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Human Absorption, Distribution, Metabolism and Excretion Studies - Origins, Innovations and Importance

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Running Title Page: hADME studies: history, current status and future directions

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Abbreviations

ADME, absorption, distribution, metabolism and excretion; AMS, accelerator mass spectrometry; AUC, area under the curve; CL, clearance; Cmax, peak plasma concentration; DMPK, drug metabolism and pharmacokinetics;EFPIA, European Federation of Pharmaceutical Industries and Associations; F, absolute oral bioavailability; Fa, fraction absorbed; FDA, U.S. Food and Drug Administration; F-NMR, fluorine-nuclear magnetic resonance; hADME, human absorption, distribution, metabolism and excretion; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LSC, liquid scintillation counting; MIST, metabolites in safety testing; MS, mass spectrometry; NMR, nuclear magnetic resonance; QWBA, quantitative whole body autoradiography study; t1/2, half-life; TLC, thin-layer chromatography; Tmax, time to reach Cmax; UPLC, ultra high-performance liquid chromatography; VD, volumes of distribution

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Abstract

Human absorption, distribution, metabolism and excretion (hADME) studies represent one of the most important clinical studies in terms of obtaining a comprehensive and quantitative overview of the total disposition of a drug. This article will provide background on the origins of hADME studies as well as provide an overview of technological innovations that have impacted how hADME studies are carried out and analyzed. An overview of the current state-of-the-art for hADME studies will be provided, impacts of advances in technology and instrumentation on timing of and approaches to hADME studies will be discussed, and a summary of the parameters and information obtained from these studies will be offered. Additionally, aspects of the ongoing debate over the importance of animal ADME studies versus a "human-first, human-only strategy" will be presented. Along with the information above, this manuscript will highlight how over 50 years *Drug Metabolism and Disposition* has served as an important outlet for the reporting of hADME studies.

Significance Statement

Human absorption, distribution, metabolism and excretion studies have and will continue to be important to the understanding and development of drugs. This manuscript provides a historical perspective on the origins of hADME studies as well as advancements resulting in the current-state-of the art practice for these studies.

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Introduction

Across human clinical studies the characterization of the absorption, distribution, metabolism and excretion (hADME) of a new drug is a necessary and important part of the suite of information submitted for regulatory review (Coppola et al., 2019). Sometimes the term "human mass balance study" is used interchangeably for the hADME study. Strictly speaking, mass balance is a parameter itself derived from the study and by referring to it merely as a mass balance study provides a perfunctory description of the information obtained. Conversely, the nomenclature of "hADME" actually belies this important experimental parameter that is derived from the study, namely the mass balance.

The hADME study has two main objectives: 1) to identify and quantify circulating parent drug and metabolites, and 2) to quantitatively determine routes of elimination for all drug-related material. An understanding of the biotransformation reactions that the drug undergoes as well as assigning and quantitating the routes and extent of elimination provide important insights. Specifically, an understanding of the biotransformation of a drug and enzymes involved may provide perspective for drug-drug interactions as well as the possible impact of pharmacogenomic differences in patients on metabolism of the drug. Additionally, appreciation of the routes of elimination of a drug may also inform on any necessary dose adjustments, for example, in patients with renal or hepatic impairment.

The sections that follow will provide additional information relating to the origins of hADME studies, the current state-of-the-art for their practice as well as additional details regarding the importance and impact of hADME studies.

The Origins of Human ADME Studies

The origins of the current hADME study were likely borne out of the use of isotopes as tracers originally proposed and established by George de Hevesy for which he earned the 1943 Nobel Prize in Chemistry. Early work by Hevesy utilized radioactive lead (^{210}Pb and ^{212}Pb) in both chemical and biological studies establishing the use of "radioelements as indicators (Hevesy and Hofer, 1934)." Incorporation of a radioisotope, generally tritium (^{3}H) or carbon-14 (^{14}C) or stable isotopes (^{2}H, ^{13}C, ^{15}N, ^{18}O, etc.) into a substrate or intermediate involved in a chemical

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reaction or biotransformation allows one to track or trace labeled intermediates or products. Use of radiolabeled compounds also allows one to quantitate intermediates and products via radiochemical detection. In later work Hevesy further expanded his tracer work into biological systems including use of a stable isotope (^{2}H) and another radioisotope (^{32}P) to determine the rate of elimination of water from the body and for the latter to determine the amounts of ^{32}P found in the organs and excreta of rats over time.

Hevesy's use of tracers was rapidly implemented by others and eventually extended to the study of intermediary metabolism and biochemistry. Early examples of these studies include exploration of photosynthesis using $^{14}CO_2$ and $^{3}H_2O$ (Wilson and Calvin, 1955; Moses and Calvin, 1959), confirmation of the Krebs cycle using both stable and radioisotope labeled compounds (Tokumitsu and Michio, 1974), and establishing that DNA, and not protein, was hereditary material using ^{32}P and ^{35}S such as in the Hershey-Chase experiment (Hershey and Chase, 1952).

While ^{3}H was first discovered in 1934 (Oliphant et al., 1934), its use in nuclear weapon development limited its availability and use for research in the 1940s and 1950s (Lappin, 2015). Early biochemical studies (Ruben et al., 1939; Evans and Slotin, 1940a; Evans and Slotin, 1940b; Evans and Slotin, 1941) employed the short half-life ($t_{1/2}$ = 20.4 min) radioactive carbon isotope, ^{11}C. However, the discovery of long half-life isotope ($t_{1/2}$ = 5730 years), ^{14}C, in 1940 resulted in greater application of this radioisotope for biochemical studies. The availability of ^{14}C obtained from the Berkeley Radiation Laboratory allowed for the radiosynthesis of the carcinogen [^{14}C]dibenzanthracine (Heidelberger et al., 1947). The resulting [^{14}C]dibenzanthracine was used for the first published example of the use of ^{14}C in an ADME study for a xenobiotic in animals reported in 1948 by Heidelberger and Jones (Heidelberger and Jones, 1948; Lappin, 2015). This study bears resemblance to modern day ADME studies in the collection and characterization of elimination of ^{14}C in excreta as well as bile.

Throughout the 1950s the availability of ^{14}C for medical research from the US Atomic Energy Commission Oak Ridge, Tennessee reactor resulted in an increase in incorporation of ^{14}C into biological molecules as well as xenobiotics (Maickel et al., 1971; Lappin, 2015). An early example of the use of ^{14}C in an ADME study in humans can be found in the study of the metabolism of [^{14}C]salicylic acid (Alpen et al., 1951). This study employed countercurrent

distribution, a form of liquid-liquid extraction (Friesen et al., 2015), as well as paper chromatography to separate salicylic acid and metabolites from patient urine. This report also describes the determination of total radioactivity and identification of salicylic acid and metabolites using various colorimetric assays and UV absorption. In addition to being one of the earliest reported hADME studies, this work exemplifies early hADME studies in a number of ways. Separation of parent drug and metabolites was limited to the above-described methods such as thin-layer chromatography (TLC). Metabolite identification efforts were often limited to derivatization for function group identification as well as spectral analyses. Lastly, early ADME studies were often limited to analyses of plasma or urinary metabolites with little attention paid to parent drug and metabolites excreted in feces.

While the specifics of when radiolabeled ADME studies became routine is difficult to pinpoint, Lappin suggests that "the use of radioisotopic tracers in ADME studies was certainly established by the early to mid-1950s (Lappin, 2015)." Furthermore, the execution and publication of the results of hADME studies, as in the pages of *Drug Metabolism and Disposition,* was commonplace by the early 1970s. Over the 50 years of *Drug Metabolism and Disposition* some 310 hADME studies have been published in its pages (Figure 1). A steady stream of hADME publications have appeared with an average of more than 6 hADME studies published per year (range = 2-15). In addition to the historical perspective, the relatively large number of hADME studies included in Figure 1 also provides evidence of the value of *Drug Metabolism and Disposition* as a repository for hADME studies.

