



August 12, 2002

Docket Management Branch (HFA-305), Docket No. 02D-0258
Food and Drug Administration
5630 Fishers Lane, Room 1061 – HFA-305
Rockville, MD, USA, 20852

SUBJECT: Comments and suggestions regarding the BA/BE guidance posted July 12, 2002

Please find enclosed our comments and suggestions regarding the guidance for industry entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations".

We hope that these comments will be helpful to the FDA in the development of the final guidance. Please do not hesitate to contact us if you need any additional information.

Sincerely,

A handwritten signature in black ink that reads "Murray Ducharme". The signature is fluid and cursive, with a long horizontal stroke at the end.

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MDS Pharma Services
And, Professeur Associé
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MDS PS comments on the July 2002 BA/BE guidance

Guidance for Industry
Bioavailability and Fed Bioequivalence Studies
For Orally Administered Drug Products – General Considerations

GENERAL COMMENTS

Please find our comments in the sequence that they appear in the Guidance.

SPECIFIC COMMENTS

Comment #1

II. BACKGROUND

A. General

The Draft Guidance states:

- *3rd line “BA studies focus on determining the process by which a drug ... moves to the site of action”*

Comment:

BA studies do not focus on this. This would be evaluated possibly in a PK/PD study where the pharmacological response would be evaluated simultaneously with the PK.

Proposed change:

Remove this section of the sentence

Comment #2

II. BACKGROUND

A. General

The Draft Guidance states:

“BA data provide an estimate of the fraction of the drug absorbed, as well as its subsequent distribution and elimination. BA can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentrations in the systemic circulation over time.”

Comment:

BA data do not provide with an estimate of the absorption of a drug, unless more sophisticated PK technique is used or a radioactive dose is given. Absorption is only one component of bioavailability ($F=F_A \times F_G \times F_H$). BA data provide with an estimate of bioavailability.

Proposed change:

“BA data provide an estimate of the fraction of the drug that arrives systemically (bioavailability), as well as is subsequent distribution and elimination. Relative BA can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentrations in the systemic circulation over time.”

Or

“BA data provide an estimate of the fraction of the drug that arrives systemically (bioavailability), as well as is subsequent distribution and elimination. BA can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentrations in the systemic circulation over time and comparing it with the profile resulting from an intravenous administration.”

Comment #3

II. BACKGROUND

A. General

The Draft Guidance states:

“For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product should exhibit the same rate and extent of absorption as the reference drug product.”

Comment:

BA data do not provide with an estimate of the absorption of a drug, unless more sophisticated PK technique is used or a radioactive dose is given. Absorption is only one component of bioavailability ($F=F_A \times F_G \times F_H$). BA data provide with an estimate of bioavailability.

Proposed change:

“For two orally administered drug products to be bioequivalent, the active drug ingredient or

*active moiety in the test product should exhibit the same rate and extent of **bioavailability** as the reference drug product.”*

Or

*“For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product should exhibit the same rate and extent of **exposure** as the reference drug product.”*

Comment #4

II. BACKGROUND

A. Bioequivalence

1. IND/NDAs (paragraph 2 on page 5)

The Draft Guidance states:

“A test product may fail to meet BE limits because the test product has higher or lower measures of rate and extent of absorption compared to the reference product....”

Comment:

BA data do not provide with an estimate of the absorption of a drug, unless more sophisticated PK technique is used or a radioactive dose is given. Absorption is only one component of bioavailability ($F = F_A \times F_G \times F_H$). BA data provide with an estimate of bioavailability.

Proposed change:

*“A test product may fail to meet BE limits because the test product has higher or lower measures of rate and extent of **bioavailability** compared to the reference product....”*

Or

*“A test product may fail to meet BE limits because the test product has higher or lower measures of rate and extent of **exposure** compared to the reference product....”*

Comment #5

III. METHODS TO DOCUMENT BA AND BE

A. Pharmacokinetic Studies

1. General considerations (paragraph 1 on page 6)

The Draft Guidance states:

“The statutory definition of BA and BE, expressed in terms of rate and extent of absorption”

Comment:

BA data do not provide with an estimate of the absorption of a drug, unless more sophisticated PK technique is used or a radioactive dose is given. Absorption is only one component of bioavailability ($F = F_A \times F_G \times F_H$). BA data provide with an estimate of bioavailability.

