Health Canada Santé Canada

Drugs Directorate
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March 7, 1996

Sent to the Attached Distribution List

Subject: Bioequivalence of Proportional Formulations

Please find attached the Drugs Directorate Policy regarding bioequivalence of proportional solid oral dosage formulations.

This policy reflects a relaxation of previous requirements for bioequivalence studies for proportional formulations. It is an initial component within an integrated policy dealing with formulation and manufacturing changes.

The comments received in response to my letter of September 7, 1995, have been reviewed and suggestions have been incorporated into the current policy, where appropriate. For your information, a summary of the comments received, together with our analysis of them, is attached (Attachment I). I hope that this information is helpful to you.

This policy is effective immediately. If you have any questions or comments, please do not hesitate to contact Dr. Norman Pound, Chief, Division of Biopharmaceutics Evaluation, Bureau of Pharmaceutical Assessment, Drugs Directorate at (613) 941-9522.

Original Signed by/

Dann M. Michols
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Attachment

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ATTACHMENT I

Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms: Consultation

Comments concerning the draft policy were solicited from the stakeholders. Five responses were received from pharmaceutical manufacturers. Specific comments are addressed below and have been incorporated into the revised policy as indicated:

1. Two respondents suggested that different criteria should be applied to different types of submissions e.g. when a manufacturer compares his own old and new products as opposed to a comparison of generic and innovator products.

Response:

Regardless of the type of submission, bioequivalence studies are only required when safety and efficacy are at issue. Safety and efficacy are at issue when changes to formulation are such that bioavailability could potentially be affected. This policy attempts to define those changes to an existing formulation which would necessitate comparative bioavailability studies. The distinction between a subsequent-entry product, and a change to an existing formulation is recognized. In some instances, only a single study in fasted subjects would be required. Whereas in others, more studies would be required.

2. Two respondents suggested that in some cases dissolution data may provide adequate evidence of safety and efficacy.

Response:

In vitro dissolution studies are not considered to be an adequate substitute for (*in vivo*) bioequivalence studies.

3. Two respondents wished to review the data upon which the proposed limits were based.

Response:

The limits proposed in Table 1 in the policy were drawn from an AAPS-FDA workshop report (Scaleup of Immediate Release Oral Solid Dosage Forms. J. P. Skelly et al. *Pharmaceutical Research* 1993;**10**(2):313-316) and are in concurrence with USFDA guidance (Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation; Guidance. *Federal Register* 1995;**60**(230):61638-61643). The sponsor is referred to the above sources for information supporting the proposed limits.

4. Two respondents have expressed concern that the limits on change in drug substance/excipient ratio and on film coats were too restrictive.

Response:

Both requirements have now been removed from the policy. The drug substance/excipient ratio was deleted in order to harmonize with the FDA guidance quoted in point 3. above. The film-coating limitation was removed since it is recognized that proportional changes in core weight do not result in similar changes in tablet surface area and hence the film coat weight need not be directly proportional across a range of strengths.

5. One respondent suggested that the dissolution methodology developed to characterize the finished product should be adequate to examine differences in dissolution without the need for additional testing in other media. Since this test is explicitly designed as a product release specification for QC purposes, it could be presumed to be sensitive to differences in product characteristics.

Response:

QC release specifications cannot be presumed to be sensitive to differences in product characteristics. This must be demonstrated through proper method development studies. The policy has now been amended to recognize instances where this work has been conducted by the manufacturer. Hence comparative dissolution profiles in at least three media will only be required in the absence of an appropriately validated QC method.

6. Two respondents suggested that when bioavailability data is available demonstrating equivalence of formulations that differ by more than the limits specified in Table 1, studies should not be required on intermediate formulations.

Response:

Section 1.1.2 of the policy makes allowance for incremental changes in formulation where differences may exceed those defined in Table 1 in the policy, without the need for studies on every formulation.

7. One respondent suggests that the test formulation should be proportional to the reference formulation.

Response:

Innovator formulation is proprietary. Therefore one cannot know whether test and reference products are proportional. It is expected that a 10 mg tablet (for example) will provide half the amount of drug that a 20 mg tablet provides, and at a similar rate. Clinical or comparative bioavailability studies may be used to assure this. However, when one or more strengths have been subjected to comparative bioavailability study, direct pharmaceutical proportionality with the studied formulation also provides an acceptable degree of surety.

8. One respondent suggests that if formulations of any "complicated" drugs are proportional, only the bioequivalence study for the highest strength should be required. There should be no need to test other strengths when they are similarly formulated, irrespective of whether the drug molecule itself represents a "complicated" drug because the formulation per se has already been shown to be bioequivalent.

Response:

The Expert Advisory Committee on Bioavailability reports strongly indicate that both the characteristics of the drug molecule and the formulation must be considered. The differences in potential risks associated with the use of different classes of drugs require that a greater degree of assurance of safety and efficacy be sought with some classes than with others.

9. Various minor editorial comments were made by one respondent with respect to dissolution criteria.

Response:

Changes have been made to the policy where appropriate.

10. Physical properties of excipients should be taken into account.

Response:

The issue of the physical properties of excipients is to be addressed in a related policy.

