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WHAT IS THE OBJECTIVE OF THE MASS BALANCE STUDY? A RETROSPECTIVE ANALYSIS OF DATA IN ANIMAL AND HUMAN EXCRETION STUDIES EMPLOYING RADIOLABELED DRUGS

Sarah J. Roffey, R. Scott Obach, Jenny I. Gedge, and Dennis A. Smith

Pharmacokinetics, Dynamics, and Metabolism, Pfizer, Inc., Sandwich, Kent, UK, and Groton, CT, USA

Mass balance excretion studies in laboratory animals and humans using radiolabeled compounds represent a standard part of the development process for new drugs. From these studies, the total fate of drug-related material is obtained: mass balance, routes of excretion, and, with additional analyses, metabolic pathways. However, rarely does the mass balance in radiolabeled excretion studies truly achieve 100% recovery. Many definitions of cutoff criteria for mass balance that identify acceptable versus unacceptable recovery have been presented as ad hoc statements without a strong rationale. To address this, a retrospective analysis was undertaken to explore the overall performance of mass balance studies in both laboratory animal species and humans using data for 27 proprietary compounds within Pfizer and extensive review of published studies. The review has examined variation in recovery and the question of whether low recovery was a cause for concern in terms of drug safety. Overall, mean recovery was greater in rats and dogs than in humans. When the circulating half-life of total radioactivity is greater than 50 h, the recovery tends to be lower. Excretion data from the literature were queried as to whether drugs linked with toxicities associated with sequestration in tissues or covalent binding exhibit low mass balance. This was not the case, unless the sequestration led to a long elimination half-life of drug-related material. In the vast majority of cases, sequestration or concentration of drug-related material in an organ or tissue was without deleterious effect and, in some cases, was related to the pharmacological mechanism of action. Overall, from these data, recovery of radiolabel would normally be equal to or greater than 90%, 85%, and 80% in rat, dog, and human, respectively. Since several technical limitations can underlie a lack of mass balance and since mass balance data are not sensitive indicators of the potential for toxicity arising via tissue sequestration, absolute recovery in humans should not be used as a major decision criteria as to whether a radiolabeled study has met its objectives. Instead, the study should be seen as an integral part of drug development answering four principal questions: 1) Is the proposed clearance mechanism sufficiently supported by the identities of the drug-related materials in excreta, so as to provide a complete understanding of clearance and potential contributors to interpatient variability and drug-drug interactions? 2) What are the drug-related entities present in circulation that are the active principals contributing to primary and secondary pharmacology? 3) Are there findings (low extraction recovery of radiolabel from plasma, metabolite structures indicative of chemically reactive intermediates) that suggest potential safety issues requiring further risk assessment? 4) Do questions 2 and 3 have appropriate preclinical support in terms of pharmacology, safety pharmacology,

Address correspondence to Scott Obach, Pfizer, Inc., Groton, CT, USA, 06340; E-mail: r.scott.obach@pfizer.com

and toxicology? Only if one or more of these four questions remain unanswered should additional mass balance studies be considered.

Key Words: ADME; Mass balance; Excretion; Nonspecific binding; Covalent binding.

INTRODUCTION

The administration of radiolabeled drugs to animal species used in toxicology studies and to humans has multiple purposes. The total material balance of drug-related material (as represented by the radiolabel) in excreta is determined, as is the time course of excretion of total drug-related material. The systemic pharmacokinetics of total radioactivity are measured, and, finally, the excreta and blood samples gathered in such studies are used for identification and quantitative profiling of metabolites and parent drug. Complete mass balance, in theory, would require that 100% of the radioactivity administered is accounted for in the excreta and, for animal species, in the cage wash. However, it is rarely the case that exactly 100% recovery is obtained. Clearly, it is not technically possible to collect every last drop of urine or particle of fecal matter in an excretion study. Thus, missing a small quantity of excreta can contribute to loss of material balance, especially if this loss occurs within a time period of a high rate of excretion of drug-related material. Furthermore, careful consideration is made as to the position of the radionuclide within the drug molecule in order to prevent a labeled fragment of the drug from entering endogenous compound metabolism and to prevent conversion of the label to a volatile metabolite (e.g., $[^{14}C]CO_2$). Although regulatory guidance exists around some aspects of human radiolabel studies, these guidelines are primarily focused on defining the dose of radioactivity with regard to exposure of various tissues to ionizing radiation and not on defining acceptable criteria for total mass balance. Acceptable values for recovery, such as 85% (Sunzel, 2004) and 90% (Beumer et al., 2006), have been proposed, but there is no widely accepted and defined cutoff value with a compelling underlying rationale.

Thus, an important question needs to be addressed: What is the lower limit percentage whereby the conclusion from the result is that mass balance has been adequately achieved? To address this question, a retrospective analysis of mass balance studies conducted at Pfizer in drug metabolism laboratories in Sandwich, UK and Groton, CT, USA was undertaken. Overall mass balance data were collected for human studies as well as the corresponding studies conducted in rats and large animal species used in drug development (i.e., beagle dogs and cynomolgus monkeys). The data were mined for trends that could suggest underlying reasons for not achieving mass balance. The results of this analysis are reported herein.

Furthermore, an examination of the scientific literature was done to determine whether trends exist regarding human mass balance data and drugs associated with toxicity. Over the years, there has been considerable evidence linking various toxicities and covalent binding of drugs to tissue macromolecules, as well as evidence linking toxicities to non-covalent sequestration of drugs in specific tissues (albeit fewer examples of the latter). However, in the vast majority of cases, accumulation or sequestration is accompanied by no detectable effect. (Accumulation or sequestration implicated in side effects or toxicity, such as phospholipidosis and aminoglycoside nephrotoxicity, is reviewed in detail later.) When the radiolabel mass balance study in humans yields low recovery, the question typically arises as to whether covalent binding or non-covalent tissue sequestration of

drug-related material is the underlying mechanism behind the observation. Observations of low balance can lead to concerns regarding the safety of the compound in question, even in the absence of observation of any clinical safety findings. Our analysis suggests that there is no link between low recovery and human toxicity; a discussion of this follows.

MASS BALANCE OR HUMAN METABOLISM: WHAT IS THE OBJECTIVE?

Elements of mass balance study design have been described previously (Tse 1995; Beumer et al., 2006) and details will not be reiterated here. Clearly, there are several study design elements and specifics on study execution that need to be adhered to in order to give the best chance possible to achieve a high recovery. These include selection of an appropriate position of the radionuclide in the molecule (preferably carbon-14), quantitative delivery of the dose, meticulous sample collection practices, and sound radiometric measurement techniques. Such aspects are hallmarks of sound scientific practice, and, clearly, the overall accuracy of the results of any complex, multistep study are diminished with each step of the study that is done with less than perfect fidelity. Nevertheless, as seen in the following description, it is rare that a radiolabel mass balance study achieves 100%, despite the great care used in designing and executing these studies.