While many characteristics of the clinical aspects of a hADME study have not changed much since the early days of hADME studies, the analyses of samples and the structural determination of metabolites from these studies have benefitted from a number of advancements in analytical approaches and instrumentation. The development of gas chromatography mass spectrometry (GC-MS) in the late 1950s (Gohlke and McLafferty, 1993) followed by the advent of high-performance liquid chromatography (HPLC) in the 1970s and 1980s and eventually ultra high-performance liquid chromatography (UPLC) in the 2000s (Arnaud, 2016) have led to these methods replacing TLC and other earlier separations methods. This has resulted in greater resolution of drugs and metabolites as well as more rapid analyses. Additionally, the coupling of these LC separation methods to a thermospray interface by Vestal (Vestal, 1984) and an electrospray interface by Fenn (Fenn et al., 1989) along with improvements in nuclear magnetic

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resonance (NMR) instrumentation have had a dramatic impact on structure elucidation of metabolites (Murphy, 2008a; Murphy, 2008b).

While metabolite separation and characterization have dramatically improved, the quantitation of drug levels using liquid scintillation counting (LSC) to determine mass balance has remained relatively unchanged over the years. Though LSC is commonplace for determination of total radioactivity in plasma and excreta, the invention and introduction of accelerator mass spectrometry (AMS), as will be discussed below, has provided an alternative analytical method for the determination of total drug-related material. The coupling of LC with radiochemical detection using either liquid or solid scintillant has enabled in-line counting of radioactivity. Alternatively, use of microplate scintillation counting after fractionation of LC eluants into solid scintillant-containing plates or after addition of liquid scintillant has increased radiochemical detection sensitivity.

Together the discoveries and advances described above have led to standardization of various aspects of hADME studies and analyses. The current state-of-the-art for hADME studies in terms of study design, sample analyses and instrumentation will be discussed in the next section. Nonetheless, future advances in analytical methods and the introduction of new techniques and instrumentation may eventually lead to changes in how and when hADME studies are performed.

Current State of the Art of Human ADME Studies

Standard Study Designs For many years the design of a human ADME study has remained largely unchanged. Study volunteers are dosed with test compound incorporated with ^{14}C at a metabolically stable position, i.e., a position resistant to metabolism so the radiolabel will not be lost. Additionally, the site of the label is chosen so as not to yield hard to track metabolites, e.g., heteroatom demethylation reactions that can yield radiolabeled one-carbon molecules like formaldehyde, formic acid, or carbon dioxide. The dose of ^{14}C is high enough to permit reliable quantitation of all drug-related material by LSC, and usually ranges between 40 and 100 μCi. The dose is administered using the same route as intended for therapeutic use (mostly oral). Since the ^{14}C-labelled material generally is a one-time administration of the drug, the formulation used in the study is not a final or commercial formulation, but rather a solution or

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suspension generated specifically for this study. As such, the pharmacokinetics of the drug may not be an exact mimic of the pharmacokinetics that would be observed following administration of a tablet or capsule formulation.

Following administration to volunteers (usually 4 to 8), urine and fecal samples are collected over set intervals in as comprehensive a manner as possible. The duration of collection can be preset, based on estimates of when all drug related material will be excreted or in a manner in which samples are analyzed in real-time and release of individual volunteers from the study is data-driven. When a predetermined recovery is achieved (typically 90%) or the rate of excretion of drug-related material drops below a predetermined threshold (such as 1% in a day), the volunteer can be released from the study. Unlike other quantitation methods described below, LSC can be done in short turnaround times to permit data-driven decisions on release of volunteers. Blood samples are also collected for determination of the pharmacokinetics of total drug-related material which can be compared to the pharmacokinetics of parent drug.

When measuring total drug related material in a standard radiolabel ADME study, urine samples can be subjected to direct analysis by LSC. The total mass of urine excreted over each collection period is measured, small aliquots are withdrawn and analyzed using LSC. Following corrections for counting efficiency and multiplying the measured value by the ratio of total urine to the aliquot measured, the total radioactivity is calculated, and this value is divided by the total radioactivity administered to yield the percentage of the dose excreted over that time interval. (Thus, measurement of the total radioactivity in the dose and assurance that the entire dose was administered is a critical component in study execution.) Data from each interval are summed to yield the total percentage of dose excreted in urine. This is a straightforward procedure. For fecal samples, the laboratory manipulations are a bit more complex in that the samples must be diluted and homogenized before analysis. Weights and aliquots are dealt with in a similar manner, however using LSC for fecal homogenates directly may not yield a complete reading of total radioactivity because ^{14}C within particulates may not be efficiently counted and colored materials may also interfere by quenching scintillation. Thus, fecal samples are subject to combustion to $^{14}CO_2$ which is trapped and measured. Calculation of dose in each fecal sample is done the same way as for urine, and the urine and feces data are combined to yield total recovery. It is not typical to collect other samples from the volunteers such as expired air or

perspiration, but it is possible for drug-related material to exit the body via such routes and in those rare instances, considerations should be given for collection and analysis of those matrices.

Plasma, and sometimes whole blood, are also analyzed for total radioactivity. This is also done by subjecting aliquots to LSC. Plasma can be measured directly but blood may require processing like fecal homogenates or these can be subjected to bleaching prior to scintillation counting to prevent quenching. In the typical ADME study, the parent drug is also measured using a specific quantitative assay (usually HPLC-MS) and the C_{max}, T_{max}, AUC, and $t_{1/2}$ of the parent drug can be compared to the corresponding parameters for total radioactivity.

Plasma, urine, and fecal homogenates are also evaluated for the quantitative metabolite profiles in each matrix. A limited sample processing procedure is employed to make the samples suitable for injection onto HPLC while striving to not selectively lose metabolites in the process. Thus, simple miscible liquid extractions are typically employed to permit removal of salts and proteins by centrifugation, and the supernatant containing the drug-related material is evaporated and reconstituted for HPLC analysis. In some cases, solid phase extraction can be employed for this purpose. Recoveries of total radiolabel through the sample work-up process should be 90% or greater to offer a level of confidence that specific metabolites were not lost in the process. Chromatographic separation of metabolites into discrete peaks that can be quantified by LSC (either by fraction collection with off-line measurement or using an in-line radiometric flow detector) is done, with a portion of the HPLC eluent diverted to a mass spectrometer to gain structural information of the metabolites.

It is general practice to not generate a metabolite profile for every individual excreta and plasma sample. When using LSC as the quantitative method (as opposed to other methods—see below), urine collected from each volunteer is pooled across the sampling intervals to yield a single sample that contains at least 90% of the drug-related material that was excreted in urine. The same is done for fecal homogenate samples. The volumes/weights of each sample must be carefully considered in a proportional manner to generate a sample for analysis that is truly representative of the total excretion. For plasma, it is also typical practice to generate a single plasma pool for each individual volunteer that is constructed in such a way to represent the AUC of radioactivity over an interval that represents at least 90% of that AUC. (Practitioners in the field colloquially refer to this as generating a “Hamilton pool” in reference to the first listed

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author of a publication that describes the underlying mathematics behind the pooling scheme to generate a time-averaged sample (Hamilton et al., 1981)). These pooled samples are processed as discussed above, the reconstituted extracts analyzed by radiometric HPLC-MS, and the percentage that each metabolite comprises of a pooled excretory matrix sample or pooled plasma sample is calculated. For excreta, these percentages are converted to percentage of total dose; for plasma the values represent the percentage that each metabolite comprises of total drug-related material. The excreta values are used to address the clearance pathways for the drug while the plasma values are useful in identifying metabolites that may merit further evaluation in drug safety studies (i.e., the "MIST" criteria, see below (Schadt et al., 2018)).