Proposed change:

*“The statutory definition of BA and BE, expressed in terms of rate and extent of **bioavailability**”*

Or

“The statutory definition of BA and BE, expressed in terms of rate and extent of exposure”

Comment #6

III. METHODS TO DOCUMENT BA AND BE

B. Pharmacokinetic Studies

1. General considerations (paragraph 1 on page 7)

The Draft Guidance states:

“In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (gastric emptying, motility, pH) ...”

Comment:

In a PK study, clearance, volume of distribution and absorption are not determined by physiological variables such as gastric emptying, motility and pH. They are simply determined using concentration time profiles.

The Draft Guidance states:

“... are assumed to have less interoccasion variability compared to the variability arising from formulation performance. Therefore, differences between two products because of formulation factors can be determined”

Comment:

We understand what the FDA is trying to say, however it is not necessary to assume this. In addition, if in a particular study the interoccasion variability is larger than the variability arising from formulation performance (which is likely for highly variable drugs) then this will likely make the study fail to meet BE unless a very high number of subjects is included. Therefore, based on our understanding, the FDA would not want us to just assume that it is due to the interoccasion variability.

Differences between drug products because of formulation factors cannot be truly determined unless the drug product is given more than once per subject and the statistical analysis used is not the ABE but the IBE or a similar approach. Alternatively, other PK approaches can also be used to do this (ex.: Population approaches), but it is our understanding that the FDA would not accept this for ANDA's but only for NDAs.

Proposed change:

Remove these sentences.

Comment #7

III. METHODS TO DOCUMENT BA AND BE

C. Pharmacokinetic Studies

2. Pilot Study (page 7)

The Draft Guidance states:

“A pilot study that documents BE may be appropriate, provided its design and execution are suitable and a sufficient number of subjects (e.g., 12) have completed the study”

Comment:

This is a good change. This means that a pilot study can be filed as a definitive one if it is appropriate as indicated by the FDA.

Comment #8

III. METHODS TO DOCUMENT BA AND BE

D. Pharmacokinetic Studies

5. Study Population (page 8)

The Draft Guidance states:

“If the drug product is intended for use in both sexes, the sponsor should attempt to include similar proportions of males and females in the study.”

Comment:

It is understandable that a product be studied in both gender during the NDA process, and that an adequate number of males and females are included so that gender differences can be found if they exist. This is necessary for clinicians to know before a drug be accepted on the market for the first time (NDAs).

For ANDA's, the requirement to study an heterogeneous population is not as clear. What would be the purpose of studying an equal number of men and female in a BE study, if it is not to test for gender differences? The FDA needs to be clearer on their intent here. If they want sponsors to prove BE and also address gender differences in the PK, study designs will have to address this *a priori*. It would not be appropriate to test *a posteriori* gender differences just because we have a sufficient number of females and males if the study was not designed to test for this to start with.

Proposed change:

Remove this requirement for ANDAs, or make it clear that from now on the FDA wants sponsor to prove BE and test for gender differences for ANDAs.

Comment #9

III. METHODS TO DOCUMENT BA AND BE

E. Pharmacokinetic Studies

5. Study Population (page 8)

The Draft Guidance states:

“If the drug product is to be used predominantly in the elderly, the sponsor should attempt to include as many subjects of 60 years of age or older as possible”

Comment:

Comment:

It is understandable that a product be studied in elderly during the NDA process, and that an adequate number of elderly subjects are included so that age differences can be found if they exist. This is necessary for clinicians to know before a drug can be accepted on the market for the first time (NDAs).

For ANDA's, the requirement to study elderly subjects is not as clear if it is known that there is no special age difference in the PK of this drug besides the usual alteration in renal function. Because the vast majority of drug products are mostly being taken by elderly people, this requirement would mean that we would have to test BE studies in an elderly population from now on in the vast majority of cases. This has major ethical ramifications, since it may not provide more robust assessment of BE at all, and puts at risk elderly subjects because they are not as healthy as young individuals and are frequently consuming other medications.

Proposed change:

Remove this requirement for ANDAs, or make it clear that from now on the FDA wants sponsor to prove BE and test for age differences for ANDAs.