11. In the opinion of one respondent, the current direction of the policy is to narrow the current tolerances for formulation adjustments when lower strengths are developed and this is at the at the expense of harmonization with the FDA.

Response:

Policy hitherto in effect states that only one strength is required in a comparative bioavailability study **only** if the different strengths in the range have the **same** proportion of ingredients. The proposed policy represents a relaxation in that some differences between formulations will now be tolerated without supporting comparative bioavailability data. Also, it should be noted that the changes proposed are in concurrence with published FDA guidance (see Federal Register, Vol. 60, No. 230, p. 61638 - 61643).

12. One respondent states that the policy appears to be inconsistent with the assumptions of the Canadian Reference Product policy. If a foreign-based reference product is deemed eligible for the Canadian Reference Product policy, the analytical basis for bioequivalence is limited to two things: a certificate of analysis on the medicinal ingredient and dissolution profiles in three media. Individual excipients are not measured.

Response:

It should be noted that generally a comparison with the Canadian reference product is required. In cases where a non-Canadian reference product is permitted, assurance is sought that it is the same as the product sold in Canada. For example, the fact that the non-Canadian reference product is made by the same manufacturer as that of the product sold in Canada and is the same with respect to colour, shape, size, weight, type of coating, dissolution profiles, etc., increases the likelihood that the products are indeed

the same. The Canadian Reference Product policy imposes sufficient restrictions to provide a high levelof assurance that products meeting these criteria are the same, or that even if slight differences existed, the differences would be of no therapeutic consequence. This is different from a comparison of test and reference products where the two products must be shown to be bioequivalent.

13. One respondent suggests that there should be a differentiation among solid oral dosage forms. For example, hard gelatin capsules are restricted to discrete shell sizes (or shell volumes), such as #4, #3, #1, 0, etc., which must be fully packed with the excipient-drug mixture if they are to be filled on modern encapsulation equipment. The ability to produce a proportional formulation for 2 strengths of a drug where the drug mixture is put in the same size capsule shell becomes virtually impossible.

Response:

The policy applies to all solid oral dosage forms, including capsules. It should be noted that the FDA guidance and the AAPS Workshop Report quoted above do not provide special exemptions for capsules. This issue will be taken into consideration in future revisions of the policy.

14. One respondent suggests that when the policy is enabled and applied, a key consideration will be the lead time before the policy becomes effective so that ongoing developmental work and its associated investment will not be lost. They suggest a lead time of approximately one year.

Response:

This statement was made on the mistaken premise that the present policy represents a narrowing of tolerances for formulation adjustment. If application of this policy is delayed, then the previous policy would remain in effect. The previous policy does not allow tolerance of any differences in formulation without supporting comparative bioavailability data. We believe it is in the stakeholders' best interest that this policy be implemented immediately.

POLICY ISSUE
FROM THE DRUGS DIRECTORATE

BIOEQUIVALENCE OF PROPORTIONAL FORMULATIONS - SOLID ORAL DOSAGE FORMS

Introduction:

Responsibility to establish the safety and efficacy of a drug rests with the manufacturer. In the case of subsequent-entry products (generics) this can often be achieved by demonstrating bioequivalence with the innovative product on the Canadian market. With some exceptions, it is generally accepted that when a product is marketed in more than one strength, if the formulation of each strength contains the **same** ingredients in the **same** proportion (i.e. the formulations are proportional), the results of a single comparative bioavailability study can be extrapolated to all strengths in the series. Extrapolation becomes more difficult, however, when the proportion of ingredients changes among the strengths or when there are pre- or post-marketing formulation changes.

This policy is intended to assist in the identification of situations where the magnitude and nature of pre- and post-marketing changes to a formulation or differences in composition, within a range of strengths of a drug product, are such that the product may, in general, be accepted on the basis of a comparative bioavailability study done on one strength only. This policy does not apply to other pre- or post-marketing changes including changes to specifications and attributes of raw materials, manufacturing site changes and manufacturing process changes.

In all instances, if comparative bioavailability data is not provided for each formulation, the sponsor must provide a scientific justification for waiver of this requirement.

With the exception of changes of a colour or flavouring agent which is not known to influence the absorption characteristics of the drug, changes in composition must be quantitative only. For example, substituting potato starch for corn starch or powdered cellulose for microcrystalline cellulose would require a comparative bioavailability study.

In order to avoid formulation creep when changes involve a marketed product, the calculation of the percentage changes in the proportion of the ingredients is to be based on the formulation on which the comparative bioavailability/clinical study was performed.

Comparative dissolution profiles must also be an integral part of any justification.

Data must be provided to demonstrate individual and mean values of the dissolution profiles of the formulation on which the bioavailability/clinical study was performed versus other proposed strengths/formulations.