Accelerator Mass Spectrometry-Enabled Study Designs The advent of the use of accelerator mass spectrometry (AMS) to measure ^{14}C in human ADME studies has changed what these studies have the potential to include (Lappin et al., 2011; Spracklin et al., 2020). AMS as a technique has been around since the 1970s however the instrumentation has only become suitable in size and cost for small laboratories over the past ten years (Young and Seymour, 2015). In application to ADME studies, AMS detects ^{14}C at levels that are orders of magnitude below levels detectable by LSC, and this enables doses in the 100-1000 nCi levels to be administered. In fact, the amount of ^{14}C in the plasma and excreta samples in an AMS-based ADME study are so low as to no longer be considered radioactive. The extremely low exposure to ionizing radiation poses no safety risk to study volunteers and thus quantitative whole-body autoradiography studies in animals used to make tissue dosimetry estimations are no longer a prerequisite for the conduct of a human ADME study. In addition to the advantage of using much lower amounts of ^{14}C, the application of AMS as the detection technique in ADME studies allows for enhanced study designs that deliver more information about the total disposition of a drug.

When discussing the use of AMS in human drug disposition studies the difference between microdose and microtracer dose is an important distinction. A microdose is one in which the ^{14}C-labelled drug will be of a high specific activity and AMS technology, through its high sensitivity, permits the administration of extremely low subtherapeutic total dose levels. This can be done in order to gain pharmacokinetic information in humans without requiring safety studies in animal species (also referred to as a "phase 0" study (Rowland, 2012; Bosgra et al., 2016)). A microtracer dose is one wherein a standard pharmacologically relevant total dose is

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administered but it contains a very small amount of ^{14}C-labelled material as a tracer. It is the microtracer dose approach that has found use in human ADME studies.

AMS technology has opened the door to inclusion of an intravenous dose as part of the ADME study (without the prerequisite of intravenous animal toxicology studies or lengthy investigations into formulation development). This permits gathering important pharmacokinetic parameters (Table 1) that can only be gained from doing a combined IV/PO study including systemic clearance (CL), volumes of distribution (VD_{ss} and VD_{β}), absolute oral bioavailability (F), and estimates of fraction absorbed (F_a). In a sequential cross-over design, study volunteers are first administered an oral microtracer dose (e.g., 100-1000 nCi ^{14}C material plus the pharmacologically relevant dose of unlabeled material), and blood and excreta are collected to obtain mass balance and metabolite profiles in the same way as in a standard ADME study. In the second leg, following a suitable wash-out period, the same oral dose level is given of non-^{14}C-labelled material and at a time approximating the T_{max} an intravenous dose of 100-1000 nCi ^{14}C material only is administered by short infusion. Blood and excreta are collected as before. By measurement of total ^{14}C in excreta and measurement of unlabeled and ^{14}C-labelled drug in plasma, multiple pharmacokinetic parameters can be measured (Table 2). Plasma, urine, and fecal homogenates can be subsequently analyzed for quantitative metabolite profiles using HPLC and collecting fractions for AMS analysis off-line. (It should be noted that coupling of HPLC directly to AMS instrumentation has been reported but is not a common practice at this time (Madeen et al., 2019). The data can be reconstructed to yield a ^{14}C chromatogram from which each metabolite can be quantitated and converted to percentage of dose. Fractions containing ^{14}C can also be analyzed by HPLC-MS to gain information on the identities and chemical structures of the metabolites.

One disadvantage of current AMS technology relative to LSC is the length of time it takes to make the measurements and the cost of the equipment. LSC is simple—the sample to be analyzed is simply mixed with scintillation fluid and, depending on the amount of radioactivity, the data for each sample is obtained in minutes. More challenging fecal homogenate samples can be combusted and the trapped $^{14}CO_2$ is measured, as described above. Excreta samples can be measured in "real-time" and thus data can be used to determine when study volunteers have excreted enough dose to permit their release from the study site. Quantitative metabolite profiles in plasma and excreta are easily obtained by radiometric HPLC, either with radiometric flow

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detectors or 96-well fraction collection and off-line LSC. However, for AMS, all samples must either be graphitized or processed to trapped $^{14}CO_2$ (Getachew et al., 2006; Miyaoka et al., 2007; van Duijn et al., 2014). While sample preparation for AMS is lengthier and more labor-intensive than for LSC excretion data can still be provided in real-time to dismiss volunteers from the study.

NMR Spectroscopy Throughout time, the vast majority of ADME studies have been accomplished by dosing ^{14}C labelled material because this offers both specificity (no interferences from endogenous materials) and universal quantifiability (drug and metabolites have the same response factor). NMR spectroscopy can offer the latter quality for quantitating drug-related materials. However, for the specificity aspect, proton NMR is lacking since biological matrices are rife with proton-containing materials (Dear et al., 2008). But fluorine is present in many drugs, and in contrast to protons, there are no endogenous fluorine-containing interferences, thus fluorine-NMR (F-NMR) can be used for ADME of fluorine-containing drugs. This offers the further advantage that special ^{14}C-labelled material, which can extend timelines by several months and cost several hundreds of thousands of dollars, does not need to be prepared; the study can be done with the drug itself.

When using F-NMR for an ADME study, sample processing procedures are not as simple as LSC but are simpler than for AMS. The greater challenge is due to the low sensitivity of NMR as compared to LSC and AMS: large sample volumes require processing and concentration to reliably quantitate drug-related material even when using high frequency instrumentation (>500 MHz). Proof of concept of F-NMR for ADME was first demonstrated in animal ADME studies (Mutlib et al., 2012) and a retrospective comparison was made between ^{14}C and F-NMR for a hADME study (James et al., 2017). Use of F-NMR for a hADME study was first reported by Pearson et al. for the phosphatidylinositol-3-kinase delta inhibitor, leniolisib (Pearson et al., 2019). More recently F-NMR was employed for the hADME for nirmatrelvir, the first protease inhibitor for the treatment of COVID-19 (Singh et al., 2022). Analysis of samples by NMR requires lengthy data acquisition times which obviates real-time sample analysis for discharge of study volunteers and also requires that samples be pooled for metabolite profiling by HPLC. Also, analogous to ^{14}C, success of the study depends upon the fluorine atom(s) not being lost through metabolism.

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Comparison of ADME Detection and Quantitation Methods ADME studies done using ^{14}C-labelled materials with radiometric analysis have been the standard for decades. A comparison of technical aspects of hADME studies is provided in Table 2. Theoretically, any quantitative detection system could supplant radiometric analysis but these new technologies, such as AMS or NMR, need to prove they give data of comparable quality. One aspect of data quality for hADME studies is overall mass balance. A meta analysis of overall mass balance for hADME studies using LSC and AMS as the detection methods is listed in Table 3 and shown graphically in Figure 2. Mass balance for published studies before 2007 that used LSC was reported by Roffey, et al. (Roffey et al., 2007) and yielded a median value of 92.0% (range = 39.0-113.0%; CV = 13.0%) and a subsequent analysis of studies available in Summary Basis of Approval documents from the U.S. FDA yielded similar results (median = 91.4%; range = 42.7-110.1%; CV = 9.5%). Studies that have used AMS detection are much fewer. However comparable mass balance values have been observed, suggesting that mass balance obtained using AMS is identical to that obtained using traditional LSC (median = 92.2%; range = 63.3-98.3%; CV = 22.2%; Table 3).

Animal ADME studies

While the focus of this article is on hADME studies, some mention of ADME studies in laboratory animal species is warranted. It has been common practice, and still is in many cases, to conduct at least one radiolabelled ADME study in a laboratory animal species prior to the conduct of the hADME study. However, there has been discussion in the literature regarding the value of animal studies to drug development (Pellegatti, 2014). Historically, the development path was initiated with an ADME study in rat, followed by an ADME study in the second toxicology species. This was followed by a quantitative whole body autoradiography study (QWBA) which would enable tissue dosimetry calculations to be made that would determine limits on the radioactive dose that could be used for the subsequent hADME study. Through the conduct of the animal ADME study some aspects of laboratory procedures could be worked out in preparation for the hADME study, such as matrix extraction techniques, chromatography systems to resolve metabolites, and metabolite structure elucidation. The potential for incomplete recovery can be assessed, and studies in animals can also be more invasive, such as

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collection of bile through surgical implantation of cannulae. However, this is all limited by the fact that these studies are in animals and thus the overall metabolism and disposition may not be entirely reflective of that which occurs in humans.

