EXPERT OPINION

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Microdosing and drug development: past, present and future

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Introduction: Microdosing is an approach to early drug development where exploratory pharmacokinetic data are acquired in humans using inherently safe sub-pharmacologic doses of drug. The first publication of microdose data was 10 years ago and this review comprehensively explores the microdose concept from conception, over the past decade, up until the current date.
Areas covered: The authors define and distinguish the concept of microdosing from similar approaches. The authors review the ability of microdosing to provide exploratory pharmacokinetics (concentration-time data) but exclude microdosing using positron emission tomography. The article provides a comprehensive review of data within the peer-reviewed literature as well as the latest applications and a look into the future, towards where microdosing may be headed.
Expert opinion: Evidence so far suggests that microdosing may be a better predictive tool of human pharmacokinetics than alternative methods and combination with physiologically based modelling may lead to much more reliable predictions in the future. The concept has also been applied to drug-drug interactions, polymorphism and assessing drug concentrations over time at its site of action. Microdosing may yet have more to offer in unanticipated directions and provide benefits that have not been fully realised to date.

Keywords: dose linearity, microdosing, pharmacokinetic prediction, pharmacokinetics, Phase 0

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1. Introduction

The concept of microdosing first appeared in the late 1990s as a method of assessing human pharmacokinetics prior to full Phase I clinical trials [1] and the first data appeared in the literature in 2003 [2]. Whilst other methods of pharmacokinetic prediction rely on extrapolation of data from *in vitro, in silico* or animal models, microdosing obtains data directly from the target species – that is human. Based upon the adage that "human is the best model for human" microdosing offers an inherently safe way of obtaining exploratory pharmacokinetic data from humans, primarily to enable the elimination of drugs from entering costly full development programs at the earliest possible stage in the clinical studies. This is the theory at least but how well microdosing has performed against other methods of pharmacokinetic prediction is partly the subject of this review.

In a human microdose study a sub-pharmacologically active dose of drug is administered and samples (typically plasma) are collected and analysed for parent drug or metabolites. Since the very small doses administered are of low toxicological risk, regulatory agencies allow a microdose to be administered to human subjects based upon a reduced safety package compared to that required for a full Phase I clinical trial [3] (that is with no genotoxicology investigations and a single-dose rodent toxicology study). The cost of a microdose study, including the safety toxicology assessments, is considerably less than a Phase I study and could be

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Article highlights.

- The definition of a microdose should be confined to situations where a maximum of 1% of the pharmacologic dose or 100 µg in total is administered to human subjects and they are not exposed to any higher level of drug by any other route of administration in the same study.
- There are currently a total 35 compounds where microdose and therapeutic dose data have been compared (oral, intravenous, human and animal). Of the 35 compounds (human and animal), 27 tested orally showed scalable pharmacokinetics between a microdose and a therapeutic dose (79%) and 100% of those tested intravenously.
- Microdosing shows great promise but care has to be taken when comparing microdosing to alternative methods as the microdose database is limited and contains mostly BDDCS class-1 drugs.
- Microdosing has also been applied to the study of drug-drug interactions, measuring drug concentrations at the site of action, and metabolic profiling.
- Combination of microdosing with physiologically based models and similar modelling methods may lead to improved pharmacokinetic scalability.
- Microdosing is an attractive approach for the study of new and existing drugs in vulnerable populations (children, pregnant women, elderly, hepatically and renally impaired), who are routinely excluded from clinical trials due to safety concerns.
- Microdose stakeholders (regulatory, industry, academia) should collaborate to systematically validate microdosing, including its economics, as a drug development approach.

This box summarises key points contained in the article.

conducted in a relatively short period of time (approximately 6 months) [4]. The data from a microdose study are, however, exploratory and there are questions regarding how well the data from a sub-pharmacologically active dose might scale to the higher doses relevant to clinical use (which is discussed in more detail below).

Despite some accounts that poor pharmacokinetics is no longer a major contributor to drug attrition [5], pharmaceutical companies still invest considerable effort in early human pharmacokinetic prediction [6]. Because human microdosing studies are performed prior to Phase I, they have become known as Phase 0 [7] studies (although the regulatory authorities never adopted the terminology and prefer to call them exploratory clinical trials [8]).

Microdosing has caused a lot of debate, and opinion can be rather polarised [9,10] with some commentators believing that it has little function in drug development, whilst others seeing greater benefit. The authors openly declare that they do see benefit in the technique, in its widest sense and so this review leans in this direction. Nevertheless, we have attempted to balance the arguments as far as possible, within the confines of the space available in a review such as this. The adoption of microdosing, as with any similar technique, will largely be driven by the economics. The argument for microdosing is that if it reduces the frequency that drugs enter full clinical development that otherwise would have been found to exhibit poor pharmacokinetics, then significant overall cost savings will result. Published examination of the economics is very limited however [11], and so the true cost-savings (or indeed cost burden) of microdosing is unknown. For this reason, the economics of microdosing is not discussed here but there is a real need for an independent and thorough study to understand what the economic benefits or burdens might be.

1.2 Microdosing and the regulatory guidelines

The first paper to directly address the concept of microdosing was published 10 years ago [2] but the maximum dose that defined a microdose was not proposed at that time. The regulatory authorities followed with a position paper from the European Medicines Agency 2004 [12], guidelines from the FDA in 2006 [13], Japan in 2008 [14] and now the current definitive international guideline in 2009 [8]. A microdose is defined in all of these regulatory documents as being a dose of drug that is 1% of the pharmacologically active dose, up to a maximum of 100 µg. The latest ICH M3 guideline [8], now universally accepted, allows a microdose to be administered to human subjects based on a single-dose toxicity study (usually in the rat), followed by 14 days observation, using the intended route of administration (or via the intravenous route), plus some *in vitro* target receptor data. The dose administered in the toxicity study should be 1000 times the human microdose. The safety data thus obtained can be used to justify the administration of a maximum of 100 µg of drug, either as a single dose or as a series of divided doses to humans (for example, a two-way crossover study of 50 µg each). The ICH M3 regulatory guideline offers other possible scenarios such as the administration of up to 500 µg in a maximum of five different administrations (a maximum of 100 µg each with a period of six half-lives between doses), based on a 7-day repeat toxicity study [15] but this review will focus on the situation where the total dose is limited to 100 µg.