A recent article by Sunzel (2004) states "the timing of the ADME study in relation to other studies in the clinical development programme varies. However, the earlier the study is performed, the more useful are the results of the study. Early information regarding major metabolites and excretion patterns is essential for rational planning of studies, e.g., for special populations." Furthermore, in a detailed description of study design, the statement is made that "it is essential that the recovery of the total radioactivity in the different biological fluids is 85–95% or above". A more recent article by Beumer et al. (2006) suggests 90% recovery as an adequate cutoff. No one schooled in the traditions of drug metabolism would argue with these statements, and they form the basis of a substantial amount of work during the preclinical and clinical development of a drug. However, although metabolism and excretion studies are important components of linking preclinical and clinical observations, how important is overall recovery? The term "mass balance" is routinely used to describe these studies, and this translates easily to a recovery objective. The origins of these studies are in the agrochemical industry, wherein very different problems are being assessed concerning the application of large amounts of potentially hazardous chemicals, the entry of these into food chains, etc. However, despite this historical perspective of conducting the work essentially unchanged in study design over the past 30 years or more (with exception to application of advances in specific technologies such as HPLC-MS/MS), it is worth asking the question as to whether the studies are as pivotal as we think: i.e., do they actually answer important questions about the drug, or do they just "fill in the E on the way to the M of ADME" (Absorption, Distribution, Metabolism, and Excretion)? That is, it is commonly held that assessing the abundance of metabolites in excreta requires precise measurements of recovery of dose, and, when total recovery in excreta is low, we cannot truly obtain this information, and that low recovery may signal more sinister findings.

However, in a recent commentary, Smith and Obach (2005) suggest that percentage-based assessment as a final measure of circulating and excreted metabolites is not optimal for gaining an understanding of metabolic profiles of humans vs. animals needed for underwriting the safety of human study subjects with preclinical safety data. Rather, the absolute mass (in excreta) or concentration (in circulation) of the metabolite is what is

important. For many modern drugs, the dosage is low due to their high potency and other design features. Most toxicity is an extension of the pharmacology, and the principal concern is therefore circulating active metabolites. Excreted metabolites are important only when they provide the clues to the way the parent drug and any active metabolites are cleared, or if they provide insight into the possibility of chemically reactive intermediary metabolites. When active metabolites contribute to the pharmacology of the parent drug, the study of their clearance should be as considered as that of the parent drug. If these considerations were applied, would we conduct excretion studies in the same way and with similar objectives on low-dose (i.e., less than 10 mg/d) drugs? Would achievement of mass balance be as important, and would there be serious concerns if recovery were less than 85% (the lower of the cutoff values previously described)?

RETROSPECTIVE ANALYSIS OF IN-HOUSE DATA

A list of the mean recovery data for 27 proprietary compounds is in Table 1, and mean values are listed in Table 2. Overall, the data suggest that greater recovery is

Table 1 Summary of mean recovery data for 27 carbon-14 labeled compounds in rats, dogs, monkeys, and humans used in this analysis. Unless otherwise indicated, all data were gathered following oral administration.

Compound Number	Species			
	Rat	Dog	Monkey	Human
1	96 (iv) 97(po)	84 (iv)76 (po)	ND	93
2	98 (iv) 92 (po)	88 (iv) 88 (po)	ND	85 (iv) 83 (po)
3	82 (iv) 99 (po)	85 (iv) 81 (po)	ND	74 (iv) 72 (po)
4	88	95	ND	101
5	97	93	ND	82 (iv)88 (po)
6	101	91	ND	85 (iv)90 (po)
7	97	87	ND	89 (iv)91 (po)
8	90	96	ND	91
9	106 (iv) 101 (po)	93 (iv)101 (po)	ND	104 (iv)105 (po)
10	96 (iv) 102 (po)	95 (iv)93 (po)	ND	102
11	97	86	ND	96
12	96	94	ND	97
13	96	89	ND	100
14	91	80	ND	83
15	93	ND	ND	97
16	92	ND	82	93 (CYP2D6 PM)88 (CYP2D6 EM)
17	93	88	ND	89 (CYP2D6 PM)61 (CYP2D6 EM)
18	97	ND	94	72
19	83	92	ND	78 (CYP2D6 PM)87 (CYP2D6 EM)
20	92	100	ND	91
21	95	93	ND	88
22	91	100	58	78
23	100	94	ND	72
24	90	ND	88	88
25	ND	88 (iv)	ND	91 (iv)
26	111	102	ND	86
27	84	100	ND	86
range	82 to 106	76 to 102	58 to 94	61 to 105

ND = not determined.

Table 2 Mean mass balance values for 27 radiolabeled compounds administered to rats, dogs, monkeys, and humans.

Species	Number of Studies[b]	Mass Balance (Mean ± SD)
Rat	31	95 ± 6[a]
Dog	28	91 ± 6[a]
Monkey	4	80 ± 16[a]
Human	36	87 ± 10

[a]Mass balance includes cage wash for all animal species and carcass for rat.
[b]In some cases, the mean includes data from both iv and po studies for the same compound.

attained in rat and dog studies. For 25 drugs, studies were conducted in three species, and, of these, the rat achieved greatest balance 15 times, the dog five times, the human three times, with two instances in which rat and human yielded the same mean mass balance value. An explanation for this observation has not been proven; however, we offer several possibilities as to why this may be the case. In rat mass balance studies, quantitative collection of excreta may be easier to attain since the animals are housed in small metabolism cages that can be easily washed to ensure that all excreted material can be recovered. Masses of excreta in animals are smaller (Table 3), and total radioactivity in these samples is more concentrated, permitting quantitation of radioactivity that does not reside near background values. Finally, rats tend to excrete drug-related material faster than larger species (and have shorter half-lives of total radioactivity), permitting mass balance to be achieved more rapidly. Quantitative and complete collection of excreta from large laboratory animal species poses more challenges due to the sizes of metabolism cages and the greater possibility that the animals may not generate all samples within the cages. For example, dogs and monkeys occasionally urinate outside their cages, and monkeys sometimes cast fecal matter from their cages. Also, successful mass balance studies depend on very accurate delivery of the entire intended dose.

