^{14}C Enabled Drug Development

Bioanalytical considerations

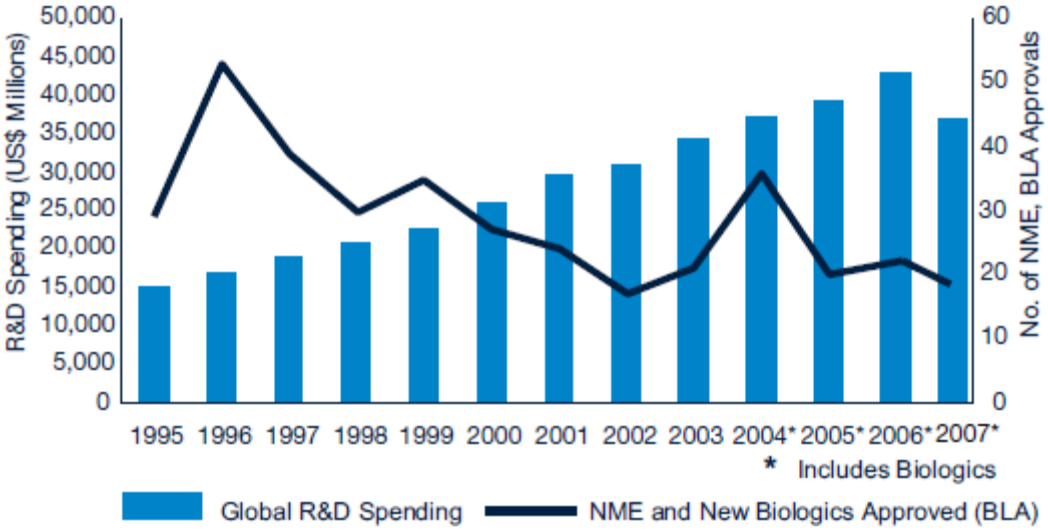
Iain Shaw,
Quotient Bioresearch

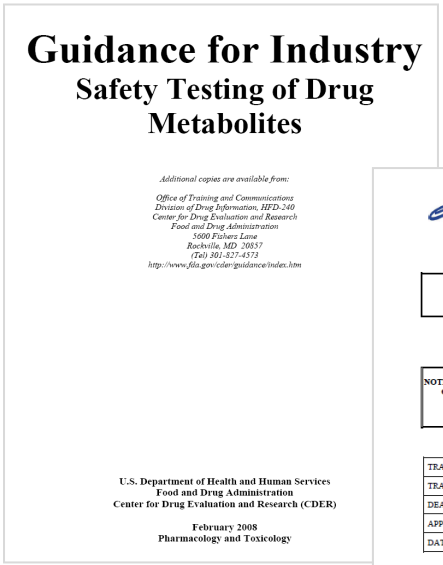
European Bioanalysis Forum
Thursday 2 December 2010

Scope of the presentation

- Drivers for change in early development
- How do we enhance scientific decision making in early development ?
  - Utility of a ^{14}C radiolabeled molecule
  - Integrated manufacturing and clinical testing to accelerate the timeline for provision of a drug product
- What are the bioanalytical challenges impacting the applications of ^{14}C enabled drug development ?

Drivers of change.....





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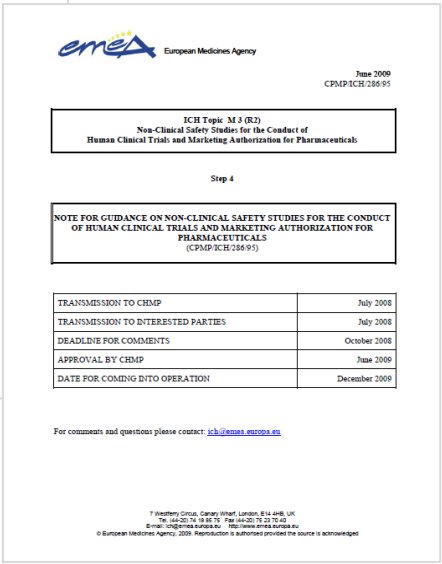
February 2008
Pharmacology and Toxicology