This review covers microdosing used to acquire traditional concentration-time pharmacokinetic data as opposed to imaging techniques such as positron emission tomography (PET). PET has been used with microdosing studies [16], and indeed in one case, traditional concentration-time pharmacokinetic data were acquired alongside PET images [17]. PET human microdose studies are, however, outside of the current review and the reader is referred to other publications in this respect [18,19].

2. Definitions

The low dose administered in a human microdose study will inevitably lead to low plasma-drug concentrations and so sensitive analytical technologies are necessary in order to make the requisite measurements over an appropriate time. For this reason, particularly for the first microdose studies conducted, the

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drug was labelled with ^{14}C and accelerator mass spectrometry (AMS) was used as a very sensitive analytical technique, capable of detecting drug concentrations in the femtogram to attogram (10^{-15} – 10^{-18} g) range [20,21]. The application of AMS to microdosing, however, has led to some confusion and it is worth pausing for a moment to clarify the terminology. Because of its initial association, microdosing is sometimes seen as synonymous with AMS. This is, however, incorrect. Not all studies using AMS are microdose studies and not all microdose studies utilise AMS. AMS has, for example, been used in human absorption, distribution metabolism and excretion (ADME) studies for regulatory submission where a therapeutic dose is administered containing a very small amount of ^{14}C-compound (typically equivalent to 100 – 500 nCi) [22]. These types of study have been described as ADME studies using a 'microdose' of ^{14}C-drug [23] but such terminology is potentially misleading. The proportion of ^{14}C-compound may be 100 µg or less but the total dose administered is at, or close to, that intended to be used for therapeutic effect. In a true microdose study the human subjects are only exposed to 1% of the pharmacologic dose or a maximum of 100 µg, whichever is lower, irrespective of whether the drug is ^{14}C-labelled or not [24].

Another type of study involving AMS that is often confused with microdosing is an absolute bioavailability intravenous tracer study [25]. In this type of study human subjects are administered a therapeutic dose of drug by an extravascular route (typically oral) along with a concomitant tracer intravenous administration of ^{14}C-labelled drug [25]. The pharmacokinetics of the oral dose is followed by measuring the concentration of non-labelled drug in plasma over time (typically with liquid chromatography-mass spectrometry (LC-MS)) and the intravenous pharmacokinetics is followed by measuring the ^{14}C-drug with LC and AMS. (The same principle can be applied to stable isotope labelling which was first developed in the 1970s [26].) The ^{14}C isotopic label in the intravenously administered drug allows the pharmacokinetics of the intravenous dose to be distinguished from that of the oral dose, thereby obtaining both the oral and intravenous pharmacokinetics from the same subject in a single dosing. The intravenous dose is sometimes referred to as a 'microdose', for example [27,28], but this is again misleading as the underlying pharmacokinetics of the tracer intravenous dose is very different to a true microdose where the human subjects are only systemically exposed to a maximum of 100 µg irrespective of the route of administration. In the intravenous tracer study, there is no question of extrapolating the pharmacokinetics from a low 'microdose' to a therapeutic dose as the systemic concentrations of drug are mostly driven by the absorbed therapeutic dose given orally. In fact the method, first developed in the 1970s, was primarily aimed at situations where the value of absolute oral bioavailability obtained from the traditional intravenous-oral crossover design was flawed by non-equivalent clearance when plasma concentrations attained from the oral and intravenous doses were significantly different [25].

In a true microdose study, the drug may be isotopically labelled but it is not an absolute necessity (see Section 3). In a tracer study, the 'tracer intravenous dose' has to be isotopically labelled to distinguish it from the extravascular dose. The confusion with microdosing and tracer dosing in this case arises from the description of the intravenous dose being < 100 µg and it is perhaps unfortunate that even the ICH M3 guideline confuses this terminology [8]. An example of where the terminology has caused confusion can be seen with the account published by Boddy *et al.* [29] where oral doses of 100 mg (13.6 kBq) ^{14}C-imatinib were administered to cancer patients with subsequent plasma samples analysed by AMS. The study has been described incorrectly as a microdose Phase 0 study, presumably because of the association with AMS [30]. In another example, it was claimed that a microdose of erythromycin exhibited linear pharmacokinetics when given by the intravenous route [9]. In fact no comparison can be made in that study as erythromycin was administered as a ^{14}C intravenous tracer dose along with a therapeutic oral non-labelled dose, not as a microdose alone [31]. A similar error was made when the pharmacokinetics of nelfinavir [9] was declared as non-linear between a microdose and a therapeutic dose, whereas the drug was administered as an intravenous tracer, not a microdose [32]. There are numerous other examples that can be cited where confusion has arisen between a true microdose study and a tracer study [33]. Such confusion is understandable given the ambiguous use of terminology in the literature. Other commentators have also pointed out the confusion in the terminology [10] and so the current authors would therefore stress the difference between a microdose study and a tracer study (sometimes referred to as a micro-tracer study) and hope that the literature of the future will become more precise. It is also worth pointing out that although the term 'microdose' in its present context is only about 10 years old, the use of tracer was first coined by Hevesy (Nobel prize in 1943) where he described "the use of a radioactive isotope as an indicator or *tracer* to mark its inseparable non-radioactive element travelled by tracking the radioactivity" [34]. Tracer studies, therefore, have a very long and established pedigree.

3. Analytical methods associated with microdosing

A microdose is typically administered to four to six healthy male subjects (although female subjects have been used [31]) followed by the collection of plasma and sometimes excreta or biopsy samples over time. The samples are analysed for target analytes such as parent drug or metabolites to ascertain the pharmacokinetic profile. The low doses administered obviously demand the use of highly sensitive analytical techniques in order to measure the plasma drug concentrations over sufficient time. The majority of human microdose studies reported in the literature have been conducted using ^{14}C-labelled drug and analysis conducted using the ultrasensitive isotope-ratio