Potential reasons for low radioactive recovery can be classified as artifactual, due to flaws in study design or execution and legitimate scientific explanations. Possible artifactual reasons include the following: 1) inaccuracy in the dose (i.e., preparation and delivery, or analysis, or both); 2) incomplete collection of excreta or missed samples (e.g., inability to recover all material from cages, excretion outside cages, especially monkeys, discarding toilet tissue for humans, human subjects inadvertently or deliberately not collecting a sample); 3) a portion of the dose is vomited without collection; 4) a very long

Table 3 Mean quantities of excreta typically obtained from laboratory animals and humans

Species (weight)	Urine excreted/day (mL)[a]	Total urine volume collected in typical study (mL)	Feces excreted/day (g)[b]	Total fecal mass collected in typical study (g)
Rat (0.25 kg)	50	250	10	50
Dog (10 kg)	300	2100	400	2800
Monkey (5 kg)	375	2625	200	1400
Human (70 kg)	1400	19600	350	4900

[a]Davies & Morris (1993).
[b]In-house data, Pfizer, Inc.

plasma radioactive half-life leading to dilution of drug-related material in excreta such that radioactivity in samples is below the limit of quantitation; 5) subjects spit out a portion of the dose (humans, monkeys); and 6) quenching of radioactivity measurements in excreta samples. Scientific reasons potentially include the following: 1) radiolabel is at a position of the molecule that is lost in expired air or enters endogenous metabolic routes; 2) tissue binding (covalent binding or non-covalent sequestration).

To better understand mass recovery data in humans and to identify characteristics of compounds that could lead to poor recovery, relationships were drawn between various compound attributes and mean human mass balance values. In some instances, plausible reasons underlying a lack of balance could be proposed for individual compounds, although as outlined later (section on Covalent Binding), hard examination of comparable data on other compounds lessens the plausibility of this hypothesis. For example, in the case of compound #17, there was poor balance in CYP2D6 extensive metabolizers (61%), yet good recovery in poor metabolizers (89%). Although counterintuitive (as one might expect more rapid metabolism to lead to more rapid excretion), CYP2D6 metabolism led to the formation of a long-lived metabolite that potentially covalently binds to macromolecules. For compounds #18 and #23, very long half-lives of drug and/or total radioactivity or both in serum appeared to contribute to a lack of good balance. For compound #18, excreta were collected for over three weeks, and retention of subjects for an even longer duration in the study was unreasonable. In that case, very small amounts of radioactivity were being excreted each day, and projection of the daily recovery data beyond the end of the study suggested that, had the study continued for longer, over 90% of mass balance would have been achieved. Thus, projection of total recovery when the excretion rate is slow appears to be a reasonable approach that permits collection of interpretable data without causing unnecessary hardship for study subjects.

A relationship between lipophilicity of the parent drug and the lack of balance (i.e., 100% – mass balance) was not apparent. A trend was observed between the lack of balance and half-life of total radioactivity in circulation (Fig. 1). If a compound exhibited a half-life of total radioactivity of 50 h or less, at least 80% mass balance was achieved.

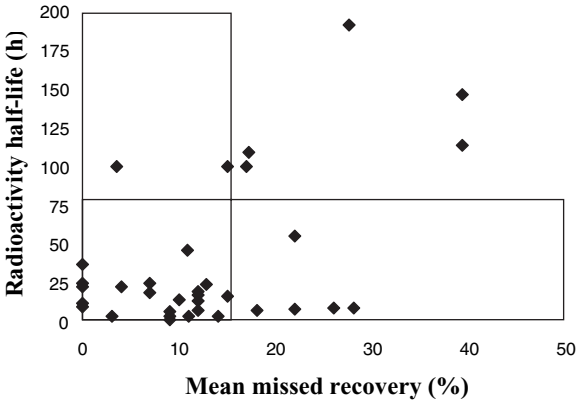

Figure 1 Relationship between a lack of balance recovery and plasma half-life for total radioactivity in humans. Using 85% (Sunzel, 2004) as the acceptable criteria of recovery, for compounds with a radioactivity half -life longer than 75 h, only 2 out of 7 (28%) drugs achieved this figure. This is in contrast to greater than 80% of compounds with a shorter radioactivity half-life achieving 85% or greater recovery.

A similar relationship between parent drug half-life and recovery was not observed. If 85% is assumed as the acceptable criteria for recovery (Sunzel, 2004), then, for compounds with a radioactivity half-life longer than 75 h, only 2 out of 7 (28%) drugs achieved this figure. This is in contrast to greater than 80% of compounds with a shorter radioactivity half-life achieving 85% or greater recovery.

Overall, from these data, recovery of radiolabel would normally be or exceed 90%, 85%, and 80% for rats, dogs, and humans, respectively. For monkeys, the number of studies is too low to define a normal value; however, quantitative collection from this species may pose the greatest technical challenges. Provided that the position of the radionuclide in the drug molecule is set such that it will not be lost due to expired CO_2 or excreted and exhaled as H_2O, or entered into endogenous metabolism, the reasons behind a finding of lower recovery can either be due to technical limitations posed by the study designs and equipment or due to a true residence of material in tissues. Excretion studies in humans and animals do not possess the type of precision to allow conclusions of possible tissue sequestration or covalent binding (except that, for the rat, the carcass can also be examined for residual radioactivity after the collection of excreta is halted). Similarly, if the mass balance value in humans is below 80%, this should not be seen as significant in the judgment of safety; however, because this represents an outcome outside the norm, technical and scientific explanations should be explored. As shown by the data presented, a long half-life of total radioactivity with material "trickling out" slowly is often the explanation. The possibility of missed samples or other technical shortcomings should be investigated. If no reasonable technical problem can be identified, investigation of an underlying mechanism is warranted, such as the potential for sequestration in specific tissues, the possibility of enterohepatic recirculation, or covalent binding to macromolecules (see the following).

However, we suggest that the need to repeat a human radiolabel study is not necessary, provided that certain key questions, which are the primary objectives of the study, are answered successfully:

1. Is the proposed clearance mechanism sufficiently supported by the identities of the drug-related materials in excreta so as to provide a complete understanding of clearance and potential contributing factors to interpatient variability and drug-drug interactions? For instance, if the principal *in vitro* metabolite is formed by a particular cytochrome P450 enzyme, does the complement of metabolites observed in the excreta support this as the major clearance route? Does perturbation of that P450 enzyme by an inhibitor *in vivo* give a pharmacokinetic result in keeping with this understanding?
2. What are the drug-related entities present in circulation that are the active principals contributing to primary and secondary pharmacology? Smith and Obach (2004) suggest that circulating human metabolites are important if they achieve unbound concentrations such that, when combined with potency values, the contribution to activity will exceed 25% of that of the parent drug.
3. Are there findings indicative of potential safety concerns? Is there low extraction recovery of radiolabel from plasma, along with a plasma half-life of radioactivity that is parallel to major plasma components (such as albumin; $t_{1/2}$ ~30 d), indicating covalent binding? Are there metabolite structures in excreta indicative of chemically reactive intermediates (e.g., mercapturic acids, dihydrodiols, etc.)?
4. Do questions 2 and 3 have appropriate preclinical support in terms of pharmacology, safety pharmacology, and toxicology?