In 2012, Obach, Nedderman and Smith touched off a debate asking whether radiolabeled-mass balance and excretion studies in laboratory animals were still necessary (Obach et al., 2012). The crux of their argument was that early understanding of human metabolites, not exhaustive studies in animals, is most important, and an early hADME study (no later than phase 2A), enabled with modern technologies, will permit identification of the major human metabolites. Once identified, appropriate comparisons can be made between clinical samples and toxicological samples using non-radiolabelled methods, to assess whether metabolites in humans are present in adequate abundance in animal species used in risk assessments (a.k.a. the MIST issue; see below). The authors acknowledge there may be individual instances that call for a radiolabelled mass balance study in animals (e.g., to investigate a species-specific metabolite potentially causing toxicity in that species, which is not relevant to human). In response, White et. al. (White et al., 2013) argued that a radiolabelled mass balance study in at least one species was critical to drug development, because it had become an "expected" part of the regulatory submission package and the studies provided knowledge of the compound which would be helpful in handling the subsequent precious human samples.

Currently, the debate continues. In an Industry white paper published in 2022 (Young et al., 2022), it was acknowledged that there is a spectrum of views across pharmaceutical research and development organizations on this issue, but there was general agreement that animal ADME studies should not be completed simply as regulatory check box but should be designed to address mechanistic ADME questions. Recently, the drug abrocitinib was approved for clinical use without conducting any radiolabelled excretion studies in animals: only the hADME (Bauman et al., 2022) and rat QWBA (for determination of tissue distribution) studies were done.

Importance of the human ADME study

One of the primary parameters obtained from excreta in a hADME study is the overall mass balance of recovered radioactivity in excreta. While the mass balance parameter provides little

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information about the drug, it does provide some confidence or questions about the understanding of drug clearance and elimination. For example, low recovery may indicate that a sample was missed or incomplete, drug being sequestered in the body or that the drug or metabolite being eliminated in exhaled air. The question of acceptable recovery in hADME studies was addressed in the aforementioned analysis by Roffey et al. where a recovery of 80% or greater was suggested to be acceptable (Roffey et al., 2007). However, a recent FDA draft guidance on radiolabeled mass balance studies (FDA, 2022) suggested that recovery should be at least 90%. In light of the recent FDA draft guidance, reported hADME recovery data were compared to the proposed recovery of 90% (Figure 2). This assessment indicates that a large number of hADME studies would fail to meet the criteria in this draft guidance. Therefore, sponsors would be required to provide "adequate justification" for failing to meet these criteria.

Most drugs are eliminated by one, or some combination of the following elimination mechanisms: 1) metabolism/transport in the small intestine, 2) metabolism/transport in the liver, 3) glomerular filtration and tubular secretion by the kidneys. If the elimination pathway of a drug is somehow impaired, this can alter the pharmacokinetics of the drug to the extent that an adjustment in dosage may be considered. The decision to adjust dose for hepatic or renal impairment considers many factors, but one factor in this decision is knowing how much of the drug is eliminated via each pathway and that is information derived from hADME studies.

Determination and quantitation of the metabolic profile of a drug in humans is important for a variety of reasons (Figure 3) that can inform the strategy for further in vitro, animal, and human studies. Metabolites are identified from the hADME study, and their relative quantities are determined. Determination of the circulating profile of metabolites is required for the MIST assessment for a compound (FDA, 2008; ICH, 2010; EMA, 2012; ICH, 2013; FDA, 2016) which requires that metabolite levels for major human metabolites (i.e., >10% of total drug-related material in circulation) be compared across humans and animal species employed for risk assessment, and only those metabolites for which the animal to human ratio exceeds 0.5 are considered to have been qualified from a safety perspective. Profiling metabolites from the hADME study will also reveal any human-unique metabolites which will require a different approach to qualify their safety. Also, the metabolite profile in circulation may reveal metabolites that could contribute to the effectiveness of the drug (i.e., active metabolites). This activity may be on- or off-target, and it is important to quantitate that contribution (EMA, 2012;

FDA, 2017). Exposures to metabolites that contribute to pharmacological activity may be subject to interpatient variability thus potentially affecting efficacy. As an off-target effect, metabolites in humans may also have effects on drug metabolizing enzymes or transporters that are different from the parent drug, so determination of their concentrations and structures in the hADME study can inform the need for in vitro and/or clinical drug interaction studies (Callegari et al., 2013; Yu and Tweedie, 2013).

The excretory metabolite profile yields insights into the mechanisms of clearance of the parent drug. From the excretory profile, a metabolic scheme can be developed by inferring pathways based on the structures of the metabolites. The quantities of each of the metabolites along a single branch of the pathway are summed and this represents the fraction of the dose of the parent drug that proceeds through that initial metabolic route. Routes deemed major should be characterized as to the identities of enzymes involved in the initial biotransformation reaction and their relative contributions, using in vitro methods (Bohnert et al., 2016). The results from these investigations are used to determine if clinical drug interaction and/or pharmacogenetic studies should be conducted to understand interindividual variability.

When conducting the metabolite profiling part of a human ADME study there frequently can be the observation of metabolites that had not been observed before in either animals or in vitro systems. Animals can yield different arrays of metabolites than humans and in vitro systems may be limited to systems derived from single organs (e.g. liver). Additionally, in vitro systems do not recapitulate the metabolite profile if the drug undergoes several sequential transformations on its path to becoming an excretable metabolite (Dalvie et al., 2009). Metabolite profiles in human circulation may not reflect the metabolite profile observed in vitro because the metabolite itself may not distribute from the plasma compartment. This is exemplified in the case of an NK-1 antagonist CP-122721 wherein a metabolite (trifluoromethoxy salicylic acid; TFMSA; Figure 4) that required four sequential transformation reactions, and thus was not observed in vitro, was shown to be a major drug-related entity in circulation (Colizza et al., 2007). This was only first observed in the human ADME study and the TFMSA metabolite was >50% of the total drug-related radioactivity while the parent drug was 0.5%. This observation triggered a cascade of activities to demonstrate whether animal species that had been previously used in risk assessment studies were exposed to TFMSA and why this metabolite was observed at such great levels in humans. While a minor metabolite in animal species, it was observed in dogs (Kamel et

al., 2007), and because of the high dose used in safety studies, exposures to TFMSA were high enough as compared to humans at a pharmacologically relevant dose level. Demonstration of this metabolism in vitro required a retrospective approach wherein the pathway was broken into its components to recapitulate the generation of TFMSA (Obach et al., 2007).

Timing of hADME Studies

Some still consider the hADME study as an afterthought for drug development and its timing is to be delayed as long as possible. That perception may persist from some time ago when the study was often carried out as a "check box exercise;" however, with additional safety aspects such as MIST to be considered, and with the application of technologies such as AMS and F-NMR, new study designs are possible that yield information from the hADME study that can proactively inform on compound safety and subsequent clinical development. Furthermore there is a regulatory expectation the data will be available before beginning large scale clinical trials, (phase 3 (FDA, 2022)), but the reason for companies' delay is to save resources to counter the relatively high rate of attrition experienced during phase 2.

A recent white paper on hADME studies (Young et al., 2022) was the output from a consortium of pharmaceutical companies, sponsored by the European Federation of Pharmaceutical Industries and Associations (EFPIA) drug metabolism and pharmacokinetics (DMPK) Network, whose purpose was to consider shifts in the overall hADME strategy in light of emergent technologies such as AMS and the experience gained in the application of ^{14}C-microtracer studies. As with the use of animal studies mentioned above, there was a range of views among the companies in regard to timing of the hADME. Often, companies will wait for a positive proof of concept signal to be obtained before the hADME is initiated due to the attrition risk associated with lack of efficacy. There is but one example where ^{14}C-labelled drug was used in phase 1 (Jensen et al., 2017). In this case, the early hADME data was useful to support MIST understanding but was also critical to show that the unexpectedly low exposure for the compound was due to first pass metabolism and not due to poor absorption. The consortium did not offer a consensus recommendation on the timing of the hADME, only considerations for when it is appropriate.