European Medicines Agency

June 2009
CPMP/ICH/286/95

ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Step 4

NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS
(CPMP/ICH/286/95)

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 85 75 Fax (44-20) 75 23 70 40
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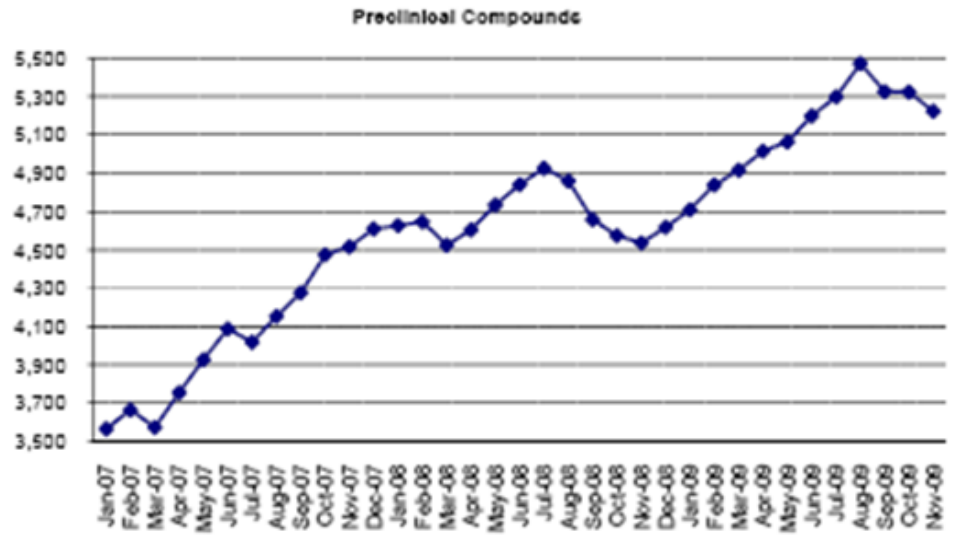
Absolute number of compounds in Development

Jan 2007 – Nov 2009, monthly data



*** Source :Pharmaprojects**

Why is a ^{14}C radiolabeled compound valuable in clinical research ?

- It allows precise quantification of drug related systemic exposure
- It allows the parent molecule and its molecules to be detected, distinguished, and quantified
- It allows the drug product from one route of administration to be distinguished from a second route of administration in the same clinical study

^{14}C enabled drug development

Study Type	Application	Position
Phase 0 Microdose	•(Back-up) Candidate selection •Early human pharmacokinetics	Discovery – Development Interface
ivMicrotracer™	•Understanding drug bioavailability •Intravenous pharmacokinetics	Pre Proof of Concept
Microtracer^{LL}	•Early insights into drug metabolism	Pre/ During Proof of Concept
Human ADME	•Regulatory metabolism studies	Pre Phase III

Phase 0 Microdosing

Generation of human pharmacokinetic and ADME data to support candidate selection

Why ?

- It enables candidate or back-up candidate selection to be based on human pharmacokinetics
- It provides an early insight into human bioavailability, half-life and metabolite burden
- Used to drive investor confidence and decision making

Experience/perspectives....

- 10 studies/programs undertaken to date
  - First study undertaken in 2004/5
- Significant customer scepticism
  - Linearity
  - Additive cost (time and money)
- “Reactive” position adopted by ourselves whilst the “science figured itself out”
- Now starting to sense changes in the marketplace
  - You have to be very specific on the question you’re asking
  - Back-up programs may be the most useful application for Phase 0

‘Phase 0’ Microdose case study

Selection of lead candidate

Intravenous and Oral Microdose Pharmacokinetics of Three Novel Inhibitors of FabI in Healthy Subjects

Lloyd Stevens[1], Jo Collier[1], Nachum Kaplan[2], Barry Hafkin[2], Mark Seymour[3], Davindera Sanghera[3], Graham Lappin[3]

1. Quotient Clinical Ltd, Mere Way, Ruddington, Nottingham, UK
2. Affinium Pharmaceuticals LTD, Austin, TX, USA
3. Xceleron Inc, Germantown, MA, USA