RETROSPECTIVE ANALYSIS OF HUMAN MASS BALANCE DATA REPORTED IN THE SCIENTIFIC LITERATURE

In Table 4, we list human mass balance data described in literature reports for 171 compounds. At the outset, it must be considered that a literature-derived dataset may be biased toward studies that appear to be more "successful" with regard to mass balance, since investigators and journal editors are generally more hesitant to publish studies that, from the standpoint of mass balance, would be viewed as failures. Nevertheless, some of the overall trends mirror those observed for the in-house dataset previously described. For these 171 compounds, the mean overall recovery was 89% (±11%). The highest and lowest values were 113% and 39%, respectively. Interestingly, 11 compounds yielded recovery values of greater than 100%, indicating that experimental scatter can play into the inaccuracy of these types of studies, since values greater than 100% are theoretically impossible.

Out of these 171 studies, 42% had overall recovery values below 90% despite the fact that, if the criteria were dropped to 80%, 15% of mass balance studies would have been considered failures. Fecal elimination appears to be of greater importance for drugs that yield lower recovery values. When total recovery was less than 80%, fecal and urinary excretion were generally split evenly (approximately a 1:1 ratio). For compounds with recovery values greater than 90%, the excretion pattern was such that the urinary route was more quantitatively important (about a 2:1 ratio).

POTENTIAL CAUSES FOR LOW MASS BALANCE RESULTS

Non-Covalent Tissue Sequestration. Sequestration and its outcomes are not species specific. A number of mechanisms can be considered under the term "sequestration," but the outcome is that the drug or its metabolites are retained by tissues in a reversible manner. This retention leads to a prolonged excretion of all or, more typically, part of the dose. Such sequestration will often lead to poor recovery, because the study becomes impractical to conduct for longer periods, and the rate or radioactivity excretion is down to a low background level. Several examples of sequestration follow. What becomes clear is that the long half-life drives the low radioactivity recovery rather than the low recovery being a signal of unknown safety implications.

Affinity for Phospholipids. Affinity for phospholipids in drugs processing a cationic lipophilic structure results in a high volume of distribution and, for some compounds, a resulting long half-life. This affinity is the result of both a lipophilic interaction with the alkyl side-chains of the phospholipids combined with an ion pair interaction between the acidic phospholipids head group and the drug's ionized cationic center. For a subset of these compounds, at the elevated doses used in animal safety testing, the association may lead to phospholipidosis. Phospholipidosis is the excessive accumulation of phospholipid in cells, resulting in membranous lamellar inclusions, often accompanied by the accumulation of the causative agent within the increased phospholipid. Phospholipidosis is extremely rare in the clinic, in contrast to the fact that all basic, lipophilic drugs will show affinity for phospholipids, with only amiodarone, perhexiline, fluoxetine, gentamicin, and 4,4-diethyl-aminoethoxyhexestrol being reported to induce the condition in humans (Reasor and Kacew, 2001). Table 5 examines the excretion of radiolabeled compound in humans for drugs that are known to induce lamellar bodies *in vivo* or *ex-vivo*, although only amiodarone and fluoxetine are reported to cause phospholipidosis in the clinic. Recoveries for fluoxetine and tamoxifen are low, and, under any conventional

Table 4 Summary of human mass balance data for 171 xenobiotics.

Drug	Total	Urine	Feces	Reference
abacavir	99	83	16	McDowell et al. (1999)
acitretin	83.5	20.9	62.6	Rubio et al. (1994)
alendronate (iv)	47	47	0	Cocquyt et al. (1999)
alpidem	83.4	6.2	77.2	Durand et al. (1992)
aminoglutethimide	96.5	96.5	0	Dalrymple et al. (1984)
amprenavir	89	14	75	Sadler et al. (2001)
azimilide	82	49	33	Riley et al. (2005)
benazepril	96.8	37	59.8	Waldmeier et al. (1991)
bicalutamide	78.4	35.8	42.6	McKillop et al. (1993)
bidisomide	74	33	41	Cook et al. (1993)
bisoprolol	91.4	90	1.4	Leopold et al. (1986)
bosentan	97	10	87	Weber et al. (1999)
bromfenac	95.7	82.5	13.2	Osman et al. (1998)
bromocriptine	88	5.6	82.3	Maurer et al. (1983)
bunazocin	95	37	58	Morishita et al. (1993)
candesartan	101	33	68	Van Lier et al. (1997)
capecitabine	98.1	95.5	2.6	Judson et al. (1999)
capravirine	86.3	44.3	42	Bu et al. (2004)
captopril	86	68	18	Kripalani et al. (1980)
carprofen	88	74	14	Ray et al. (1982)
carumonam	99	96	3	Weidekamm et al. (1984)
carvedilol	76	16	60	Neugebauer et al. (1987)
cefcanel daloxate	82.1	54.5	27.6	Edwall et al. (1993)
cefepime	96	96	0	Barbhaiya et al. (1991)
cefotaxime	95.8	87.7	8.1	Coombes (1982)
celecoxib	84.8	27.1	57.6	Paulson et al. (2000)
cetirizine	80	70	10	Wood et al. (1987)
cevimeline	97.8	97.3	0.5	Washio et al. (2003)
cibenzoline	98.9	85.7	13.2	Massarella et al. (1986)
ciclesonide	91.4	13.5	77.9	Nave et al. (2004)
cilastatin	105	103	2	Norrby et al. (1984)
cimetidine	97	92	5	Mitchell et al. (1982)
ciramadol	94.2	93.5	0.7	Sisenwine et al. (1986)
citalopram	85.2	74.7	10.5	Dalgaard and Larsen (1999)
clarithromycin	78	38	40	Ferrero et al. (1990)
clopidogrel	92	41	51	Lins et al. (1999)
clozapine	78.6	49	29.6	Dain et al. (1997)
colesevelam	74	0.05	74	Heller et al. (2002)
cyclosporin G	79.4	2.9	76.5	Mangold et al. (1994)
daptomycin	83	78	5	Woodworth et al. (1992)
delmopinol	95	92	3	Eriksson et al. (1998)
desloratadine	88	41	47	Molimard et al. (2004)
dexloxiglumide	93.2	19.5	73.7	Webber et al. (2003)
diosmin	93.9	13.8	80.1	Winternitz et al. (1987)
distigmine	94.5	6.5	88	Vree et al. (1999)
dolasetron	84	59	25	Reith et al. (1995)
domperidone	95	30	65	Meuldermans et al. (1981)
donepezil	72	57	15	Tiseo et al. (1998)
drotaverine	87	39.9	47.1	Vargay et al. (1984)
duloxetine	90.5	70.2	20.3	Lantz et al. (2003)
DX-9065a (iv)	83.8	77.6	6.2	Murayama et al. (2000)
emedastine	101	94.2	6.4	Brunner et al. (2002)

