

**sanofi aventis**

Because health matters

August 3, 2005

Via fax and UPS

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0203

Draft Guidance for Industry on Safety Testing of Drug Metabolites

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciate the opportunity to comment on the above-referenced Draft Guidance entitled "*Safety Testing of Drug Metabolites*".

The draft guidance provides recommendations on when and how to identify, characterize, and evaluate the safety of unique human metabolites and major metabolites of small molecule (nonbiologic) drug products.

We appreciate this initiative in providing guidance in the area of safety assessment of drug metabolites where numerous challenges exist in defining criteria for triggering metabolite characterization, determining metabolite exposure, designing specific studies on their effects, and interpreting safety study results.

We have evaluated the content of the draft guidance and offer the following comments for your consideration.

GENERAL COMMENTS

We suggest re-organizing Sections II and III so that the guidance clearly differentiates between the background information (current practice and the principle drivers for the new guidance) and recommendations. It would also be very helpful if the guidance was clear about which existing practices should be continued and what modified or new practices should be implemented.

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Additionally, we request further clarification on the following:

- The definition of what constitutes a major metabolite and the distinction from unique metabolite and what would trigger the need for additional investigations of potential toxicity.
- What is meant by human > animal when referring to exposure? The proportion of a metabolite (e.g. as a function of dose) may be higher in humans than animals, but doses in animals may be sufficiently high to provide a margin of safety for both parents and metabolites.
- The use of human and animal in vitro data to characterize metabolites.
- The role of pharmacological activity of metabolites as a criterion to influence decisions regarding safety assessment.

The guidance should also clearly distinguish between 1) the need to evaluate the safety of a human metabolite to which the animals in the toxicology studies are not considered to have been adequately exposed following administration of the parent, and 2) the need to assess the contribution of a metabolite to the toxicity resulting from exposure to both parent and metabolites.

Finally, the guidance should acknowledge that there are other ways to characterize the contribution of a metabolite to toxicity other than independent dosing of the metabolite to animals.

SPECIFIC COMMENTS:

Lines 22-25: "These metabolites may not be adequately assessed during standard nonclinical studies because they occur only in humans (unique metabolite), or at much higher levels (major metabolite) in humans than in species used during standard nonclinical toxicology testing."

The distinction between "unique" and "major" metabolite requires clarification. It is not clear when metabolite characterization would be triggered. Should this distinction be maintained, a threshold for unique metabolites would need to be set as well. We recommend setting the threshold at 5% for unique metabolites.

The definition of major metabolite also requires clarification and is discussed below (lines 26-30).

Lines 26-30: *"This guidance defines major metabolites primarily as those identified in human plasma that account for greater than 10 percent of drug related material (administered dose or systemic exposure whichever is less) and that were not present at sufficient levels to permit adequate evaluation during standard nonclinical animal studies."*

For the purposes of comparing exposure between animals and humans, we recommend the use of data from single-dose animal studies and single-dose human study conducted with radiolabeled compound. In other words, extrapolation of single-dose data to repeated dosing and extrapolation of doses (radiolabeled human study versus normal clinical studies and radiolabeled animal study versus toxicology animal studies) should be considered an acceptable practice and indicated in the guideline.

With respect to the 10% threshold, we suggest that characterization of a metabolite be required when it exceeds 10% of circulating radioactivity in plasma and 10% of total recovered radioactivity.

With regard to what constitutes sufficient exposure in animals to permit adequate evaluation, we suggest the following.

- For human metabolites $\geq 10\%$ we propose that it is sufficient to demonstrate that the plasma exposure to the relevant metabolite at a NOAEL (or depending on the effect at LOAEL) in toxicology studies is \geq the plasma exposure in humans.
- For human metabolites $< 10\%$, demonstration of their presence in animals, or indirect evidence of their formation should be sufficient to qualify the metabolite.