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technique of AMS although studies have also been performed using non-labelled drug and sensitive LC-MS [35,36] and the relative merits of both techniques have been previously discussed [16]. The choice of analytical technique is largely driven by the expected plasma-drug concentrations and the limit of quantification of the analytical method. The sensitivity of LC-MS assay is highly compound dependent, whilst the sensitivity of an AMS assay depends entirely upon the specific radioactivity of the analyte and is independent of structure and matrix effects. It has been estimated that LC-MS assays would have been adequate for microdosing studies for over 70% of the best-selling drugs worldwide, assuming that a 100 µg dose was administered [36], although in practice at the time a microdose study would have been conducted the expected human plasma concentrations may not have been known with any certainty. In addition, care has to be taken when comparing the sensitivity of an LC-MS assay developed over long periods of time to one developed early in the drug development process, such as would be the case when a microdose study is performed. As a general guide a drug with a volume of distribution of 300 L administered intravenously to human volunteers as a 100 µg dose will exhibit a plasma concentration of approximately 10 pg/mL after 5 half-lives. Drugs dosed at 100 µg therefore with expected volumes of distribution greater than 300 L or orally administered drugs with limited bioavailability may therefore require assays with greater than 10 pg/mL sensitivity [37]. Some LC-MS assays can achieve these levels of sensitivity but by no means all [16]. Of course, if the microdose is < 100 µg, more sensitive analytical assays are required. If AMS is used as the analytical method, then the drug has to be isotopically labelled with ^{14}C. Given that the microdose study is performed at a relatively early stage of drug development, the likelihood is that a ^{14}C-drug had not been synthesised previously. This means, therefore, that a ^{14}C-drug synthesis is likely to be necessary for the microdose study, which adds cost and time. On the other hand, inclusion of ^{14}C in the drug can have advantages in terms of determining the metabolic profile of the drug, albeit at a low dose [38] and this is discussed further below (Section 4.2.5).

Despite some limitations on the assay sensitivity, there is a growing use of LC-MS in microdosing as it can offer certain advantages. For example, the administration of mixtures of compounds as a microdose cassette has the advantage that several candidate drugs could be tested in a single dosing. This approach has been investigated using LC-MS [39] and LC and AMS [40]. Unlike LC-MS, AMS does not reveal any structural information and cannot resolve compounds based on molecular weight. Resolution of compounds for AMS analysis relies entirely upon the chromatographic separation, which may demand, for example, two-dimensional HPLC, to be confident of complete separation of a target analyte from a mixture where other unknown interfering compounds could be present [40]. In addition, AMS analysis involves a degree of sample processing to form graphite after chromatographic separation, which also demands the accurate addition of an isotopic dilutor [41]. This coupled to the limited number of suitable AMS instruments, with GlaxoSmithKline being the only pharmaceutical company currently with its own AMS facility [42] and LC-MS can often be a winning pragmatic choice.

4. The utility of microdosing

The original concept of microdosing was to provide pharmacokinetic data as early as possible in humans, which could be used to assess the pharmacokinetics at higher therapeutic doses. The technique has moved on from there insomuch as it has been extended to assess the magnitude of potential drug-drug interactions, early indications of the metabolic profile of the drug as well as in the study of polymorphisms and transporters. In addition, microdosing can be used to assess if the drug is reaching its intended target tissues in human subjects. Each of these applications of microdosing, along with the literature, will be explored below.

4.1 Exploratory pharmacokinetic data

The literature-reporting studies where microdose pharmacokinetics can be compared to those observed at the therapeutic dose are a mixture of study designs, species and analytical methods. The microdose literature is also limited because of confidentiality issues at the early stage of development (for example [43]). In addition, for drugs in development, microdose studies can be performed before the drug might be administered at therapeutic doses and so it can be some time before the therapeutic data are published. There are therefore a number of accounts of microdosing in the literature where a therapeutic dose of drug has not yet been given [35,44,45]. A comprehensive summary of the peer-reviewed literature comparing human microdose with therapeutic dose pharmacokinetics is shown in **Table 1**.

Some testing of the microdose concept has also been conducted in animal models and these data are summarised in **Table 2**. The last review by one of the current authors (GL) that appeared in this journal was in 2008, where 18 drugs were reported [46]. In the current review, 35 separate drugs have now been examined (total of oral, intravenous, human and animal data). A further breakdown of the data is provided in **Table 3**, showing the number of human microdose studies against each Biopharmaceutics Drug Disposition Classification System (BDDCS) class that showed linear or non-linear pharmacokinetics for oral and intravenous dosing. Taking all the data into account, 79% of drugs so far tested between a microdose and a therapeutic dose have demonstrated scalable pharmacokinetics within a factor of two-fold for any given parameter. The two-fold factor is discussed further below, but if this is widened to three-fold, then 91% of drugs so far tested are within this range. For oral administration, approximately 62% of the drugs tested showed pharmacokinetics scalable within a factor of 2 and 85% within a three-fold range. It should be noted that the three drugs

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Table 1. Drugs reported in comparing the pharmacokinetics at a microdose with that observed at a therapeutic dose in humans.

Drug	BDDCS*	Dose range‡	PK scalability. $t_{½}$ in h, AUC (as 0 – inf) in ng·h/mL, Cl in L/h, V in L			Comments	Citation
			PK parameter (microdose)§	PK parameter (therapeutic dose)§ $AUC_{(norm)} = AUC_{0-inf}$ normalised to microdose (i.e., AUC divided by dose range)	Linear within factor of 2?		
Oral route							
Warfarin	2	50	$t_{½}$ = 274 AUC = 157	$t_{½}$ = 48.6 AUC = 16,152 $AUC_{(norm)}$ = 323.0 Literature (5 mg) $t_{½}$ = 37.0	No. Shape of the PK curve poorly predicted by the microdose		Microdose versus therapeutic dose [31] Therapeutic dose Literature [76]
ZK253	Unknown	500	$t_{½}$ = ND AUC = ND F (%) = 0.16	$t_{½}$ = 0.5 AUC = 4.4 F (%) ≤ 1%	Yes	F for microdose a maximum value based on AUC estimate from C_{max}	[31]
Midazolam	1	75	$t_{½}$ = 0.56 AUC = 0.89 F (%) = 22.8	$t_{½}$ = 0.63 AUC = 81.8 $AUC_{(norm)}$ = 0.10 F (%) = 22.1 Literature (7.5 mg) $t_{½}$ = 1.9 F (%) = 44	Yes. Shape of PK curve well predicted.		Microdose versus therapeutic dose [31] Literature therapeutic dose [77]
Fexofenadine	3	1200	AUC = 2.77 F (%) = 41	AUC = 2210 $AUC_{(norm)}$ = 1.84 F (%) = 30	Yes. Shape of PK curve well predicted		Microdose versus therapeutic dose [78,79]
Clarithromycin	3	2500	$t_{½}$ = 4.0 AUC = 0.99 F (%) = 22	$t_{½}$ = 3.4 AUC = 4905 $AUC_{(norm)}$ = 1.96 F (%) = 39 Literature (100 – 1200 mg) $t_{½}$ = 2.8	Yes (just within two-fold). Shape of PK curve well predicted		Microdose versus therapeutic dose [48] Literature therapeutic dose [80]
Sumatriptan	1	500	$t_{½}$ = 1.9 AUC = 0.44 F (%) = 7.6	$t_{½}$ = 1.4 AUC = 76 $AUC_{(norm)}$ = 0.15 F (%) = 20 Literature (50 mg) $t_{½}$ = 1.6 F (%) = 14.1	$t_{½}$ predicted but F (%) > two-fold difference. Shape of PK curves predicted reasonably well		Microdose versus therapeutic dose [48] Literature therapeutic dose [81]

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Table 1. Drugs reported in comparing the pharmacokinetics at a microdose with that observed at a therapeutic dose in humans (continued).

