule and guidance document.*
- *DOB wants to see studies conducted in response to toxicological or excipient concerns.*
- *DOB wants to see summaries or references to studies conducted by others (i.e., competitors or academic institutions) when they are known to the applicant.*
- *DOB is considering requesting a short (one page) summary in cases where there is a study conducted with a foreign reference listed drug (RLD). Information such as drug/food interaction will be of interest to DOB. Also, there may be cases where the foreign RLD may be the same formulation as the U.S. RLD*

- *DOB is considering a tiered approach to the data requirements, such as comprehensive reports on true/real failed studies, and only summaries of less germane studies.*

6. CONTENT AND FORMAT OF BIOSTUDY SUMMARY REPORTS

The format and content of the summary reports needs to be defined. Particular consideration needs to be paid to the following situations: (1) old biostudies analyzed on the original (not log-transformed) scale, and for which significant statistical analysis would need to be done to present the data per current methods (ANOVA on log-transformed data) and criteria (confidence intervals); (2) biostudies conducted by third parties for which the applicant has no right of reference and for which any sort of traditional summary report might be impossible.

Discussion point:

- *DOB will clarify the criteria and format.*

7. BIOSTUDIES CONDUCTED OTHER THAN BY OR FOR THE APPLICANT

The proposed rule requires submission of all biostudies “conducted by or otherwise obtained by the applicant.” How much burden, if any, rests on the applicant to search out such information (e.g., conduct literature searches)? How can an applicant possibly provide FDA with a report on a study conducted by a third party (e.g., competitor), even if the applicant were aware of the existence of such a study. We suggest that the wording of the rule be changed to read “conducted by or for the applicant” to eliminate any such onerous and, perhaps, unintended burdens on generic firms.

Many ANDAs have undergone a change in ownership, so that the current ANDA holder is not the same firm that sponsored the biostudies. In such cases, if the new ANDA holder files a supplement that would trigger submission of all prior biostudies per the new rule, it may be difficult for the new ANDA holder to obtain information on pilot biostudies or dissolution profile testing conducted by the previous owner. How much burden then rests on the new ANDA holder to try to collect such old information from the previous owner?

Discussion points:

- *DOB should be informed of third party studies.*
- *DOB is considering whether this information could be submitted as part of the Annual Report as a literature citation.*

8. WHAT EVENT DETERMINES WHEN A BIOSTUDY IS CONDUCTED?

For purposes of deciding whether a biostudy needs to be submitted, what event (e.g., administration of first dose, issuance of final report, or some other event) determines the date upon which the study was deemed to have been conducted?

Discussion point:

- *DOB will clarify. Administration of the first dose may be the trigger for the date upon which the study was deemed to have been conducted.*

9. NON-CLINICAL AND *IN VITRO* STUDIES

While not commonly done, it is possible that there may be some pilot pharmacokinetic studies done in animals. Would such studies potentially need to be submitted per the new rule?

Although the title of the Federal Register notice suggests that the new rule would apply only to *in vivo* studies, the proposed change in CFR language does not specify *in vivo* studies. Because 21 CFR currently does describe “*in vitro* bioequivalence studies”, would such studies also need to be submitted? *In vitro* studies that could potentially fall in this category could be dissolution profiles upon which biowaivers are based, and *in vitro* tests for nasal sprays as described in the draft guidance on nasal sprays. In this sense, does the filing of a new “*in vitro* bioequivalence study” then trigger the requirement to file all such prior “*in vitro* BE studies” which could potentially involve huge amounts of experimental dissolution data?

Discussion point:

- *There is no reason to submit conventional in vitro studies. However, in vitro studies that are a substitute for an in vivo study should be submitted.*

10. PUBLIC DISCLOSURE OF SUBMITTED STUDIES VIA FOI?

One of the comments received from Hyman, Phelps, & McNamara raises the question and associated concerns about whether the reports of the additional studies that will be submitted under the new rule will be disclosable via FOI, and if so, how might such FOIable information be used in practice. We share the same question and concerns.

Discussion points:

- *These additional studies will be discussed during the review and used in approval determinations; therefore, they will be treated as similar communications/data from the applicants.*
- *DOB feels that receiving these studies will add public confidence that manufacturers are reporting all data, but DOB realizes that there will be more public awareness of failed studies.*

11. SAMPLE RETENTION

Pilot biostudies are not currently subject to any test and reference product sample retention requirements as long as they are not relied upon for approval. If a report from such a pilot

biostudy must now be submitted per the new rule on submission of all biostudies, will the pilot biostudy now be subject to sample retention requirements? If the new rule were, in effect to impose sample retention requirements on pilot biostudies, this would put an undue burden on the industry.

Discussion point:

- *DOB is discussing retention issues with DSI.*

12. IMPLEMENTATION TIMELINES

We believe that it is critical for the Agency to issue at least a draft version of the promised guidance on the submission of additional bioequivalence studies no later than the time that the final rule is issued, so that firms know how the rule is to be implemented. Failure to do so would impose an significant and unnecessary burden on both the industry and the Agency for at least two reasons. First, publication of such an ambiguous final rule without a corresponding guidance would result in numerous inquiries from generic firms to the Agency, both by phone and in writing, to seek clarification of the rule. Second, in the absence of clear guidance from the Agency, many generic firms would likely submit every conceivable study that they had, just to be sure that they could not possibly be criticized by the Agency for not submitting a required study. This would result in the submission of many studies that the Agency never intended to be submitted. Both of these significant and unnecessary burdens could be prevented if the Agency issues its promised guidance in a timely fashion.

Discussion point:

- *DOB is reviewing comments and will be taking the comments into consideration as the final rule is written and the guidance document prepared.*

Closing Comments:

- GPhA is committed to providing information that would assist in preparing the final rule and guidance document. DOB would like examples of any situations that may occur so they may be addressed in the guidance.
- The final rule may be placed on the agenda of the Fall 2004 Advisory Committee for Pharmaceutical Science (ACPS) meeting.
- Electronic data for old studies (i.e., SAS transport) will not routinely be requested from DOB.
- At this time, DOB does not feel that additional studies to set *in vitro* specifications will be required for submission.

Prepared by: Ted Sherwood June 15, 2004
Reviewed by: Gary Buehler June 17, 2004