(Continued)

Table 4 (Continued)

Drug	Total	Urine	Feces	Reference
eptifibatide (iv)	73	71.5	1.5	Alton et al. (1998)
ertapenem	89.7	80.5	9.2	Wong et al. (2004)
etintidine	99	86	13	Wong et al. (1990)
etoperidone	88.4	78.8	9.6	Caldwell et al. (2001)
etoricoxib	80	60	20	Rodrigues et al. (2003)
ezetimibe	89	11	78	Patrick et al. (2002)
falipamil (iv)	91.8	61.2	30.6	Roth et al. (1990)
famciclovir	98.9	72.3	26.6	Filer et al. (1994)
FCE 22891	94.2	53.2	41	Efthymiopoulos et al. (1992)
felbamate	95	90	5	Shumaker et al. (1990)
fenflumizole (iv)	54.3	3.8	50.5	Vinge et al. (1986)
fenofibrate	84	59	25	Weil et al. (1990)
fentiazac	85	18	67	Franklin et al. (1984)
fexofenadine	91	11	80	Molimard et al. (2004)
flecainide	91	86	5	McQuinn et al. (1984)
fluoxetine	80	65	15	Lemberger et al. (1985)
fosinopril	90	44	46	Singhvi et al. (1988)
gemopatrilat	58.6	18.7	77.3	Wait et al. (2006)
GI1817771 (ams)	92.2	0	92.2	Young et al. (2001)
girisopam	84	51	33	Tomori et al. (1992)
glipizide	102.9	86.2	16.7	Pentikainen et al. (1983)
imatinib	80	13	67	Gschwind et al. (2005)
imipenem	102	101	1	Norrby et al. (1984)
imipramine	87	65	22	Crammer et al. (1968)
indapamide	92.8	70.3	22.5	Klunk et al. (1983)
indinavir	102.1	18.7	83.4	Balani et al. (1996)
indisulam (iv)	84.5	62.6	21.9	van den Bongard et al. (2002)
indoramin	81.4	31.7	49.7	Franklin et al. (1983)
irinotecan (iv)	95.8	32.1	63.7	Slatter et al. (2000)
isomazole	97	62.6	32.4	Woodworth et al. (1991)
isotretinoin	75.8	33.8	42	Colburn et al. (1985)
isradipine	92.3	63.3	29	Tse et al. (1987a)
ketanserin	92	24	68	Meuldermans et al. (1988)
levocetirizine	98	85	13	Strolin Benedetti et al. (2001)
libenzapril	97.1	5.5	91.6	Egger et al. (1989)
linezolid	93.8	83.9	9.9	Slatter et al. (2001)
lisuride	88	45.6	42.4	Huempel et al. (1984)
lofexidine	98	94	4	Midgley et al. (1982)
losigamone	97	85	12	Peeters et al. (1998)
losoxantrone (iv)	70	9.1	60.9	Joshi (2001)
lumiracoxib	96.8	54.1	42.7	Mangold et al. (2004)
M100240	98	49.4	48.5	Shah et al. (2003)
maxipost	97	37	60	Zhang et al. (2005)
meropenem (iv)	99	99	0	Harrison et al. (1993)
metioprim (iv)	99.3	96.4	2.9	Plozza-Nottebrock et al. (1982)
mirtazepine	87	75	12	Delbressine et al. (1998)
mizolastine	100	11	89	Molimard et al. (2004)
molsidomine	95.9	92.6	3.3	Wilson et al. (1987)
montelukast	86.4	0.12	86.3	Balani et al. (1997)
moricizine	90.2	31.8	58.4	Pieniaszek et al. (1999)
nefazodone	82.8	51.6	31.2	Barbhaiya et al. (1996)
netivudine	87	78.1	8.9	Peck et al. (1995),
nevirapine	91.4	81.3	10.1	Riska et al. (1999)

(Continued)

Table 4 (Continued)

Drug	Total	Urine	Feces	Reference
nicardipine	94.8	60	34.8	Rush et al. (1986)
olanzapine	87	57	30	Kassahun et al. (1997)
omapatrilat	72	64	8	Iyer et al. (2001)
omeprazole	93.9	75.7	18.2	Regaardh et al. (1990)
orlistat	97.5	1.1	96.4	Zhi et al. (1996)
oxendolone (im)	58	37	21	Midgley et al. (1983)
palonosetron (iv)	86.4	83	3.4	Stoltz et al. (2004)
penticainide	95.9	92.9	3	Davi et al. (1986)
pentoxifylline	96.9	93.3	3	Bryce et al. (1989)
phenprocoumon	96.1	62.8	33.3	Toon et al. (1985)
phenytoin	100	65	35	Kadar et al. (1983)
posaconazole	91.1	14	76.9	Krieter et al. (2004)
pravastatin	91	20	71	Singhvi et al. (1990b)
premazepam	92.8	89.6	3.2	Vitiello et al. (1984)
propofol (iv)	90	88	1	Simons et al. (1988)
R115777 (ams)	93.5	13.7	79.8	Garner et al. (2002)
raltitrexed	42.8	28.8	14	Beale et al. (1998)
ramipril	95.2	55.9	39.3	Eckert et al. (1984)
repaglinide	98	8	90	van Heiningen et al. (1999)
remoxipride	96	89	7	Widman et al. (1993)
resveratrol	78.6	67.3	11.3	Walle et al. (2004)
rifapentine	86.8	16.6	70.2	Reith et al. (1998)
risperidone	84	70	14	Mannens et al. (1993)
ritonavir	97.6	11.3	86.3	Denissen et al. (1997)
rizatriptan	94.2	82.6	11.6	Vyas et al. (2000)
rofecoxib	85.7	71.5	14.2	Halpin et al. (2002)
rosaramicin	93.7	7	86.7	Lin et al. (1984)
rosiglitazone	83.8	62.3	21.6	Cox et al. (2000)
rosuvastatin	100.6	10.6	90	Martin et al. (2003)
Sandoz 58–112	113	108	5.1	Tse et al. (1984)
SDZ FOX 988	88.1	27.3	60.8	Lau et al. (1995)
sucralose*	92.8	14.5	78.3	Roberts et al. (2000)
tacrine	74.9	54.1	20.8	Pool et al. (1997)
tacrolimus	94.9	2.3	92.6	Moller et al. (1999)
tamoxifen	50	11.5	38.5	Fromson et al. (1973)
tazarotene	89.2	26.1	63	Attar et al. (2005)
temozolomide	39	38	0.8	Baker et al. (1999)
tesaglitazar	100	91	9	Ericsson et al. (2004)
thymoxamine	97.7	95.5	2.2	Vollmer et al. (1985)
tianeptine	81	66	15	Grislain et al. (1990)
tiaramide	97.3	91.3	6	Klunk et al. (1982)
tibolone	84.9	31.2	53.7	Vos et al. (2002)
tiopinac	95.8	93.2	2.6	Mroszczak et al. (1980)
tizanidine	76.5	55.5	21	Tse et al. (1987b)
tolcapone	97.8	57.3	40.5	Jorga et al. (1999)
tolfenamic acid	104	93	11	Pentikainen et al. (1982)
tolterodine	94	17	77	Brynne et al. (1997)
topirimate	72	71	1	Caldwell et al. (2005)
trabectedin (iv)	61.4	5.9	55.5	Beumer et al. (2005)
triamcinolone acetonide	93.7	39.5	54.1	Argenti et al. (2000)
trithiozine	103	98.6	4.4	Renwick et al. (1982)
troglitazone	88	3	85	http://www.fda.gov/cder/foi/label/1999/20720s12lbl.pdf