Drug	BDDCS*	Dose range‡	PK scalability. $t_{½}$ in h, AUC (as 0 – inf) in ng·h/mL, Cl in L/h, V in L			Comments	Citation
			PK parameter (microdose)§	PK parameter (therapeutic dose)§ $AUC_{(norm)} = AUC_{0-inf}$ normalised to microdose (i.e., AUC divided by dose range)	Linear within factor of 2?		
Propafenone	2	1500	$t_{½}$ = 3.8 AUC = 0.12 F (%) = 5.8	$t_{½}$ = 2.6 AUC = 399 $AUC_{(norm)}$ = 0.26 F (%) = 13.0 Literature (150 mg) $t_{½}$ = 4 h F (%) = 12.7	F just outside of two-fold difference		Microdose versus therapeutic dose [48] Literature therapeutic dose [82]
Paracetamol (acetaminophen)	1	10,000 – 15,000	$t_{½}$ = 5.8 F (%) = 88	Literature (1000 mg) $t_{½}$ = 2.6 F (%) = 90	Yes. $t_{½}$ appears to over-predict (although within two-fold range) but reported values vary	Microdose data compared to literature therapeutic dose data only	Microdose [48] Literature therapeutic dose [83]
Phenobarbital	1	2400	$t_{½}$ = 108	Literature (240 mg) $t_{½}$ = 98	Yes	Microdose data compared to literature therapeutic dose data only	Microdose [48] Literature therapeutic dose [84]
Diphenhydramine	1	500	$t_{½}$ = 12 AUC = 1.52 F (%) = 34	$t_{½}$ = 4.3 – 9.2 AUC = 549 $AUC_{(norm)}$ = 1.1 F (%) = 35 – 72	Yes	Microdose data compared to literature therapeutic dose data only	Microdose and literature data for therapeutic dose [85]
IDX899	Unknown	1000	$t_{½}$ = 4.4 AUC = 7.6 F (%) = 61	$t_{½}$ = 6.8 (fasted) AUC = 15800 $AUC_{(norm)}$ = 15.8	Yes		Microdose [38] Therapeutic dose [86]
α_{1A} – adrenoceptor antagonist	Unknown	100	$t_{½}$ = 40	$t_{½}$ = 40	Yes		[2]
Nicardipine	1	200			Yes	PK parameters not reported but comparisons of metabolic profiles were similar	[87]
ZDV (zidovudine)	1	3000	$t_{½\ plasma}$ = 4.5 $t_{½\ PBMC}$ = 6.6 $t_{½\ CD4+}$ = 4.8	$t_{½\ plasma}$ = 4.5 $t_{½\ PBMC}$ = 6.3 $t_{½\ CD4+}$ = 8.2	Yes. See note 4	Intracellular concentrations of ZDP-phosphate measured	[65-67]

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Table 1. Drugs reported in comparing the pharmacokinetics at a microdose with that observed at a therapeutic dose in humans (continued).

Drug	BDDCS*	Dose range‡	PK scalability. $t_{½}$ in h, AUC (as 0 – inf) in ng·h/mL, Cl in L/h, V in L			Comments	Citation
			PK parameter (microdose)§	PK parameter (therapeutic dose)§ $AUC_{(norm)} = AUC_{0-inf}$ normalised to microdose (i.e., AUC divided by dose range)	Linear within factor of 2?		
Tenofovir	3	3000	$t_{½\ plasma} = 14.1$ $t_{½\ PBMC} = 159$ $t_{½\ CD4+} = 67.2$	$t_{½\ plasma} = 21.4$ $t_{½\ PBMC} = 63.8$ $t_{½\ CD4+} = 99.8$	Yes	Intracellular concentrations of tenofivir-phosphate measured	[66]
Caffeine	1	2500	$t_{½} = 4.13$	$t_{½} = 4.9$	Yes	Microdose data compared to literature	Microdose [40] literature [88]
Tolbutamide	2	1250	$t_{½} = 8.13$	$t_{½} = 7.7$	Yes	Microdose data compared to literature	Microdose [39] literature [89]
Telmisartan	2	800			No. Differences in shape of parent drug and formation of glucuronic acid metabolite	Elimination phase could not be measured in microdose and so only shape of absorption phase compared	[90]
Atenolol	3	500	$t_{½} = 4.5$ AUC = 88.8	$t_{½} = 4.1$ AUC = 3636 $AUC_{(norm)} = 72.7$	Yes. Shape of PK curve well predicted		[91]
Enalapril	1	100	$t_{½} = 12.1$ AUC = 13.0	$t_{½} = 11.6$ AUC = 1200 $AUC_{(norm)} = 12.0$	Yes. Shape of PK curve well predicted		[91]
Losartan	2	500	$t_{½} = 3.3$ AUC = 3.6	$t_{½} = 3.4$ AUC = 1707 $AUC_{(norm)} = 3.4$	Yes. Shape of PK curve well predicted		[91]
Metformin	3	2500	AUC = 2.13	AUC = 5600 $AUC_{(norm)} = 2.24$	Yes. Shape of PK curve well predicted		[92]
Raltegravir	2	10,000			Yes. Shapes of curves scaled well		[37]
Celiprolol	3	2666.6	$t_{½} = 13.4$ AUC = 0.087	$t_{½} = 6.1$ AUC = 1294 $AUC_{(norm)} = 0.48$	No. Shape of curve poorly predicted		[60]
Quinidine	1	100	$t_{½} = 5.1$ AUC = 0.813	$t_{½} = 5.2$ AUC = 148 $AUC_{(norm)} = 1.5$	Yes (over 100-fold dose-range). $t_{½}$ linear over 1000-fold dose range. AUC linear over 100-fold dose range	Microdose versus therapeutic dose measuring parent and metabolites. Parent data only shown	[93]
		1000	$t_{½} = 5.1$ AUC = 0.813	$t_{½} = 5.6$ AUC = 2080 $AUC_{(norm)} = 2.1$			

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Table 1. Drugs reported in comparing the pharmacokinetics at a microdose with that observed at a therapeutic dose in humans (continued).