Irrespective of the usefulness of the knowledge that can be obtained on the total disposition of a new drug candidate, conducting the human ADME as part of the first-in-human (FIH) studies is

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an aspirational goal that is difficult to meet because of the high up-front investment needed to be made in preparing GMP quality radiolabelled material for administration to humans. Thus, it is seldomly done, and any work done to understand the metabolism of the compound uses HPLC-HRMS approaches to gain a qualitative sense of the metabolite profile, observing only those metabolites detected using this technology. However, if the new drug candidate possesses fluorine, then F-NMR can be employed to gain a quantitative excretion and metabolite profile data. While previously demonstrated to be feasible in a retrospective manner (James et al., 2017), this was recently accomplished in support of a drug candidate during the phase 1 FIH study for nirmatrelvir, the active anti-viral agent of Paxlovid for the treatment of COVID-19 (Singh et al., 2022). The results showed that nirmatrelvir itself was the main drug-related entity in urine, feces, and plasma and that the most abundant metabolite at ~12% of dose arose via a hydrolysis reaction that is most likely generated by gut microflora. The data were valuable in supporting PBPK modelling used to predict drug interactions and pharmacokinetics in special populations. Some limitations of and challenges with NMR as an approach include the fact that the compound must possess fluorine at non-metabolized sites, the dose cannot be too low (i.e. at least 100 mg or more), and sample work-up volumes need to be much larger than those used in LSC or AMS analysis. ^{1}H-NMR has also been reported to be used in generating a quantitative profile of metabolites in plasma from early phase 1 studies (Dear et al., 2008). Again, large matrix volumes are needed to be extracted for analysis due to sensitivity limitations and unlike F-NMR, background interferences in biological matrices are massive for ^{1}H-NMR which precludes generation of mass balance data. The drug candidate requires downfield proton resonances that are distinct from endogenous materials.

The importance of the human ADME study and the benefits for conducting the study early in the clinical development program can be exemplified by the studies done to investigate the disposition of the ALK inhibitor, lorlatinib (Stypinski et al., 2020). In a study wherein the carbon label was placed at a benzylic carbonyl carbon (for ease of radiosynthesis), a cleavage pathway that had not been previously observed in animal species or in vitro incubations was observed, and the metabolite arising from these transformations, M8, was shown to be a major metabolite that surpassed the MIST threshold (Figure 5). This observation led to the conduct of a second human ADME study with lorlatinib labelled at a different position which permitted following the other major portion arising from the cleavage reactions. Had the first study been

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conducted late in development, there would not have been enough time to complete the second study, nor would there have been time to do follow up evaluations of M8 in laboratory animal species used in risk assessment.

Two additional drugs, opicapone and ozanimod, serve as additional examples of where data from an early hADME may have been beneficial. Both the catechol *O*-methyltransferase inhibitor, opicapone, and the sphingosine 1-phosphate (S1P) receptor modulator, ozanimod, contain a central oxadiazole ring bearing the radiolabel. As shown in Figure 6, metabolism, most likely involving gut microbes, results in scission of the oxadiazole, release of ^{14}Cbenzoic acid metabolites, and subsequent decarboxylation releasing the radiolabel as $^{14}CO_2$. While expired air was captured in one of the hADME studies run for opicapone accounting for 20% of dose (Loureiro et al., 2022b), the hADME study for ozanimod did not include the capture of expired air which likely contributed to the low recovery (63%) reported for this study (Surapaneni et al., 2021). Interestingly, in an ADME study run in rats for opicapone only 1.5-2.2% of dose was recovered in expired air (Loureiro et al., 2022a) indicating that gut microbial metabolism of opicapone likely differs between rat and human. For ozanimod, in addition to the low recovery, the hADME study, which was run concurrent with phase 3 studies, was further complicated by the identification of a major (~90% of circulating drug-related material), long-lived, disproportionate metabolite in plasma with similar activity and selectivity to ozanimod. The low recovery of radioactivity, the complicated metabolism and occurrence of a major, long-lived and disproportionate human metabolite were likely exacerbated by the late execution of ozanimod's hADME study, and, while the number of complications encountered in the case of ozanomid is unusual, it provides a number of situations where early execution of a hADME study may be beneficial.

Conclusion

hADME studies represent one of the most important clinical studies in terms of obtaining a comprehensive and quantitative overview of the total disposition of a drug candidate. From their origins in the use of radioisotopes as tracers in biochemical studies, hADME studies have become a routine part of the characterization of a drug candidate and are regularly included in filing documents to regulatory agencies to aid in the understanding of safety and efficacy. While

the design of these studies has changed little over the years until recently, advances in the technologies used to analyze samples from hADME studies have changed considerably. These advances have made dramatic improvements to sample analyses and expanded the quality and quantity of information obtained in these studies. Though issues such as the necessity of animal-based ADME studies, optimal timing of hADME studies, and the acceptable radioactivity recovery in a hADME study still remain to be settled, the importance hADME studies to our understanding of a drug candidates disposition is undeniable.

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Authorship Contributions

Performed data analysis: Cerny

Wrote or contributed to the writing of the manuscript: Cerny, Spracklin, Obach

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Figure Legends

Figure 1. hADME studies published in *Drug Metabolism and Disposition* between 1973 and 2022. Search criteria and references used to generate this figure can be found in the *Supplemental Information*.

Figure 2. Comparison of total radioactivity recoveries from liquid scintillation counting (LSC)-based and accelerator mass spectrometry (AMS)-based hADME studies. Radioactivity recovery data reported by Roffey et al. (Roffey et al., 2007) and from FDA-approved drugs 2005-2020 (www.FDA.gov) were used to construct this figure. Red horizontal lines for each data set represent the median. Blue horizontal dotted, dashed, and solid lines represent recoveries of 90, 85 and 80%, respectively.

Figure 3. The output from hADME Studies Triggers Further Mechanistic Investigations.

Figure 4. Sequential biotransformation reactions CP-122721 resulting in TFMSA as a major metabolite in circulation.

Figure 5. Metabolic pathways of lorlatinib cleavage

Metabolism of lorlatinib in humans showing the products arising from two cleavage reactions of the cyclic structure in the drug. The asterisk indicates the position of the carbon-14 label used in the first study and the hashmark indicates the position of the carbon-14 label in the follow up study. PF-6894480 was not inself observed but subsequent metabolites of this portion were observed.

Figure 6. Metabolic transformations resulting in loss of radiolabel for opicapone and ozanimod as $^{14}CO_2$.

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Table 1. Data Obtained from an AMS-Enabled Human ADME Study with Sequential Oral and Intravenous Administration

Parameter	How Measured
Mass Balance Excretion	Total ^{14}C in urine and feces by AMS
Clearance (CL)	HPLC fractionation of plasma following intravenous dosing with AMS analysis of the fraction(s) containing the parent drug
Volume of Distribution (VD)	HPLC fractionation of plasma following intravenous dosing with AMS analysis of the fraction(s) containing the parent drug
Oral Bioavailability (F)	HPLC fractionation of plasma following intravenous dosing with AMS analysis of the fraction(s) containing the parent drug and compared to HPLC-MS analysis of the parent drug following oral administration
Oral Absorption (F_a)	Total ^{14}C in urine by AMS following intravenous and oral administration
Metabolite Profile	HPLC fractionation of plasma and excreta following oral dosing with AMS analysis of the fractions and HRMS analysis of metabolite peaks for structural information

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Table 2. Comparison of Technical Approaches to Human ADME Studies

	Standard Radiometric	Accelerator Mass Spectrometry (Microtracer)	^{19}F-NMR
Dose	40-100 μCi	<1 μCi	No radioactivity
Label	^{14}C or ^{3}H; Requires Radiosynthesis	^{14}C; Requires Radiosynthesis	Study drug must possess fluorine in its structure
Detection Method and Instrumentation	Liquid Scintillation Counting	AMS of ^{14}C/^{12}C Ratio	600 MHz NMR with fluorine cryo microprobe
Sensitivity	High	Extremely High	Low
Dose Route	Intended for Therapy	Intended for Therapy with Option for IV study leg	Intended for Therapy
HPLC Metabolite Profiling	Can be done with in-line flow detectors	Requires fraction collection and post-run analysis	Requires fraction collection and post-run analysis
Sample Pooling	Pool of Each Matrix for Each Individual Study Volunteer	Pool of Each Matrix is Combined Across All Volunteers	Pool of Each Matrix is Combined Across All Volunteers

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Table 3. Mass Balance of Human ADME Studies Conducted Using Scintillation Counting and Accelerator Mass Spectrometry. Values for mean, CV, median and range are percentages.