(Continued)

Table 4 (Continued)

Drug	Total	Urine	Feces	Reference
tropisetron	87	72	15	Fischer et al. (1992)
valaciclovir	93	46	47	Soul-Lawton et al. (1995)
valdecoxib	94.1	76.1	18	Yuan et al. (2002)
velnacrine	94.4	70.5	23.9	Turcan et al. (1993)
venlafaxine	94	92.1	1.9	Howell et al. (1993)
vesnarinone	75.8	39.8	36	Miyamoto et al. (1988)
vigabatrin	96.4	95.4	1	Durham et al. (1993)
zatebradine	92.2	48.8	43.4	Roth et al. (1993)
zetidoline	94.7	84.7	10	Assandri et al. (1985)
zileuton	96.7	94.5	2.2	Wong et al. (1995)
zofenopril	96	70	26	Singhvi et al. (1990a)
zolmitriptan	91.5	64.4	27.1	Seaber et al. (1997)
zolpidem	92.3	55.8	36.5	Durand et al. (1992)
zomipirac	96.8	95.5	1.3	Grindel et al. (1980)

*Food additive.

Table 5 Human mass balance data on drugs known to be sequestered in phospholipid.

Drug	Half-life in circulation	% Recovery	Reference
amiodarone	40 d[a]	No data available	Latini et al. 1984)
fluoxetine	15 d[b]	80	Lemberger et al. (1985)
tamoxifen	>7 d	35–65	Fromson et al. (1973)
tobramycin	96 h	100	Winslade et al. (1987)
imipramine	30 h[c]	87	Crammer et al. (1968)

[a]Half-life of amiodarone.
[b]Half-life of norfluoxetine.
[c]Half-life of desimipramine.

design, recovery of radiolabel from an amiodarone study would be expected to be low, given the very long half-life of the parent drug and its principal deethylated metabolite (Latini et al., 1984).

Binding to Specific Proteins in Tissues. Aminoglycoside-induced nephrotoxicity appears to be directly related to the concentrated accumulation and sequestration of aminoglycosides in the renal proximal tubular cells by a receptor- mediated event. The aminoglycosides are excreted rapidly into the urine without being metabolized. Recoveries of administered drug are generally close to 100% (Winslade et al., 1987). Aminoglycosides taken up by the renal proximal tubular cells remain for a considerable period, leading to renal damage such as structural change and functional impairment of plasma membrane, mitochondria, and lysosomes. The sequestration of the drugs into the kidney, and perhaps some other organs, is readily detectable in distribution studies in animals, but it is also evident in a terminal elimination phase seen in plasma and urine (Winslade et al., 1987). Megalin, an endocytic receptor expressed at the apical membrane of renal proximal tubules, is suggested to play an important role in binding and endocytosis of aminoglycosides in renal proximal tubular cells (Nagai et al., 2001). Megalin belongs to the low-density lipoprotein (LDL) receptor family and has been shown to bind Ca^{2+}; vitamin-binding proteins, such as vitamin D-binding protein and retinal-binding protein; lipoproteins, such as

apolipoprotein E and apolipoprotein H; enzymes, such as lipoprotein lipase and lysozyme; cytochrome *c*; hemoglobin; and drugs such as aminoglycosides, polymixin B, and aprotinin.

Binding to Melanin. Eumelanin is a pigment polymer of L-dopa that resides in skin, eyes, hair, and some other tissues. It is often associated with sequestration of drugs, particularly in the eye, as often highlighted by animal whole body autoradiography studies. Most basic drugs, particularly those with high lipophilicity, bind to melanin, because its polyanionic nature allows both ionic and hydrophobic interactions to occur for these types of drugs. In the vast majority of cases, melanin association, similar to the other forms of sequestration covered earlier, is without any adverse effects. It has been proposed that, for certain drugs, toxicities are associated with their accumulation in melanin: chloroquine, chlorpromazine, and thioridazine may, when used at high doses (800 mg/d) for a considerable period, lead to retinopathies. However, other reasonable mechanisms of ocular toxicity for these drugs are also possible, such as bioactivation to reactive intermediates that can result in oxidative stress (Toler, 2004; 2005) or lysosomal accumulation leading to dysfunction of this organelle (Mahon et al., 2004).