Purpose

- A structure guided drug discovery programme at Affinium Pharmaceuticals has resulted in the identification of new and potent inhibitors of bacterial fatty acid biosynthesis via the enoyl-acyl carrier protein reductase 1 (FabI). These inhibitors selectively target a previously unexploited bacterial pathway (fatty acid biosynthesis) essential for bacterial growth and survival. Affinium has optimised FabI inhibitors for potency, spectrum of activity against several bacterial pathogens, and various drug-like properties using structure guided drug design techniques. This has resulted in identification of a series of novel FabI inhibitors with unique, narrow spectra of anti-bacterial activity that comprise a novel class of antibiotics with a novel mechanism of action.
- AFN-1492, AFN1534 and AFN 1672 are three FabI compounds selected as potential candidates for novel, oral therapeutics for gram negative bacterial infections. These compounds were selected based on excellent *in vitro* potency against a wide range of organisms, potent whole cell Minimal Inhibitory Concentrations (MICs) and desirable pharmacokinetic properties in the mouse, rat and dog. Each molecule has demonstrated oral efficacy in the mouse infection models. Preclinical pharmacokinetic studies in rat and dog have shown inconsistent species differences in bioavailability and half-life.
- This exploratory microdosing study in healthy subjects was designed to provide clearance, bioavailability, half-life and supporting pharmacokinetic information that could be used to aid the selection of one or more of these molecules for further clinical development.

Methods: Clinical

This study was designed as a two-way crossover in three cohorts of four healthy male subjects. Each cohort received an oral and intravenous dose of one of the three candidate molecules. Each dose comprised 100µg drug incorporating 100nCi ^{14}C. The same solution formulation was used for both routes of administration with a one week washout between doses. The intravenous doses were administered as an infusion over 15 minutes.
Plasma samples for determination of drug concentrations were taken out to 72 hours after dosing. The plasma sampling regimen was designed to describe the maximum plasma concentrations and the terminal elimination phase. Voided urine and feces were collected daily out to 72 hours after oral dosing to define the urinary and fecal excretion of each molecule.
The clinical study was approved by an independent Ethics Committee and the UK regulatory authority, MHRA prior to recruitment and obtaining informed consent from the subjects who participated in the study.
Adverse events and subject safety were monitored throughout the entire study which was conducted at the Quotient Clinical facility in Nottingham, UK.

Methods: Bioanalytical and Pharmacokinetics

The concentrations of ^{14}C-AFN-1492, ^{14}C-AFN-1534 and ^{14}C-AFN-1672 in plasma were determined after extraction into acetonitrile using a 96-well protein precipitation plate. The plasma extracts were subjected to HPLC and fractions corresponding to AFN-1492, AFN-1534 and AFN-1672 were analysed using Accelerator Mass Spectrometry (AMS). Samples of the dosed formulations were also subjected to AMS analysis in order to determine the specific activity of the administered dose.
Urine and lyophilised fecal samples were submitted for AMS analysis to determine the total radioactivity content. Fecal samples were homogenised with water prior to lyophilisation.
Non-compartmental pharmacokinetic analysis of the resultant plasma concentration vs time data was carried out using WinNonlin v5.1 (Pharsight, CA). Actual blood sampling times and oral and IV doses were used to calculate the derived pharmacokinetic parameters. All AMS analytical procedures and pharmacokinetic analysis were carried out by Xceleron Inc. (Germantown, MA).

Results: Clinical conduct

Twelve healthy male subjects completed the study providing complete oral and IV PK data sets for all three molecules.
One subject reported an unpleasant taste after oral administration of one of the molecules. This was possibly related to the study drug.
All other adverse events were minor and not related to the study drugs.