Drug	BDDCS*	Dose range‡	PK scalability. $t_{½}$ in h, AUC (as 0 – inf) in ng·h/mL, Cl in L/h, V in L			Comments	Citation
			PK parameter (microdose)§	PK parameter (therapeutic dose)§ $AUC_{(norm)} = AUC_{0-inf}$ normalised to microdose (i.e., AUC divided by dose range)	Linear within factor of 2?		
Intravenous route							
Diazepam	1	100	CL = 1.38 V = 90	CL = 1.30 V = 123 Literature (10 mg) CL = 1.6 V = 77	Yes	Therapeutic IV PK calculated from IV dose of 10 mg in crossover study with 0.1 mg IV microdose	Microdose versus therapeutic dose [31] Literature therapeutic dose [94]
ZK253	Unknown	See comments column	CL = 9.29 V = 1207	CL = 14.8 V = 1201	Yes	Therapeutic IV PK calculated from IV tracer dose of 0.1 mg over 50 mg oral dose in crossover study	[31]
Midazolam	1	See comments column	CL = 21.2 V = 145	CL = 20.4 V = 75.1 Literature (5 mg) CL = 22.7 V = 77	Yes	Therapeutic IV PK calculated from IV tracer dose of 0.1 mg over 7.5 mg oral dose	Microdose [31] Literature therapeutic dose [77]
Fexofenadine	3	See comments column	CL = 13 V = 116	CL = 16 V = 114	Yes	Therapeutic IV PK calculated from IV tracer dose of 0.1 mg over 120 mg oral dose. Fexofenadine not previously administered as IV and therefore no literature values	[78]
Clarithromycin	3	See comments column	CL = 23 V = 136	CL = 21 V = 136 Literature (250 mg) CL = 31 V = 125	Yes	Therapeutic IV PK calculated from IV tracer dose of 0.1 mg over 250 mg oral dose	Microdose versus therapeutic dose [48] Literature therapeutic dose [80]
Sumatriptan	1	See comments column	CL = 46 V = 397	CL = 50 V = 426 Literature (3 mg) CL = 70 V = 170	Yes. Differences between microdose and literature but in the crossover study in the same subjects the PK was scalable	Therapeutic IV PK calculated from IV tracer dose of 0.1 mg over 50 mg oral dose	Microdose versus therapeutic dose [48] Literature therapeutic dose [81]

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Table 1. Drugs reported in comparing the pharmacokinetics at a microdose with that observed at a therapeutic dose in humans (continued).

Drug	BDDCS*	Dose range‡	PK scalability. $t_{1/2}$ in h, AUC (as 0 – inf) in ng·h/mL, Cl in L/h, V in L			Comments	Citation
			PK parameter (microdose)§	PK parameter (therapeutic dose)§ $AUC_{(norm)} = AUC_{0-inf}$ normalised to microdose (i.e., AUC divided by dose range)	Linear within factor of 2?		
Propafenone	2	See comments column	CL = 49 V = 273	CL = 44 V = 214 Literature (35 – 70 mg) CL = 61.5 V = 248	Yes	Therapeutic IV PK calculated from IV tracer dose of 0.1 mg over 150 mg oral dose	Microdose versus therapeutic dose [48] Literature therapeutic dose [82]
Paracetamol (acetaminophen)	1	See comments column	CL = 19 V = 123	CL = 19.7 V = 66.5	Yes	Microdose data compared to literature therapeutic dose data only	Microdose [48] Literature therapeutic dose [83]
Diphenhydramine	1		CL = 24.7 V = 302	Literature CL = 26 V = 315	Yes		Microdose [85] Literature data [95]
IDX899	Unknown		CL = 8.1 V = 76	CL = 7.1 V = 66.6	Yes	Calculated from CL/F and V/F	Microdose [38] Therapeutic dose [86]
Raltegravir	2	10,000			Yes. Shapes of curves scaled well		[37]
R-Verapamil S-Verapamil	1	 See comments column	CL = 61.0 V = 528.2 CL = 89.7 V = 912.9	CL = 46.9 V = 465.7 CL = 78.2 V = 789.0	Yes	Therapeutic IV PK calculated from IV tracer dose of 0.05 mg over 80 mg oral dose. Combined AMS/PET study	[17]

All data are from the peer-reviewed literature.

*The BDDCS class system is used as described by Benet *et al.* [49].

‡The dose range is given between a microdose and a therapeutic dose in the study cited or for a typical therapeutic dose if compared to the literature (see comment column).

§Summarised mean parameters.

¶Data for zidovudine were ambiguous in that one publication reported scalable pharmacokinetics in PBMCs [65], whilst the other reported non-linear pharmacokinetics [66]. Since the plasma pharmacokinetics for both papers reported saleable pharmacokinetics, zidovudine has been included with those drugs where microdosing was predictive within a factor of 2.

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Table 2. Drugs reported in the peer-reviewed literature comparing the pharmacokinetics at a microdose with that observed at a therapeutic dose in non-human species.