Since melanin occurs in other tissues and organs, such as the skin, it is possible that sequestration by melanin could have effects on drug half-life and recovery in a human radiolabel study. To better understand this, knowledge of the total melanin- binding capacity in the body, along with the affinity for specific drugs, would need to be known; however, a straightforward report on the amount of eumelanin in the human body is not readily available. In highly pigmented individuals, estimates of total eumelanin in skin in a 70-kg human is in the range of 450 mg (as assessed using remittance spectroscopy; Kollias and Baqer, 1986) to 1450 mg (as assessed using chemical degradation to pyrrole-2,3,5-tricarboxylic acid; Takadoro et al., 2003), whereas the quantity of eumelanin in the skin of pale individuals can be 5- to 30-fold less. *In vitro* studies have described the binding capacity of eumelanin for some drugs to be as high as a few hundred nanomoles per milligram of melanin (Larsson and Tjalve, 1979). Thus, the total drug-binding capacity of eumelanin in a highly pigmented individual and a typical single dose used in a human mass balance study are in a similar range. However, to date, there is no report of a human excretion study or even an animal study that attributed a low mass balance result to losses due to melanin binding. For example, chloroquine has one of the highest binding affinities to melanin (Larsson and Tjalve, 1979). An excretion study in the rat for chloroquine showed no difference between pigmented and albino animals (Ono et al., 2003). Similarly, no differences in the pharmacokinetics of chloroquine between Africans, Caucasians, and albino subjects have been observed (deVries et al., 1994; Walker et al., 1987), which would suggest that melanin binding is not a likely factor in mass balance with this drug. However, chloroquine is administered at high doses, and it is possible that, for low-dose drugs, factors not observed with high- dose drugs may be observed. If radioactivity is being excreted at the time of study termination and 1) the recovery is lower in highly pigmented study subjects vs. pale subjects, 2) the drug had demonstrated sequestration in melanin-containing tissues in animals, and 3) the dose given in the excretion study was relatively low (<20 mg), then the possibility that melanin binding could be contributing to the racial differences in balance should be considered. Overall, at this time, it is doubtful that melanin binding plays a role in safety (Leblanc et al., 1998), but it is not clear whether this phenomenon could have an impact on human mass balance of low-dose drugs.

Other Mechanisms of Non-Covalent Sequestration. Other examples of sequestration of drug or metabolites are shown in Table 6. With the cases of alendronate

Table 6 Human recovery data for drugs sequestered by other mechanisms.

Drug	$T_{1/2}$	% Recovery of ^{14}C in excreta	Method of sequestration	Reference
alendronate	12 yr	47	Uptake into skeleton	Cocguyt et al. (1999)
raltitrexed	11 d	43	Polyglutamated inside cells	Beale et al. (1998)
temozolomide	1.9 h	39	Metabolism to 4-amino-5-imidazole-carboxamide and incorporation into purine pool	Baker et al. (1999)
omapatrilat	9 d	72	Reversible disulfide bonds with protein	Iyer et al. (2001)
gemopatrilat	7 d	77	Reversible disulfide bonds with protein	Wait et al. (2006)
captopril	16 h	86	Reversible disulfide bonds with protein	Kripalani et al. (1980)

and raltitrexed, the sequestration is the basis of the pharmacological activity. The thiol-containing drugs represent an extreme example of sequestration and could be classed in the following section on covalent binding. Omapatrilat binds to plasma and tissue proteins via reversible disulfide bonds. Reversibility in the reaction separates it from the following compounds, which form irreversible covalent bonds via metabolites with proteins and are only recovered in a conjugated form after protein degradation. Recovery of radioactivity after 14C-omapatrilat administration to humans was 72% over a 168-h collection period, with most of the radioactivity recovered in the first 72 h post dose (Iyer et al., 2001). Beyond this period, less than 1% per d was collected. Similar observations were made for the structurally related compound gemopatrilat (Wait et al., 2006). Plasma concentrations of radioactivity showed a very slow decline (half-life 8–9 d) in line with this reason for retention. Captopril also forms similar bonds, due to its free thiol group, but the terminal half-life is shorter and recovery of radiolabel is much higher (Kripalani et al., 1980).

These examples indicate that it is the terminal half-life that influences recovery and not the actual sequestration per se or its mechanism. Many studies are terminated around criteria such as less than 1% of dose excreted per day. Often, there is an initial rapid phase, followed by a slower phase, as exemplified above by omapatrilat. Figure 2 shows how excretion of 1% per d may represent a considerable portion of the drug when the terminal phase is considered.

Covalent Binding. To understand whether mass balance recovery is likely to be altered by covalent binding, we have examined the excretion studies reported for drugs

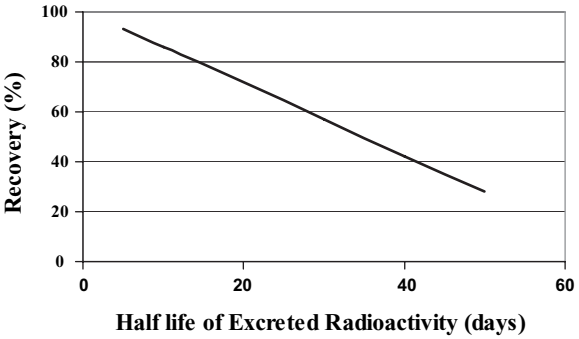

Figure 2 Relationship between total recovery and half-life of excreted radioactivity when the study cessation criterion is such that subjects are released from the study when less than 1% of the dose is excreted over a 24-h period.

Table 7 Drugs with known covalent binding interactions and their recoveries following radiolabeled drug administration in humans

Drug	% Recovery of radioactivity	Reference
acetaminophen	100[a]	Slattery et al. (1987)
bromfenac	96	Osman et al. (1998)
clopidogrel	92	Lins et al. (1999)
clozapine	79	Dain et al. (1997)
felbamate	95	Shumaker et al. (1990)
maxipost	97	Zhang et al. (2005)
mirtazepine	87	Delbressine et al. (1998)
nefazodone	71–91	Barbhaiya et al. (1996)
phenytoin	100	Kadar et al. (1983)
remoxipride	96	Widman et al. (1993)
tacrine	79/75[b]	Pool et al. (1997)
tianeptine	81	Grislain et al. (1990)
tolcapone	98	Jorga et al. (1999)
troglitazone	88	http://www.fda.gov/cder/foi/label/1999/20720s12lbl.pdf (accessed 24 March 2006)
trovafloxacin	87	Vincent et al. (1998)
vesnarinone	76	Miyamoto et al. (1988)
zileuton	97	Wong et al. (1995)
zomepirac	97	Grindel et al. (1980)

[a]Non-radiolabeled study; recovery was assessed by quantitative analysis of metabolites.
[b]Data at 10- and 40-mg doses.

known or suspected of covalent binding. A good proportion of these compounds have been withdrawn due to accompanying toxicity. What is noticeable is the good recovery in almost all cases (Table 7). Therefore, mass balance excretion studies are not reliable indicators for demonstrating whether covalent binding occurs or not. Covalent binding to tissue macromolecules or to blood proteins may comprise very small quantities of the total mass of drug administered. The precision needed to define losses of very small percentages from the total mass is not offered by the mass balance study design.