Comment #10

III. METHODS TO DOCUMENT BA AND BE

F. Pharmacokinetic Studies

5. Study Population (page 8)

The Draft Guidance states:

"In some instances it may be useful to admit patients into BE studies for whom a drug product is intended"

Comment:

We believe that the FDA is referring to situations where a drug product has a lot of side effects and where it may not be ethical to be doing a BE study in healthy volunteers (e.g., cancer drugs)

Proposed change:

*"In some instances it may be **safer** to admit patients into BE studies for whom a drug product is intended"*

Comment #11

III. METHODS TO DOCUMENT BA AND BE

G. Pharmacokinetic Studies

8. Pharmacokinetic Measures of Systemic Exposure

a. Early exposure (page 9)

The Draft Guidance states:

“In this setting, the guidance recommends use of partial AUC as an early exposure measure. The partial area should be truncated at the population median of Tmax values for the reference formulation.”

Comment:

We understand that the FDA wants to inquire about new informative ways of proving BE between two products. The partial AUC measure, if done correctly, may provide valuable information when one uses the noncompartmental PK approach. The approach suggested in the guidance, however, does not appear scientifically robust. In particular, the use of the population median Tmax for the reference formulation would not lead to accurate partial exposure results.

We have commented extensively on this approach 3 years ago following the release of this draft guidance for comments. Here are some of the limitations that we alluded to and that are important to consider:

- 1) The PK of a lot of drugs is associated with a lag-time before the absorption process starts. This is very common with orally administered drugs, so much that it is usually not appropriate to determine the pharmacokinetics of a drug with compartmental methods not taking into account this parameter. Drugs associated with a significant lag-time usually demonstrate a very large within-subject variability in this parameter (ex. cyclosporine, omeprazole) but not necessarily in the absorption parameters themselves (Ka). With drugs associated with a lag-time, giving the same drug formulation to the same individual will result in a different Tmax. In vivo assessment of BE between two drug formulations that exhibit a lag-time cannot be performed reliably using the Tmax or the partial AUC.
- 2) Concentration-time profiles of modified-release products are frequently associated with concentrations changing little over time during the absorption process. Timing of the peak concentration may be highly variable with these formulations due to experimental errors associated with any plasma concentration. If the Tmax is not adequately characterized, the partial AUC method will not be appropriate.

Sponsors can provide additional PK parameters that can be robustly calculated using the compartmental approach. These parameters (K_{Arel} and F_{rel}) can give additional insight on the

rate and extent of bioavailability when presented together with the standard noncompartmental PK parameters AUC and Cmax.

Proposed change:

Unfortunately, we do not support scientifically the use of this partial AUC the way it is proposed to be calculated

Comment #12

III. METHODS TO DOCUMENT BA AND BE

H. Pharmacokinetic Studies

8. Pharmacokinetic Measures of Systemic Exposure

c. Total exposure (page 9)

The Draft Guidance states:

“...measurement of total exposure should be:

. (AUC_{0-t})....”

Comment:

The AUC_{0-t} is not a parameter reflecting the total exposure. It reflects a partial exposure, understanding however that it has to cover as much as possible the complete exposure (>80%).

The AUC_{inf} is the only parameter that reflects total exposure after a single dose.

Proposed change:

Please revise the wording

Comment #13

VI. SPECIAL TOPICS

A. Food-effect studies (page 18)

Comment/Suggestion:

We agree with what is stated in this paragraph but we wonder if it would not be useful to specify to the reader that a separate guidance exist on Food effect and that we refer the reader to that guidance for further information.

Comment #14

Attachment A General PK study design and data handling Data deletion due to vomiting (page 23)

The Draft Guidance states:

“Data from subjects who experience emesis during the course of a BE study for IR products should be deleted ... at or before 2 times median Tmax”

Comment:

The decision on whether a subject's data should be analyzed in a BE study after he experienced an emetic episode will be dependent on whether or not the complete “absorption” has taken place or not. Depending on the relationship between the absorption rate constant of the drug with its elimination rate constant, the Tmax will indicate different things:

- 1) If the $KA \gg \gg \gg K_{el}$ then the absorption will be virtually finished at Tmax. Twice the Tmax as a cut-off value is therefore quite conservative and may be too stringent in some cases.
- 2) If the $KA = K_{el}$, then 50% of the absorption will be finished at Tmax. This means that a period of twice the Tmax will cover 75% of the absorption process. A cut-off value of twice the Tmax will therefore not be sufficient and will bias the BE results.
- 3) If the $KA \ll \ll \ll K_{el}$, then there is no question that twice the Tmax will also not be sufficient.