Drug	BDDCS*	Dose range‡ and species	PK scalability. $t_{½}$ in h, AUC (as 0-inf) in ng h/mL, Cl in L/h, V in L			Comments	Citation
			PK parameter (microdose)§	PK parameter (therapeutic dose)§ $AUC_{(norm)} = AUC_{0\text{-}inf}$ normalised to microdose (i.e., AUC divided by dose range)	Linear within factor of 2?		
Intravenous route							
PHA-XXX	Unknown	20,000 Monkey	AUC = 0.88	AUC = 17,675 $AUC_{(norm)}$ = 0.88	Yes	Intragastric dose	[96]
Antipyrine	1	1000 Rat	$t_{½}$ = 1.45 AUC = 3.63	$t_{½}$ = 1.6 AUC = 3790 $AUC_{(norm)}$ = 3.79	Yes		[97]
Carbamazepine	2	1000 Rat	$t_{½}$ = 1.62 AUC = 0.79	$t_{½}$ = 1.16 AUC = 809 $AUC_{(norm)}$ = 0.81	Yes		[97]
Atenolol	3	1000 Rat	$t_{½}$ = 3.16 AUC = 0.47	$t_{½}$ = 2.49 AUC = 351 $AUC_{(norm)}$ = 0.35	Yes		[97]
Digoxin	3	1000 Rat	$t_{½}$ = 2.39 AUC = 0.44	$t_{½}$ = 2.22 AUC = 830 $AUC_{(norm)}$ = 0.83	Yes. AUC just within two-fold difference		[97]
Metoprolol	1	1000 Rat	$t_{½}$ = ND AUC¶ = ND	$t_{½}$ = 0.9 AUC = 1.18	No conclusion. See text		[97]
Fluconazole	3	5000 Rat	$t_{½}$ = 0.7 AUC¶ = 51.6	$t_{½}$ = 2.2 AUC¶ = 158691 $AUC_{(norm)}$¶ = 31.7	Yes ($t_{½}$ marginally outside two-fold but AUC well within the criterion		[98]
Tolbutamide	2	1000 Rat	$t_{½}$ = 0.7 AUC¶ = 575	$t_{½}$ = 1 AUC¶ = 269902 $AUC_{(norm)}$¶ = 267	Yes		[98]
MLNX	Unknown	1000 Rat	$t_{½}$ = 0.5 AUC¶ = 12.8	$t_{½}$ = 0.5 AUC¶ = 48067 $AUC_{(norm)}$¶ = 48	No. $t_{½}$ predicted but AUC outside two-fold		[98]
7-Deaza-2'-C-methyl-adenosine	1	50 Dog	AUC = 66	AUC = 3016 $AUC_{(norm)}$ = 60.3	Yes		[11]
Animal studies intravenous route							
7-Deaza-2'-C-methyl-adenosine		20 Dog	$t_{½}$ α = 0.13 $t_{½}$ β = 0.71 $t_{½}$ χ = 22.7 AUC = 78.4	$t_{½}$ α = 0.1 $t_{½}$ β = 0.8 $t_{½}$ χ = 17.5 AUC = 1166 $AUC_{(norm)}$ = 58.3	Yes		[99]

*The BDDCS class system is used as described by Benet et al. [50].
‡The dose range is given between a microdose and a therapeutic dose in the study cited or for a typical therapeutic dose if compared to the literature (see comment column).
§Summarised mean parameters.
¶AUC were reported in units of nM/h.

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Table 3. Summary of microdose outcomes for human studies categorised against BDDCS class.

BDDCS class	PK scalability within two-fold	PK scalability greater than two-fold
Oral administration		
1	Midazolam Paracetamol (acetaminophen) Phenobarbital Diphenhydramine Nicardapine Caffeine Enalapril Quinine Zidovudine	Sumatriptan (within three-fold)
2	Tolbutamide Losartan Raltegravir	Warfarin (shape poorly predicted) Propafenone (within three-fold) Telmisartan (shape poorly predicted)
3	Fexofenadine Clarithromycin Tenofovir Atenolol Metformin	Celiprolol (shape poorly predicted)
Unknown	ZK-253 IDX899 A1A adrenoceptor antagonist	
Total	20	5 within two-fold and 3 within three-fold
Intravenous administration		
1	Diazepam Midazolam Sumatriptan Paracetamol (acetaminophen) Diphenhydramine Verapamil	
2	Propafenone Raltegravir	
3	Fexofenadine Clarithromycin	
Unknown	ZK253 IDX899	
Total	12	0

considered non-scalable outside the three-fold range are classified in this way as the microdose did not predict the shape of the drug-concentration-time curve well for the oral dose (see **Table 3**). For intravenous administration, the pharmacokinetics for all drugs so far examined have been scalable (i.e., a 100% success rate).

There appear to be two main reasons, so far identified, that explain pharmacokinetic non-linearity when it occurs with oral dosing. The first is typified by warfarin, a low volume of distribution drug with a high affinity for a low-capacity binding site (hepatic vitamin K epoxide reductase). The kinetics observed at the microdose is classical for target-mediated disposition, where the plasma concentrations decrease rapidly as the drug attaches to its binding site. At higher doses, as the binding site becomes saturated, then the plasma concentrations are proportionally higher and the rapid decrease in concentration at the early time points is no longer observed. The phenomenon has been observed in human microdosing [31] as well as in studies in the rat [47]. This type of disposition kinetics is also typical for monoclonal antibodies, which are well known for exhibiting non-linear pharmacokinetics. Microdosing for the purpose of predicting drug pharmacokinetics is therefore probably ruled out for therapeutic proteins that exhibit target-mediated disposition. In addition, although the pharmacokinetics of warfarin has not been compared between a microdose and a therapeutic dose via the intravenous route, it is a reasonable assumption that the intravenous pharmacokinetics in this case would be non-linear. Very few small molecules exhibit target-mediated disposition and therefore non-linearity due to this property is unlikely to arise very often.

The other major cause of non-linearity arises when the therapeutic dose saturates some enzyme or transporter system. Propafenone typifies such a drug, where bioavailability increases disproportionally to dose, as CYP 2D6 become saturated as the dose increases, thereby reducing the effect of first-pass metabolism [31]. In most cases failure of the oral microdose to predict the pharmacokinetics of therapeutic doses appears to be saturation in the gut wall [10,48]. The question under these circumstances is, will the microdose data be close enough to the therapeutic dose data to enable an appropriate choice to be made on the continued development of the drug? In the case of propafenone, the absolute oral bioavailability obtained from the microdose study was 5.8% and for the therapeutic dose it was 13% [48]. Although the comparative values were just outside the two-fold threshold, the overall conclusion that the drug exhibited limited bioavailability was nevertheless predicted from the microdose. It is important to interpret microdose data in the context that it is exploratory and also how it compares with other predictive methods. It has, for example, been claimed that diazepam exhibited non-linear pharmacokinetics between a microdose and therapeutic dose because of a 0.3-fold difference in volume of distribution [9]. In reality, however, attaining this degree of precision is likely to be an impractical standard for any method of pharmacokinetic prediction. Diazepam is in fact a good example of where microdosing could be useful, as its clearance is significantly over-predicted by allometric scaling. Diazepam, along with certain other drugs such as warfarin, reboxetine and tamsulosin, are classed as having "a large vertical allometry" where clearance is over-predicted, by over 3000% in the case of diazepam [49]. These magnitudes of errors have not been seen thus far with microdosing, even in the case of warfarin where target-mediated disposition is a demonstrated mechanism on non-linearity.