Covalent binding poses one of many possible explanations for a low recovery, but its likelihood as an explanation is fairly low. Nevertheless, a good example of this is with compound #17 (cited earlier). Metabolism-dependent covalent binding is a likely explanation for the low recovery observed in CYP2D6 extensive metabolizer subjects. Extraction recovery of radiolabeled material from plasma samples was incomplete in EM subjects and was lower for samples from later time points (Johnson et al., 2003). Such a finding can be indicative of covalent binding to plasma proteins. However, it is the low extraction recovery data from plasma for compound #17 that are more supportive of covalent binding than the low mass balance of dose in excreta.

Compliance. Of note in certain reports is the low recovery being explained by compliance of the subjects. For instance, the variable recovery of nefazodone (Barbhaiya et al., 1996) is explained by "lack of rigorous compliance with study procedures or improper homogenization of fecal samples." Rosiglitzone gave recoveries of 66–95% (Cox et al., 2000). The authors noted "two known instances of significant noncompliance," but, after exhaustive examination, they had to conclude, concerning the individual with the lowest recovery, that there was "no reason for the poor recoveries other

than the possibility of consistent non-compliance in sample collection." Tacrolimus showed highly variable recovery: 75.4 ± 12.3% after infusion and 92.6 ± 30.7% after oral administration, the authors commenting on a "marked intersubject variation in fecal excretion" (Moller et al., 1999).

Other Variables in Low Recovery. Prolonged excretion into feces represents a huge technical barrier still not yet fully mastered. Feces are not homogenous samples. This applies particularly in humans, where stool weight, times, and regularity of defecation, firmness, etc. are hugely variable, even for individuals on a diet carefully controlled by clinical study sites that conduct radiolabeled ADME studies. The problem is exacerbated by the sheer mass collected over a long period in a human study. Typical sample weight is shown in Table 3, and the total mass collected is shown for rat (5 d), dog (7 d), monkey (7 d), and human (14 d). The generally longer half-life for radioactivity seen in humans necessitates a longer study, driven by the need to achieve near baseline levels of radioactivity in excreta before release of study subjects from the clinic.

The other reasons quoted for low recovery are study and data integrity. Although not an apology for poor science, drugs with prolonged excretion pose large technical problems for sample collection and analysis procedures. In our experience, these compounds are more likely to give lower or more variable recoveries. Such studies are also the most difficult and expensive to repeat. Instead of a repeat study, better utilization of resources may be applied to examining the reasons for the prolonged excretion or presence in the circulation. Within Table 7 are two compounds that show very long plasma half-lives of radioactivity (maxipost and clopidogrel) due to reactive metabolites and covalent binding. (Note that both yielded total recoveries of greater than 90%, again indicating that, despite "significant" readily detectable covalent binding, the radioactivity recoveries are excellent and would not give any cause for concern per se.)

A typical example from our files is that of a compound under development for a psychotherapeutic indication (referred to here as "compound #23"). Two human ADME studies were run, which illustrate the aforementioned pitfalls regarding mass balance studies. [^{14}C]Compound #23 had been uneventfully examined in ADME studies in rats, dogs, and mice. When the first human study was done with the same labeled material, at a dose of 10 mg/100 μCi in four subjects, low and erratic recovery was obtained (60.8 ± 22.8%) with sampling of excreta out to 12 d. This generated concern, with speculation on underlying reasons ranging from artifactual technical flaws in sample collection to authentic phenomena such as sequestration in tissues (covalent and non-covalent) and enterohepatic recirculation. A second study was conducted in six more subjects to verify or refute the findings, with even greater attention paid to sample collection and radiometric analysis and a more extended sample collection period. Although nominally better recovery was obtained (78.9 ± 5.6%), the recovery was still low. It should be noted that plasma pharmacokinetics for both the parent drug and total radioactivity were the same in both studies, with $t_{1/2}$ values of 32.1 and 31.5 h for the parent drug and 114 and 88.4 h for total radioactivity.

These samples were analyzed for metabolite profile in plasma and excreta, and the results were remarkably similar, despite the increase in recovery (Table 8). It should be noted that samples were pooled and processed using identical criteria regarding the percentage of total included in the pools in the two studies and gaining >87% recovery through the sample work-up procedures. This case illustrates the fact that a simple repetition of a mass balance study yields no additional information and that mass balance, as

Table 8 Comparison of two human ADME studies for [^{14}C]compound #23[b.]

	Urine		Feces		Total	
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Recovery (%, ± SD)	15.3 ± 4.7	21.0 ± 1.9	45.4 ± 20.8	57.9 ± 4.2	60.8 ± 22.8	78.9 ± 5.6
	Urine (% of dose)		Feces (% of dose)		Plasma (% of total)	
Metabolites:	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
M1B	2.9	5.1	–	–	–	–
M2	–	–	}31[a]	34	–	–
M3	–	–		6.2	–	–
Parent drug	3.3	5.0	3.5	5.5	}36[a]	20
M9	–	–	–	–		3.8
M10	7.1	7.8	}4.2[a]	}5.6[a]	}53[a]	5.5
M10a	–	–				65

[a]Not resolved on radiometric HPLC.
[b]In Study 1, N = 4; in Study 2, N = 6. All subjects were healthy male subjects.

collected in human excretion studies, may not be a very meaningful parameter to interpret. These data, like others in our file, strongly support the idea that overall recovery is not the criterion by which to judge human radiolabeled studies.

SUMMARY AND RECOMMENDATIONS

From this analysis, we recommend the following with regard to execution and interpretation of animal and human radiolabel mass balance studies. These suggestions bear in mind that the primary objective of human mass balance studies is to obtain excretory and circulatory samples for use in determining the profile of metabolites and comparison across species. Absolute recovery in humans should not be used as a major decision criterion for whether a radiolabeled study has met its objectives. Instead, the study should be seen as an integral part of drug development answering four principal questions: 1) Is the proposed clearance mechanism sufficiently supported by the identities of the drug-related materials in excreta so as to provide a complete understanding of clearance and potential contributors to interpatient variability and drug-drug interactions? 2) What are the drug-related entities present in circulation that are the active principals contributing to primary and secondary pharmacology? 3) Are there findings (low extraction recovery of radiolabel from plasma, metabolite structures indicative of chemically reactive intermediates) that suggest potential safety issues requiring further risk assessment? 4) Do questions 2 and 3 have appropriate preclinical support in terms of pharmacology, safety pharmacology, and toxicology?

ABBREVIATIONS

ADME absorption, distribution, metabolism, and elimination
EM extensive metabolizer
PM poor metabolizer

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