In addition, if a drug is absorbed through a zero-order process then the absorption will be finished at Tmax. In these instances, one time the Tmax should be the cutoff value.

Proposed change:

Please revise the wording

Comment #15

Attachment A General PK study design and data handling Data deletion due to vomiting (page 23)

The Draft Guidance states:

“... In the case of modified release”

Comment #14

Attachment A

General PK study design and data handling Data deletion due to vomiting (page 23)

The Draft Guidance states:

“Data from subjects who experience emesis during the course of a BE study for IR products should be deleted ... at or before 2 times median Tmax”

Comment:

The decision on whether a subject's data should be analyzed in a BE study after he experienced an emetic episode will be dependent on whether or not the complete “absorption” has taken place or not. Depending on the relationship between the absorption rate constant of the drug with its elimination rate constant, the Tmax will indicate different things:

- 1) If the $KA \gg \gg \gg Kel$ then the absorption will be virtually finished at Tmax. Twice the Tmax as a cut-off value is therefore quite conservative and may be too stringent in some cases.
- 2) If the $KA = Kel$, then 50% of the absorption will be finished at Tmax. This means that a period of twice the Tmax will cover 75% of the absorption process. A cut-off value of twice the Tmax will therefore not be sufficient and will bias the BE results.
- 3) If the $KA \ll \ll \ll Kel$, then there is no question that twice the Tmax will also not be sufficient.

In addition, if a drug is absorbed through a zero-order process then the absorption will be finished at Tmax. In these instances, one time the Tmax should be the cutoff value.

Proposed change:

Please revise the wording

Comment #15

Attachment A

General PK study design and data handling Data deletion due to vomiting (page 23)

The Draft Guidance states:

“... In the case of modified release”

Comment:

This is scientifically sound.

Comment #16

Attachment A

General PK study design and data handling

The following pharmacokinetic information is recommended for submission (page 23)

The Draft Guidance states:

“... *Partial AUC*...”

Comment:

The calculation of the partial AUC as described in this guidance does not appear robust enough and should not be requested as it can lead to dangerous misinterpretation.

Proposed change:

Please remove this line.

FedEx International Air Waybill

1 From Date 08/19/02 Sender's FedEx Account Number 1571-6210-9

Senders Name Bruno B. B... Phone
 Company
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2 Your Internal Reference 464
 City, State, Province, CANADA Postal Code

3 To Recipient's Name Mr. J. J. J... Phone
 Company
 Address 5130 Fisher Home, Room 1061-HA...
 City, State, Province, ZIP Postal Code 90252

Shipment Information

All shipments can be subject to Customs charges

Total Packages: lb kg DIM cm

Commodity Description: LABORATORY

Country of Manufacture: USA Harmonized Code: 90252 Value for Customs: 1

Total Declared Value: 100 Currency: USD

5 Express Package Service Packages up to 150 lb, 68 kg for packages over 150 lb, 68 kg, use the FedEx Expanded Service International First

6 Packaging FedEx Letter/Pak (not available) FedEx International Economy FedEx Letter/Pak (not available)

7 Special Handling HOLD at FedEx Location SATURDAY Delivery Shipper must check Dangerous Goods cannot be shipped using this Air Waybill

8a Payment Bill transportation charges to: Sender Act No. in Section 1 will be billed Recipient Third Party Cash Credit Card No. below Enter FedEx Act. No. or Credit Card No. below

8b Payment Bill Customs charges to: Sender Act No. in Section 1 will be billed Recipient Third Party Cash Cheque Enter FedEx Act. No. below

9 Required Signature Sender's Signature Recipient's Signature

Use of this Air Waybill constitutes your agreement to the Conditions of Contract on the back of this Air Waybill. Certain international treaties, including the Warsaw Convention, may apply to this shipment and limit our liability for damage, loss, or delay, as described in the Conditions of Contract

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