	N	Mean	CV	Median	Range
Scintillation Counting - Roffey, et al.	169	88.0	13.1	92.0	39.0-113.0
Scintillation Counting - FDA approved drugs 2005-2022	278	88.8	9.5	91.2	42.7-110.1
AMS	25	88.5	22.2	92.2	63.3-98.3

Figure 1

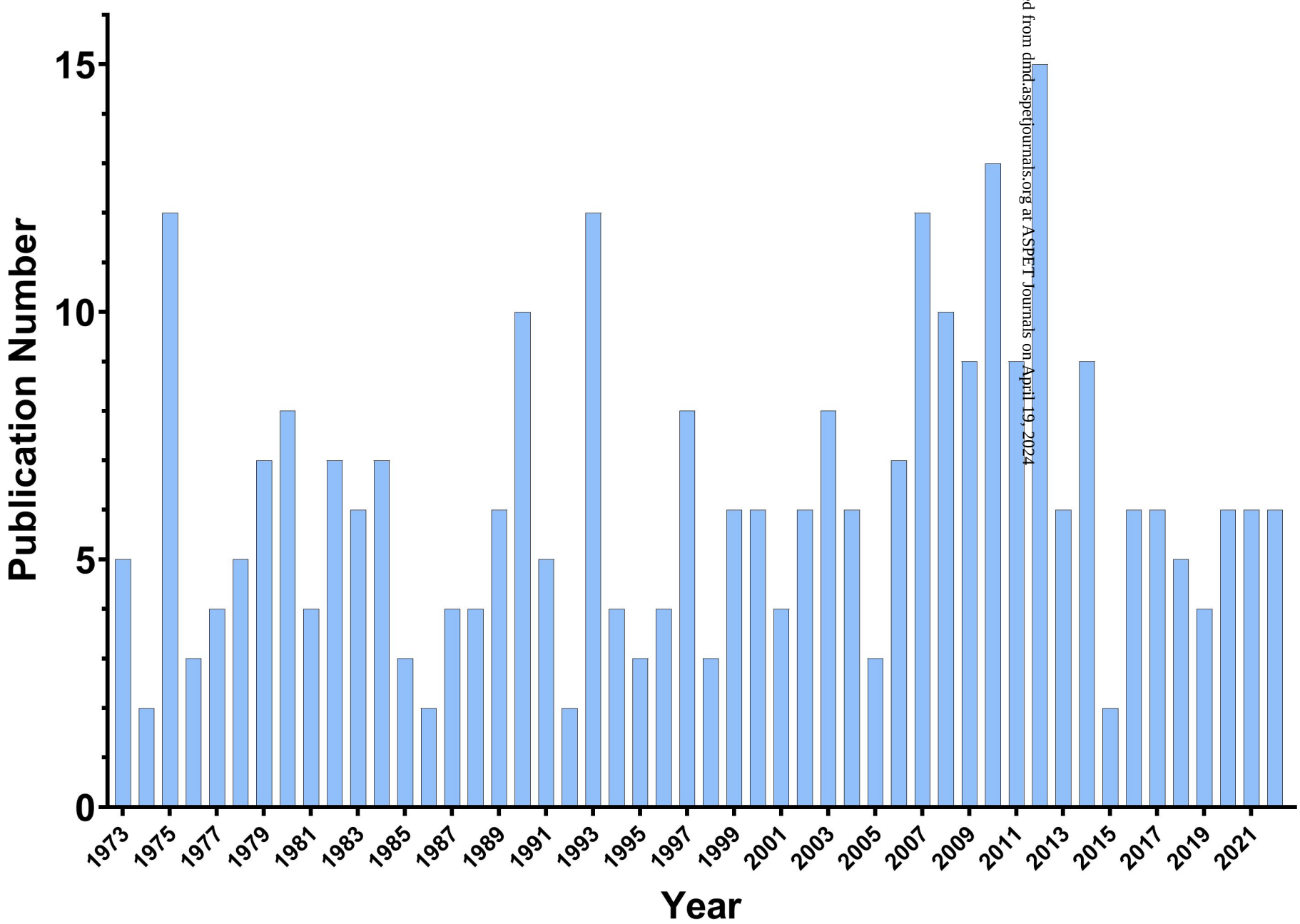