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Attempts have been made to identify classes of drug based upon physiochemical or pharmacokinetic properties, which are better- or worse suited to microdosing [46] but no conclusions have been drawn. **Tables 1 – 3** in the current review examine pharmacokinetic scalability in relation to the BDDCS class for the drug. Drugs in BDDCS class 2 (high permeability, low solubility compounds where efflux transporter effects predominate in the gut) might be particularly challenging for microdosing as absorption may be governed by solubility. (BDDCS, as proposed by Benet *et al.* [50], is considered a more appropriate classification system in the current context as the more widely used Biopharmaceuticals Classification System considers the magnitude of absorption whereas BDDCS also accounts for the rate.) Nevertheless, there are six BDDCS class-2 drugs represented in **Tables 1** and **2** and the microdose data get very close to being scalable to the therapeutic dose with four of those. From the current data, however, it is hard to draw any conclusions based on drug classification systems [10] as indeed it was based upon a range of physiochemical and metabolic properties reported in 2008 [46].

When assessing the utility of microdosing it is important to keep conclusions in the context of other methods of pharmacokinetic prediction. The three most commonly used 'traditional' methods are allometry, physiologically based pharmacokinetic (PB-PK) modelling and *in vitro-in vivo* extrapolation (IVIVE). These methods rely on the input of the drug's physiochemical properties and its behaviour *in vitro* and in animal species into mathematical models in order to output pharmacokinetic predictions in humans. The models rely on an understanding of the complex mechanisms of drug metabolism or are largely empirical [51]. (One is reminded of the statistician George Box, when he said, "All models are wrong, but some are useful".) The data from a microdose study, however, are largely the end result in itself and only require dose-normalisation to provide the output (although the prospect of including some pharmacokinetic modelling with microdose data is emerging – see later in this section). The question that then remains is, will the pharmacokinetics observed with a microdose reflect that at a therapeutic dose sufficiently well for appropriate decisions to be made in the drug's development? When making such assessments on the performance of microdosing it is important to place any conclusions in the context of the above-mentioned mathematically based models and to consider how microdosing can be best used alongside these models to obtain the most reliable data.

At the time of the first publication in 2003 there were virtually no data to support the hypothesis that microdosing data would scale sufficiently well to the therapeutic dose. Nowadays there is a database that overall looks very promising (see **Tables 1** and **2**) but as will be explained below, some caution has to be taken when comparing the microdose database with the performance of pharmacokinetic prediction from the methods that involve mathematical models. It is very difficult to compare exactly like with like as the microdose database is relatively small compared to the many hundreds or thousands of papers on pharmacokinetic modelling. Comparisons are complicated by the fact that the microdose database consists of many older drugs (BDDCS class-1 dominates), whereas many of the more modern compounds are in BDDCS class-2. In addition, it somewhat depends on how the data are compared. A commonly used criterion in allometry is to accept that the pharmacokinetics is predictive if they are within a factor of 2 [52]. This is a very convenient comparator and it is also used in this review in respect to microdosing (although three-fold has been used in places) but its limitations should be understood. Normally, the metric evaluated is a PK parameter such as CL, V or oral bioavailability, although arguably shape of profile is often equally important to predict [10]. Furthermore, caution should be exercised in the application of a defined tolerance (such as two-fold) given that most pharmacokinetic parameters are bounded. For example, percent bioavailability lies between 0 and 100 and organ clearance between 0 and organ blood flow. If, for arguments sake, the reference value for bioavailability is 15%, application of a two-fold tolerance seems reasonable but if the reference value is 70% then this application would clearly be inappropriate. On the other hand, if the true bioavailability was, say, 1%, and a microdose study predicted 5%, then the result would still be valuable in terms of drug selection although well outside of the two-fold criterion. The pharmacokinetic tolerance is also highly dependent upon the therapeutic window, which is drug-specific.

A recent study sponsored by the Pharmaceutical Research and Manufacturers of America examined the performance of allometry, PB-PK and IVIVE as predictors of human pharmacokinetics. A total of 89 drugs administered by the oral route and 19 by the intravenous route were assessed and the best methods could only predict events after oral administration in the order of 45% of the time [6,53-57]. It is particularly poignant that only 21% of the drugs examined were ever administered to humans by the intravenous route, and this will be discussed again in Section 4.2.4.

4.2 Emerging uses of microdosing

Although the emphasis has been on pharmacokinetic prediction there are other applications of microdosing that are emerging, which are discussed below. In order for pharmacokinetic prediction to improve, it is important to understand the underlying mechanisms responsible for non-linearity, such as rate-limiting steps in hepatic clearance [58]. Attempts have been made to account for the saturability of enzyme and transporter systems in predicting non-linear pharmacokinetics in microdose studies. For example, the relationship between dose-normalised AUC and dose/Km value has been termed the linearity index (LIN). Substrates with a small LIN tend to exhibit linear pharmacokinetics [59]. The combination of pharmacokinetic models and microdosing, particularly in cases where there are significant doubts over the inputs

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to the models, may prove to be a powerful tool of the future. Microdosing and methods of PK modelling are not, therefore, necessarily mutually exclusive. In particular, this might apply to the estimate of clearance in humans (discussed in Section 4.2.4) [10].

4.2.1 *Drug-drug interactions and polymorphism*

Potential drug-drug interactions have been investigated during a human microdose study [40]. The principle here is that the magnitude of such interactions can be difficult to predict prior to clinical studies. The limited safety toxicology required to conduct a microdose study (see Section 1) allows a drug-drug interaction study to be performed in humans before the drug enters Phase I. The pharmacokinetics of a development drug administered as a microdose before and after administration of pharmacological active doses of a suitable inducer or inhibitor of a chosen enzyme or transporter (ketoconazole and fluvoxamine in the case of [40]) is compared. The scenario is only applicable when the development drug is a potential victim of a drug-drug interaction and the marketed drug is the perpetrator. Questions as to what drug-drug interactions might be caused by the development drug itself have to be conducted after pharmacological active doses can be administered (post Phase I). Similarly, microdosing has been used to study food-drug interactions [60] and microdose probes have also been used to examine polymorphisms associated with drug transporters [61]. In the case of polymorphism studies, microdosing was applied principally from a safety perspective, where the sub-pharmacologic doses represented a very low risk in a genetically diverse population.