Therefore, it should be clarified that demonstration of the metabolite (or downstream products) in matrices other than plasma can be used as evidence of exposure (See comments on lines 137-142 regarding the use of in vitro data and on lines 184-186 regarding systemic exposure.)

Lines 114-116: *"Sulfate and some glucuronide metabolites (e.g., acyl glucuronides of carboxylic acids) may retain pharmacological activity as well as toxicity of the parent drug and may require toxicological evaluation."*

The applicability of phase II metabolites (e.g., glucuronides, glutathione adducts) for safety testing is limited. Would in vitro testing be an acceptable alternative approach in this case?

Lines 124-130: *“Generally, compounds with the following characteristics are of particular concern and may warrant additional investigation:*

- *Narrow therapeutic indices*
- *Significant toxicity*
- *Significantly diverse metabolic profiles between human and nonclinical species*
- *Irreversible toxicity, or adverse effects not readily monitored in the clinic.”*

Clarification is requested on the purpose of this statement, as it is not apparent what additional investigation is being advocated here or why.

The first two bullets and the fourth bullet suggest that the toxic potential of the molecule has been adequately explored in the animal specie, e.g., the nonclinical studies have fulfilled their primary purpose of identifying hazard. In these cases, further investigation might be warranted to inform the assessment of risk for humans. Such investigations might in some cases (but not inevitably) include an exploration of the contribution of metabolism to the observed toxicity (e.g., if disposition in humans is expected to involve significant metabolism and this could show inter-subject variability).

As mentioned elsewhere in these comments this is a different question than whether or not the animals have been adequately exposed to major human metabolites.

Lines 137-142: *“Metabolism studies are generally performed through a combination of in vitro studies using animal and human tissues and in vivo studies in animals. The in vitro studies are generally conducted prior to the in vivo studies and provide an initial comparative metabolic profile. Results from these studies can assist in the selection of the appropriate animal species for toxicological assessments, should qualitative interspecies differences in metabolism be detected.”*

This could be interpreted to mean that the use of in vitro data is limited to the selection of toxicology species only. However, in vitro data provides useful information for estimating exposure. In certain cases, human and animal in vitro data may be used to characterize the in vivo situation in humans and animals, even if specific metabolites are not observed in the in vivo situation in animals (since they are intermediates which are further metabolized). Therefore, we request clarification on whether in vitro data would be considered sufficient in this case.

See also the discussion on human metabolites <10% under lines 26-30.

Lines 148-152: *“Additionally, when a potentially clinically relevant toxicity is observed during standard nonclinical studies, it is prudent to determine if metabolites contribute to that finding. In such cases, we recommend that the metabolites be synthesized and directly administered to the appropriate animal species for further pharmacological/toxicological evaluation.”*

If the metabolite profile is qualitatively and quantitatively similar between the animal species and human, further investigation of the role of metabolites is not necessarily warranted, except perhaps to explore whether altering metabolism can modulate the toxicity (would be influenced by the likelihood of human metabolism being altered by intrinsic or extrinsic factors). Therefore, we propose modifying this sentence to read as follows: *“Additionally, when a potentially clinically relevant toxicity is observed during standard nonclinical studies and if there are major quantitative metabolic differences between the affected species and human, it is prudent to determine if metabolites contribute to that finding.”*

Regarding the approach advocated to investigate metabolite toxicity, we would argue that that this is not necessarily the right approach in every case. Instead, the approach should be chosen on a case-by-case basis.

Lines 172-177: *“For metabolites detected in humans as well as in nonclinical species (although at lower levels in the latter), adequacy of exposure should be considered on a case-by-case basis. Generally, systemic exposure is assessed by measuring the concentration of the compound in serum or plasma. However, when measurements cannot be made in plasma for any one or a number of reasons, measurements can be made in other biological matrices such as urine, feces, or bile.”*

We request further clarification on what constitutes *“adequacy of exposure”*. Further below in the text, it seems that it may be sufficient that systemic exposure in nonclinical species is equivalent to human exposure (see comments on *“equivalent systemic exposure”*, lines 184-186).