Figure 2

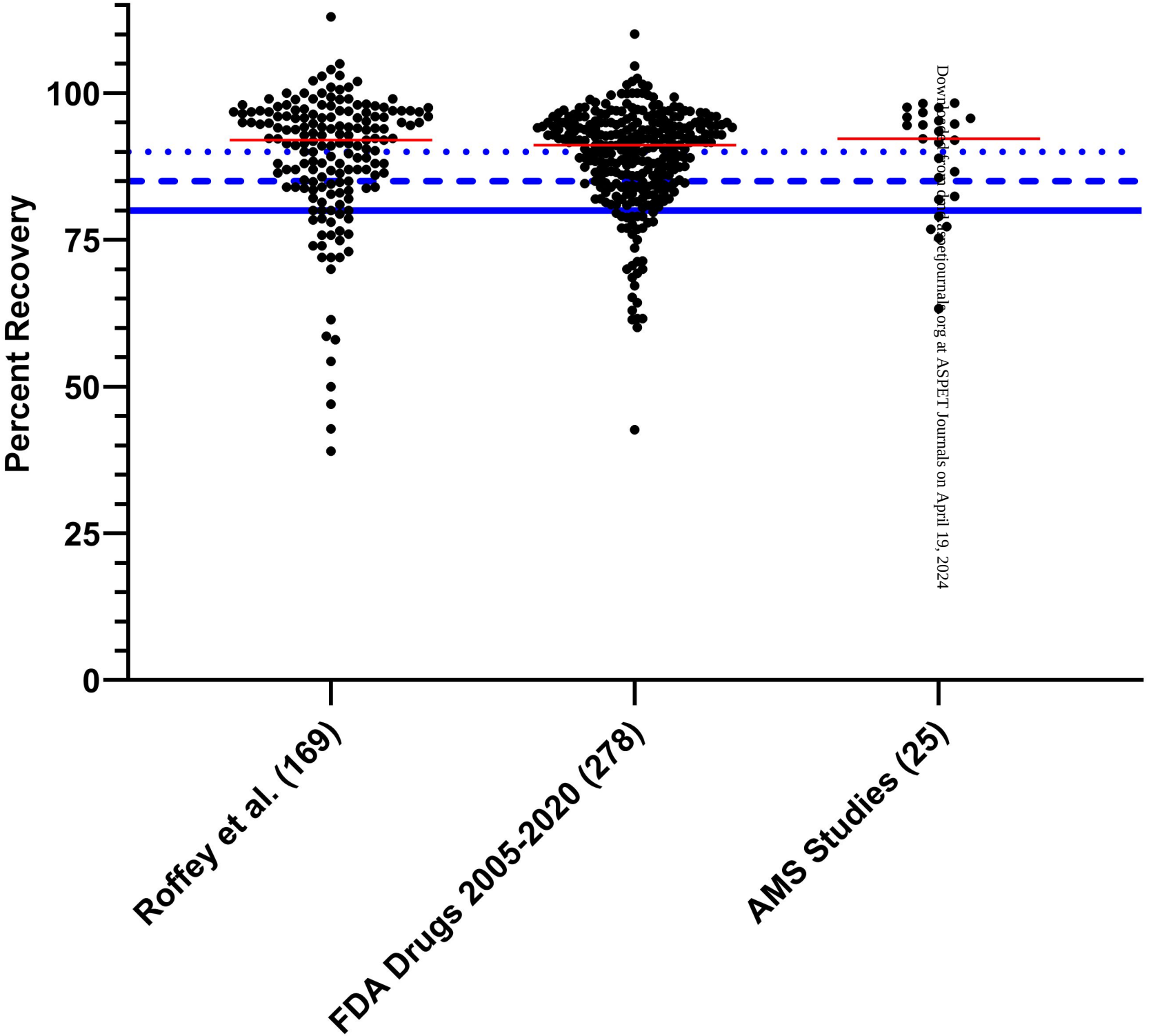

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Figure 3

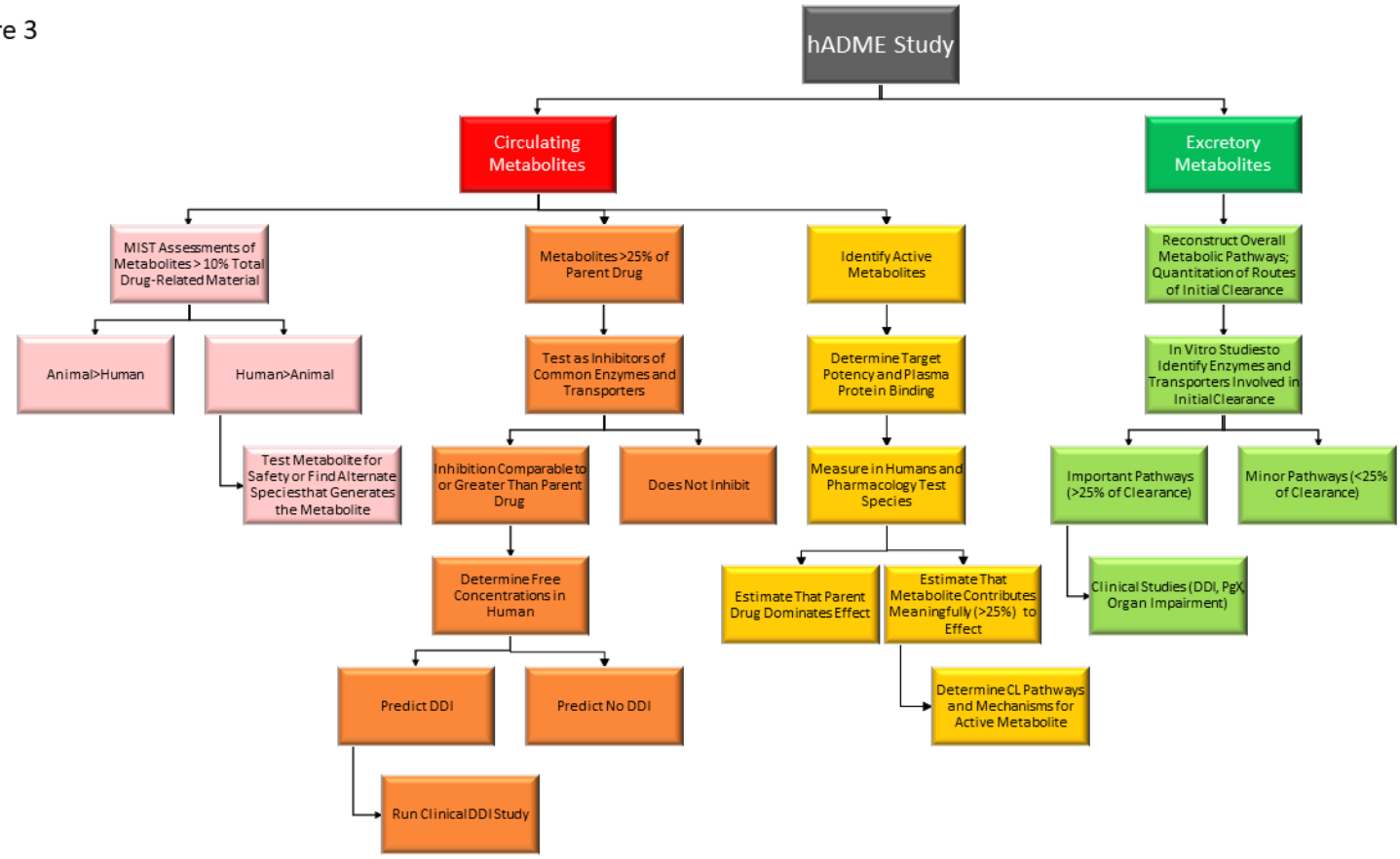

Figure 4

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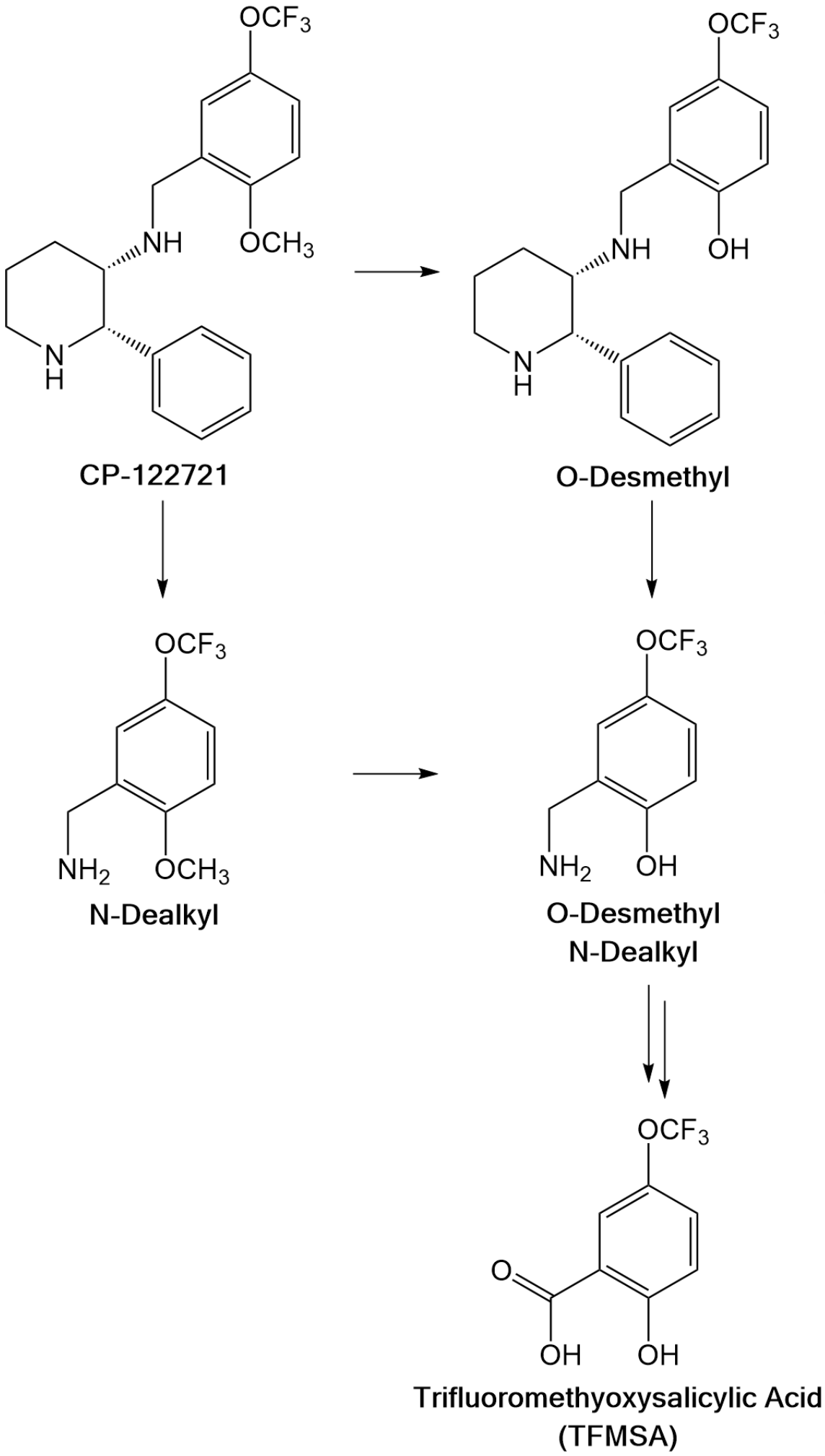