4.2.2 *Site of action*

A drug that exhibits an appropriate concentration at its site of action for a required period of time, but is also present off-target (e.g., in the plasma) to only a limited extent, will stand the best chance of having the necessary balance between high efficacy and low toxicity. Although plasma samples are routinely taken in pharmacokinetic studies, few studies attempt to sample tissues in order to measure drug concentrations. Tissue sampling is of course difficult in humans for obvious ethical reasons. Nevertheless, certain tissue samples have been obtained such as gastrointestinal tract during surgery [62,63] and lung samples by bronchoalveolar lavage and bronchial mucosal biopsy [64]. In the latter case, the use of ^{14}C-drug and AMS allowed for alveolar macrophages to be profiled to determine the concentrations of active parent drug versus metabolites.

Zidovudine and tenofovir require intracellular phosphorylation for antiviral activity. It is thought that the lack of intracellular phosphorylation might explain the lack of efficacy of certain nucleotide analogues but this is often only discovered once the drug is in full development [65]. The prospect of screening anti-HIV drugs in humans using microdosing prior to Phase I clinical trials is therefore an attractive prospect. Measurement of the parent drug in plasma does not correlate well with efficacy, and assays for the phosphorylated drug in peripheral blood mononuclear cells (PBMCs) are required. In a series of studies, the degree of phosphorylation of zidovudine and tenofovir was demonstrated in human microdose studies using ^{14}C-drug and highly sensitive AMS [66-68]. Interestingly, one paper indicated that intracellular zidovudine concentrations showed linear pharmacokinetics between a microdose and a therapeutic dose [67], whilst the other paper reported non-linear intracellular pharmacokinetics [66]. Both papers reported linear plasma pharmacokinetics. Where tenofovir was studied, the pharmacokinetics was linear in plasma and intracellular concentrations.

In a series of recent studies the extent of DNA methylation occurring in brain tumours in cancer patients was investigated. Temozolomide is an alkylating agent shown to have antitumor activity in patients with recurrent and refractory high-grade glioma and melanoma in Phase I and II trials [69]. Recent clinical evidence suggests that glioblastoma multiforme is a heterogeneous disease with 50% of the population responding poorly to temozolomide treatment [70]. To date, it has not been readily possible to measure temozolomide-induced tissue endpoints in a clinical setting. Recent clinical studies have demonstrated the sensitivity of AMS in the quantitation of ^{14}C-tamoxifen [71] and ^{14}C-PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) tumour uptake and DNA binding [63]. A recent clinical trial in glioblastoma multiforme patients is using AMS to quantify tumour uptake and temozlomide-induced DNA methylation after the administration of oral microdoses (50 µg) of ^{14}C-temozlomide. The aim of the study was to identify potential markers of efficacy based on a tracer dose of the therapeutic agent with an ultimate goal of developing personalised approaches to therapy in individual patients (Ali Arjomand, Acciumbiosceince, personal communication).

4.2.3 *Vulnerable populations*

The inherent toxicological low risk of a microdose allows pharmacokinetic studies to be performed in populations where higher doses are difficult to administer. Microdose studies have, for example, been performed in paediatric populations [72]. The authors are aware of a paediatric microdose study being run in the European Community but no data have yet been published.

4.2.4 *Intravenous data*

It remains the case that only few drugs intended for oral administration are ever administered to humans via the intravenous route. Yet, intravenous data can be invaluable in the development of the drug, as the fundamental pharmacokinetic parameters of clearance and volume of distribution are attained. Whilst volume of distribution tends to be predicted from allometry [53], the reliable prediction of clearance remains much more of a challenge [56]. Many of the pharmacokinetic non-linearity observed in microdosing but intravenous microdosing currently has a 100% record in predictability (**Tables 1** and **3**),

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excluding drugs that display target-mediated disposition. By incorporating an intravenous microdose study into pharmacokinetic simulations, reliable values for drug clearance in humans could be included, thereby generating much better overall predictions. In a case study, a development compound, PF-4776548, was quickly terminated based on a combination of microdose and physiologically based pharmacokinetic studies [73]. Another compound, PF-184298, was selected for development, mitigating risks due to oral exposure and metabolism by CYP2D6. The authors were cautious in their conclusions however, and pointed out that the alternative of accepting the risk and proceeding to Phase I is always a consideration in terms of time and cost for any particular programme.

4.2.5 *Metabolic profiling*

To obtain preliminary data on the metabolism of a candidate, drug samples from microdose studies have been metabolically profiled [38]. Although the profiles were obtained from a pharmacologically inactive dose, they were used to gauge the potential for the presence of human metabolites being disproportional to those seen in the toxicology species as defined in the regulatory guidelines [8,74]. In this case, the drug was ^{14}C-labelled in order to quantitatively obtain the profile by AMS analysis.

5. Expert opinion

The fundamental strengths of microdosing – improved safety, reduced cost, and time to developmental decisions – are likely to get only stronger. The most important order of business for the microdosing field is to understand the very modest utilisation of microdosing by drug developers and address any deficiencies or concerns methodologically and comprehensively. A systematic survey of industry, academia and regulators would hopefully identify the challenges and the ways to address them. Microdosing studies and the approach in general may need to undergo systematic validation in large-scale, government-sponsored trials for universal adoption to take place. In addition, the true economics of the technique versus other methods needs to be properly addressed. Since the main benefit of microdosing to developers would be in elimination of unsuccessful candidates (successful candidates would have to go through the full developmental path), clarification of microdosing impact on the rest of the pipeline needs to be made. Exploration of the utility of microdosing in vulnerable populations will likely become attractive with regulatory and societal pressures increasing in favour of equity of science and therapeutic development. Since most exclusions in drug development are due to safety concerns (pregnant women, children, elderly, hepatically and renally impaired), microdosing studies are optimally poised to provide valuable data.

Microdosing has reached its first decade and in many ways it has failed to deliver the fervour of expectation that accompanied the initial concept [75]. Nevertheless, the authors believe that it does have a place in drug development and the data support the role of microdosing in drug development and it may contribute human data to a phase of development where the majority of decision-making is currently based on non-human data. Combination of microdosing and modelling may lead to much more reliable predictions in the future. The concept has been widened from a purely pharmacokinetic predictive method towards addressing other questions, such as drug-drug interactions, polymorphism and looking at whether a drug is likely to reach its site of action. Microdosing may yet have more to offer in unanticipated directions and provide benefits that have not been fully realised to date.

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Declaration of interest

G Lappin is a consultant and member of the Scientific Advisory Board of Xceleron, Inc., Maryland, USA, a company that offers AMS microdosing studies as part of its portfolio of services. He holds no stock in Xceleron or receives payment from any other potentially conflicting interests. T Burt and R Noveck declare that they have no conflicts of interest and have received no payment in the preparation of this manuscript.

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