Does exposure to the metabolite have to be *“adequate”* in one or both nonclinical species? We propose that adequate exposure in one species should be sufficient. This would be consistent with the recommendation in Section IV A, that safety testing of a metabolite should be done in one appropriate animals specie.

Further clarification is also requested on whether bioanalytical determination of metabolites in these matrices is needed to determine exposure or whether radiolabeled data would suffice.

Lines 184-186: *"If the systemic exposure in nonclinical species is equivalent to human exposure when measured in plasma and/or excreta, levels may be considered sufficient and alleviate the need for additional toxicity testing."*

Does "equivalent systemic exposure" refer to exposure of metabolites in absolute values at the NOAEL of the parent compound (which is what we advocate - see comments on lines 26-30)? Does this mean that a safety margin of 1 is considered sufficient for metabolites? Would it be acceptable to demonstrate exposure to the metabolite in animals \geq human at an adverse effect dosage? In this case the question is a different one - does the metabolite contribute to the observed toxicity? (See comments on lines 148-152.) This point requires clarification.

As under lines 172-177, clarification is requested on what type of analytical studies would be acceptable for determining metabolite exposure.

Lines 210-215: *"It is important to consider combined exposure to parent and pharmacologically active metabolites in safety assessment. A pharmacologically active metabolite can be more, equal, or less active than the parent drug at the target receptor. Similarly, a metabolite may cause toxicity by (1) eliciting exaggerated pharmacological effects via the target receptor, (2) activating receptors different from the parent drug target receptors, or (3) through nonreceptor mediated mechanisms (e.g. physico-chemical)."*

We request clarification regarding the purpose of including the first statement. Is it advocating the use of safety ratios based on parent and pharmacologically active metabolites?

Regarding the last two sentences on pharmacologically active metabolites and possible mechanisms of activity, it is not clear what these statements contribute. Elsewhere (lines 116-117) it states that demonstration that a metabolite is pharmacologically inactive at the target receptor does not guarantee that it is not toxic. There is no recommendation provided as to how knowledge of direct or indirect (or absence of) pharmacological activity of the molecule would influence the strategy, e.g., Is screening for pharmacological activity the first step in characterization of a metabolite?

Lines 286-293: *"If toxicity studies of a human metabolite are warranted, we recommend studies be completed and the study reports be submitted to the Agency before beginning large-scale phase 3 trials. In some cases, it may be appropriate for these nonclinical safety studies with unique human metabolites to be conducted before phase 3 studies; for example, (1) if the metabolite belongs to a chemical class with known toxicity; (2) if the metabolite has positive structural alerts for genotoxicity, carcinogenicity, or reproductive toxicity; or (3) if clinical findings suggest the metabolite or related compounds have indicated special clinical safety concerns, such as QT prolongation."*

We request further clarification on the timing of the nonclinical toxicity studies with a metabolite relative to clinical development. Specifically, is there a distinction between large-scale phase 3 trials (line 288) and phase 3 studies (line 289)?

Lines 301-302: *"Major metabolite- A metabolite in humans that accounts for plasma levels greater than 10 percent of the administered dose or systemic exposure whichever is less."*

The definition of major metabolite given in the glossary is not consistent with that given in the text (lines 27-30 for example). We suggest that "major" be consistently defined not only by the quantitative exposure in human but also by the relationship of this to the exposure in animals.

Lines 352-356: *Appendix A: Decision Tree Flow Diagram*

We are proposing the following alternate decision tree based on the comments provided above. Please see Attachment 1: Metabolite Decision Tree.

On behalf of Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry Safety Testing of Drug Metabolites* and are much obliged for your consideration.