The comparative dissolution profiles should be determined using a validated QC method. In this regard, a validated method is one that has been demonstrated to be sensitive to changes in formulation and manufacturing, including the physical-chemical attributes of formulation ingredients, as documented in method development studies. In the absence of a validated method, the comparative dissolution profiles should be determined in at least three (3) media within the physiological range (pH 1 - 7.5), e.g., water, 0.1N HCl, and pharmacopoeial buffer media at pH 4.5, 6.5 or 7.5. One dissolution medium should be that described in the USP or BP monograph, if one exists. Media should be selected to emphasize possible differences between the products, e.g., a medium in which the dissolution rate is relatively slow (e.g., pH of the medium close to the pK_a value of the drug) may offer some advantages. The percentage of drug content released should be measured at a number of suitably spaced time points, e.g., at 10, 20 and 30 minutes, and continued to achieve virtually complete dissolution. At least six dosage units of each batch should be tested using the same apparatus and, if possible, on the same day.

Requirements:

1. Drugs with uncomplicated characteristics, as defined in Drugs Directorate guideline *"Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A"*

1.1 Conventional-Release Dosage Forms:

1.1.1 If different strengths are proportional in formulation, or have only "minor" differences in the proportion of ingredients, a comparative bioavailability study is required on only one strength (preferably the highest). Differences in proportion are considered to be "minor" when no strength within a range differs from a studied strength, by more than the percentages shown in Table 1 for various classes of excipients. Changes in coatings that are not designed to play a role in the drug release mechanism are also generally concluded to be "minor".

Drug substance is formulated to 100% of labelled drug content. The total additive effect of all excipient changes should not be more than 5%. (Example: In a product containing filler A and filler B, these excipients should not vary by more than an absolute total of 5% (e.g. filler A increases by 2.5% and filler B decreases by 2.5%) relative to the total core weight, if the differences are to be considered to be "minor".)

Table 1

Excipient type	**Difference in percent of core weight**
Filler	5 %
Disintegrant	
Starch	3%
Other	1 %
Binder	0.5 %
Lubricant	
Ca or Mg stearate	0.25 %
Other	1 %
Glidant	
Talc	1 %
Other	0.1 %

The proportion of each ingredient is calculated as a percentage (w/w) of the total core weight. Therefore the percentages shown in Table 2 for excipients (in an example of a range of proportional formulations) are calculated as:

(Weight of excipient/total core weight) X 100

Table 2

Strength	25 mg		50 mg		100 mg	
	mg	%	mg	%	mg	%
Drug	25	25	50	25	100	25
Excipient 1	40	40	80	40	160	40
Excipient 2	25	25	50	25	100	25
Excipient 3	3.5	3.5	7	3.5	14	3.5
Excipient 4	3.0	3	6	3	12	3
Excipient 5	3.5	3.5	7	3.5	14	3.5
TOTAL	100	100	200	100	400	100

1.1.2 If different strengths have differences in the proportion of ingredients which exceed those in Table 1, but within the progression of strengths the changes are incremental, a comparative bioavailability study is required on the lowest and highest strengths. Incremental changes are those in which proportions of ingredients increase or decrease successively from the lowest to the highest strengths in the range.

1.1.3 If different strengths contain different ingredients, or if the differences between formulations exceed those defined in Table 1 and are not incremental within the progression of strengths, comparative bioavailability studies are required on each different formulation.

1.2 **Modified-Release Dosage Forms**

1.2.1 The policy stated in section 1.1 applies to modified-release dosage forms, as defined in Report B of the Expert Advisory Committee: "*Report on Bioavailability of Oral Dosage Formulations of Drugs used For Systemic Effects: Modified Release Dosage Formulations*", except for ingredients that affect the release of drug from the formulation. Where differences exist in the proportion of ingredients which may affect the release, comparative bioavailability studies are required on each different formulation.

2. **Drugs with "complicated" characteristics, as defined in Report C of the Expert Advisory Committee: "*Report on Bioavailability of Oral Dosage Formulations, Not in Modified Release form, of Drugs used For Systemic Effects, Having Complicated or Variable Pharmacokinetics*"**

2.1 **Conventional Release Solid Oral Dosage Forms**:

2.1.1 Pre- and post-marketing changes to a formulation, or the introduction of additional strengths for conventional release formulations containing drugs with "complicated" characteristics will be considered on a case by case basis.

For example, it may be possible to provide a scientific rationale to justify the application of the proportionality policy (in section 1.1) to drugs with long elimination half-lives, those for which pharmacodynamic studies are appropriate and some combination drug products. On the other hand, additional bio-studies would be required to establish the bioequivalence of non-proportional or revised formulations containing drugs which are highly toxic, have non-linear kinetics, are considered to have a narrow therapeutic range, or those for which an early onset or rapid absorption is important.

It may be possible, however, to employ a reduced testing protocol. For example, although studies under fasted, fed and steady state conditions may be required to establish the equivalency of a new product, it may be possible to provide data to justify changes to, or the addition of, non-proportional strengths to such a formulation, based on only one or two comparative bio-studies for each formulation.

2.2 **Modified-Release Dosage Forms**

2.2.1 Although, as in the case of conventional dosage forms (2.1.1), the number of additional comparative bioavailability studies required may be reduced, changes in formulation or the addition of non-proportional strengths to modified-release dosage forms containing "complicated" drugs will require at least one bio-study on each strength.