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Figure 5

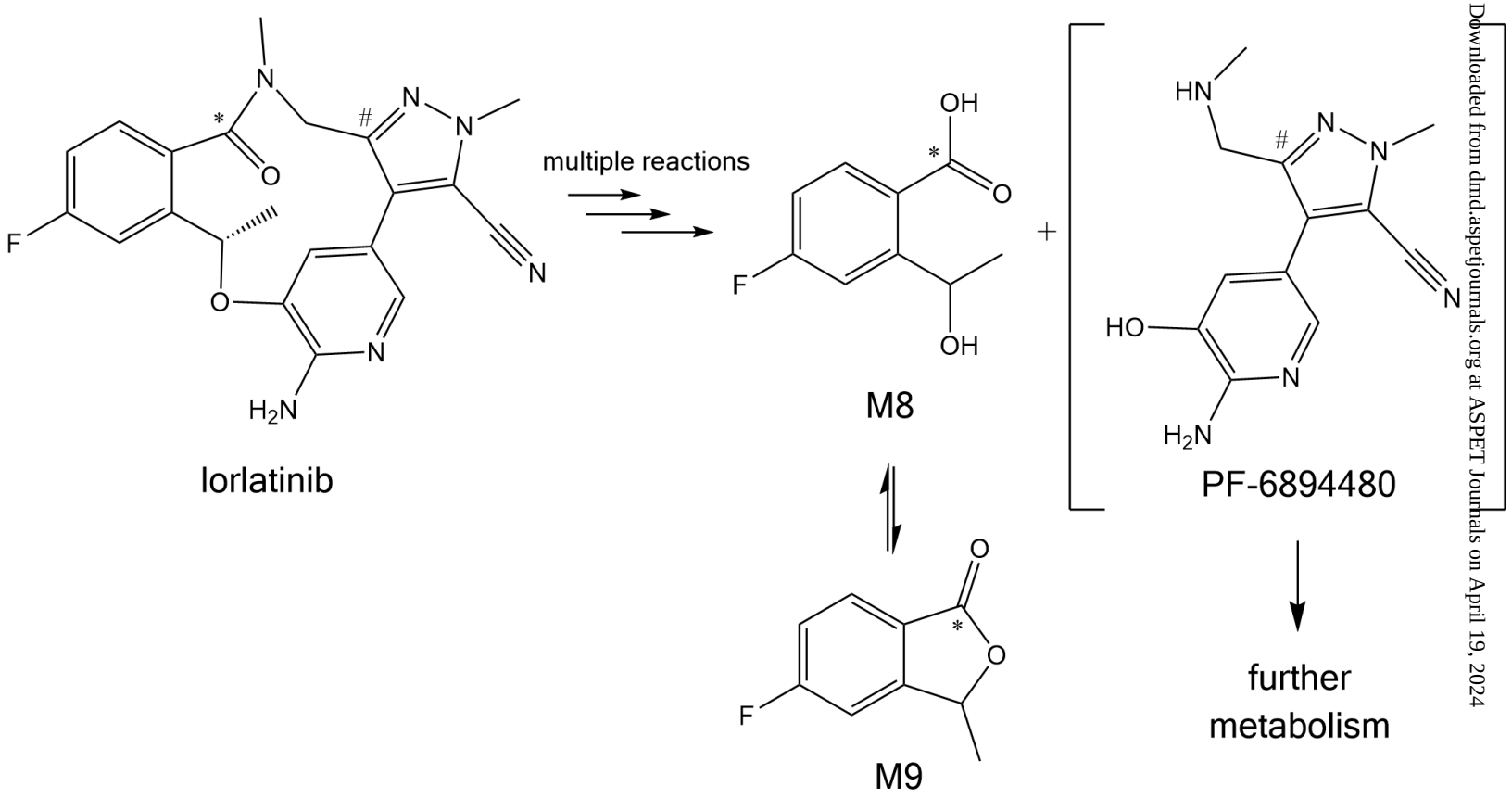

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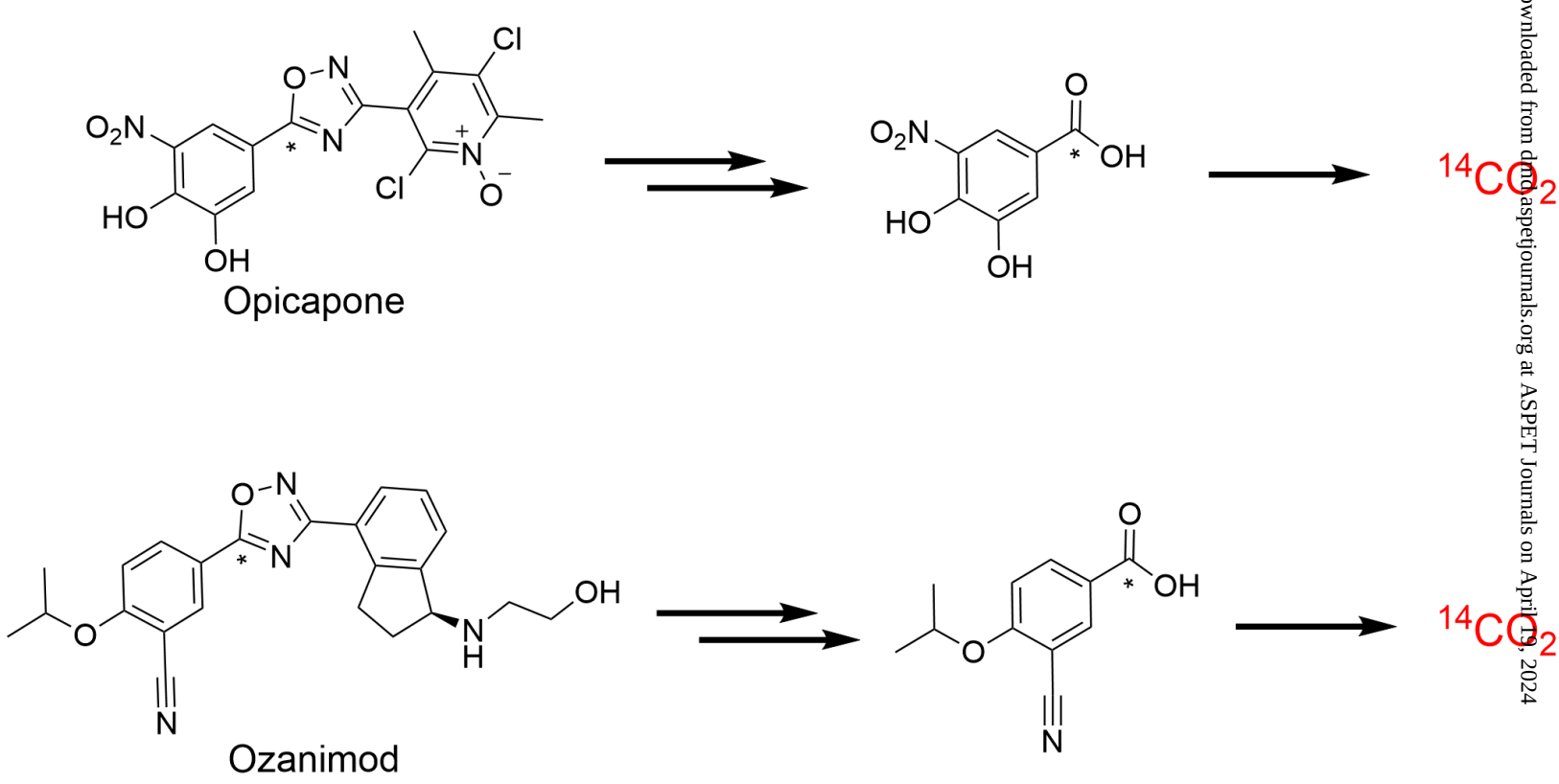
Figure 6



Human Absorption, Distribution, Metabolism and Excretion Studies - Origins, Innovations and Importance

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Drug Metabolism and Disposition – DMD-MR-2022-001006

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