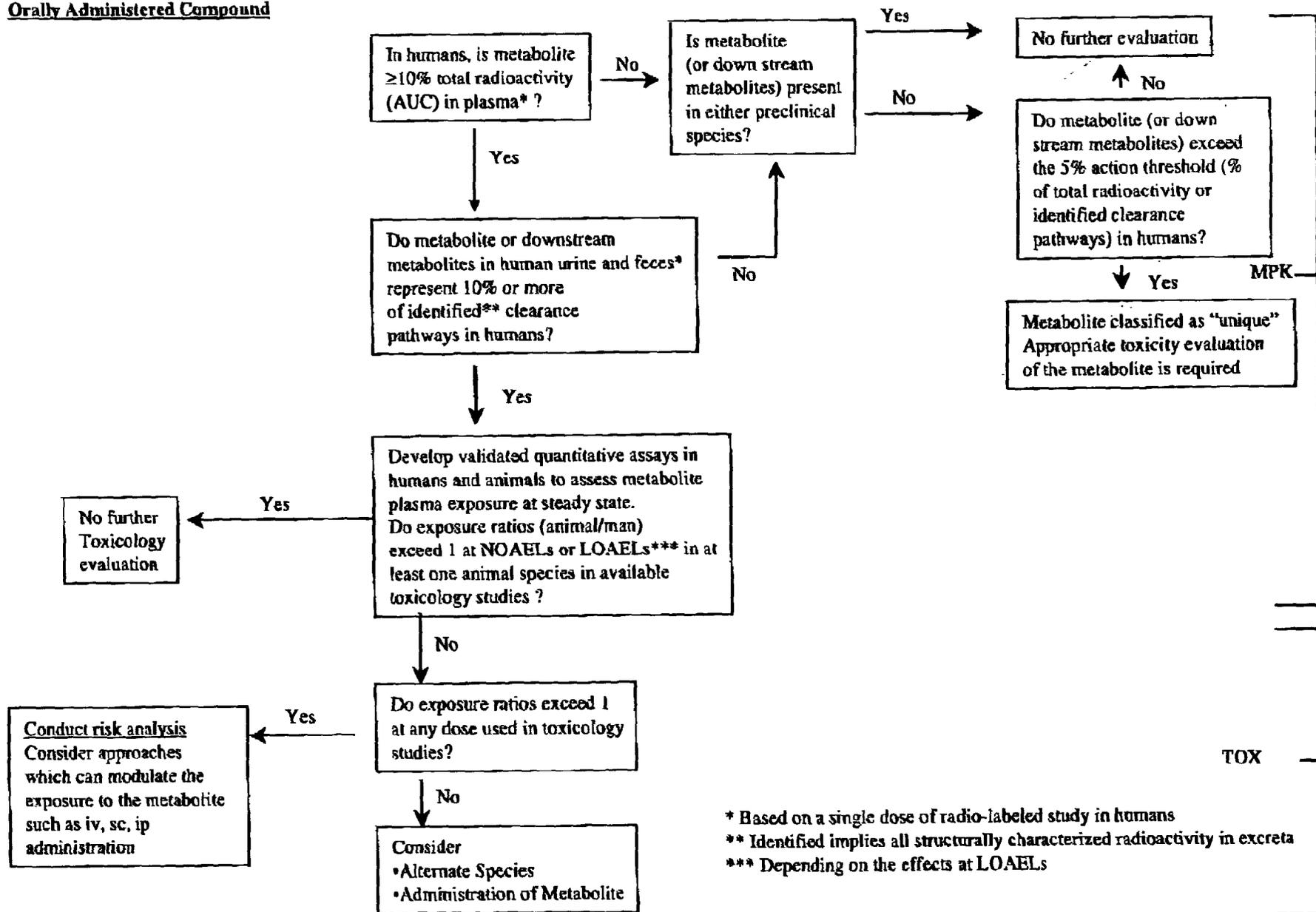
Sincerely,



Steve Caffé, M.D.
Vice President, US Deputy Head
Regulatory Development

Attachment 1: Metabolite Decision Tree

Orally Administered Compound



* Based on a single dose of radio-labeled study in humans
 ** Identified implies all structurally characterized radioactivity in excreta
 *** Depending on the effects at LOAELs