Results: Pharmacokinetics of AFN-1492

Figure 1: Mean parent drug concentrations in plasma after a single intravenous and oral dose of [14C]AFN-1492

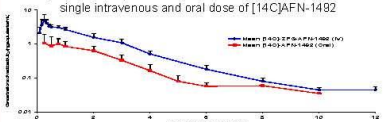
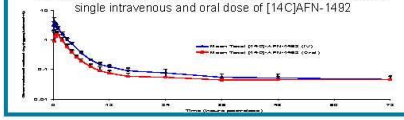


Figure 2: Mean total radioactivity concentration in plasma after a single intravenous and oral dose of [14C]AFN-1492



Results: Pharmacokinetics of AFN 1534

Figure 3: Mean total radioactivity concentration in plasma after a single intravenous and oral dose of [14C]AFN-1534

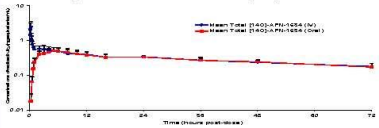
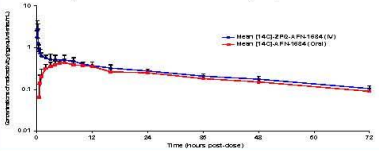


Figure 4: Mean parent drug concentrations in plasma after a single intravenous and oral dose of [14C]AFN-1534



Results: Pharmacokinetics of AFN-1672

Figure 5: Mean total radioactivity concentration in plasma after a single intravenous and oral dose of [14C]AFN-1672

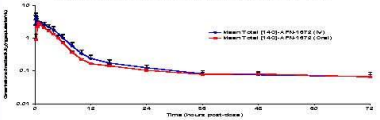
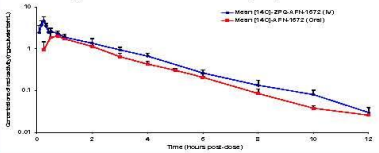


Figure 6: Mean parent drug concentrations in plasma after a single intravenous and oral dose of [14C]AFN-1672



Results: Collated Pharmacokinetic Data

Table 1: Mean PK parameters for IV and oral 100µg microdoses of radiolabelled AFN-1492, AFN-1534 and AFN-1672 to healthy subjects

	Route	t_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng/mL*h)	Cl (L/h)	Vd (l)	$t_{½}$ (h)	F_{abs} (%)
AFN 1492	IV			9.0	11.5	23.7	1.4	
	Oral	0.9	1.3	2.8			0.9	31.5
AFN 1534	IV			23.6	4.3	1850	29.9	
	Oral	6.3	0.5	19.1			30.0	81.0
AFN 1672	IV			8.0	12.5	3.3	1.8	
	Oral	0.7	2.2	5.5			1.6	67.9

Table 2: Percent dose recovery of radioactivity in urine and feces over 72 hours post oral doses of AFN-1492, AFN-1534 and AFN-1672

Compound	% dose in urine	% dose in feces	% dose total
AFN-1492	19	47	66
AFN-1534	26	14	40
AFN-1672	20	37	57

Discussion and Conclusions

Sensitive quantitative HPLC-AMS assays with a detection limit of ≤0.05ng/mL were successfully validated for all three molecules.
The determination of oral and intravenous pharmacokinetics for the three compounds has successfully highlighted both similarities and differences in their absolute bioavailability and disposition. It is interesting to note the near perfect superimposition of total radioactivity and parent drug profiles for both oral and IV doses of AFN-1534. This suggests almost complete bioavailability (81%) and little metabolic clearance. A high volume of distribution and low clearance have resulted in a long half-life of approximately 30 hours for both routes of administration.
For both AFN-1492 and AFN-1672 parent drug profiles are within the detection limits by 12 hours after dosing whereas total radioactivity can still be measured at 72 hours. This shows the presence of low amounts of radiolabelled drug products in the body after parent drug has been eliminated. Both of these molecules have parent drug half-lives of approximately 1-2 hours for oral and intravenous doses.
In conclusion: Oral and intravenous microdosing of the three candidate FabI inhibitors has provided quantitative data on their bioavailability and pharmacokinetics. This information, together with *in vitro* MIC and physicochemical considerations will be invaluable in assisting in the selection of one or more of these molecules as potential clinical development candidates.

Tel: +44 (0) 115 974 9000 Email: clinical@quotientbioresearch.com www.quotientbioresearch.com

Poster: AAPS Conference 2009, Los Angeles, CA

Do/ Will we always need AMS?

- 2 recent Phase 0 studies achieved decisions on cold data
  - Studies dosed with ^{14}C compound so AMS sensitivity was available
  - LCMSMS assays provided decision making data
  - AMS data runs cancelled

- Is sequential analysis strategy the way forward for microdosing?
  - Dose with ^{14}C compound
  - Initial sample analysis by cold LCMSMS assay
  - Progress to AMS analysis only if required
  - Currently implementing this approach through a number of client discussions

  - NB: this is only relevant for Phase 0, not ivMicrotracer

ivMicrotracer

Generating iv pharmacokinetic data for oral drugs in early development

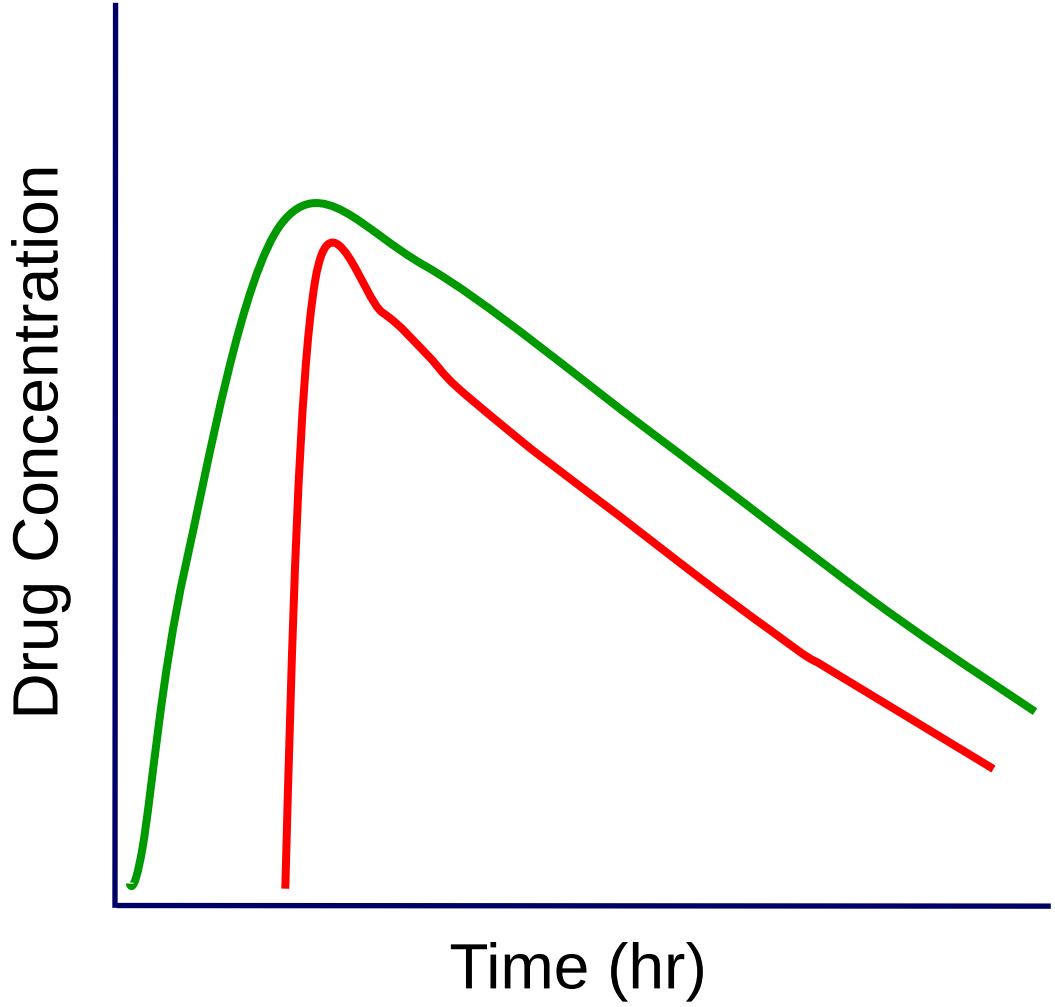
Why ?

- It allows absolute bioavailability to be determined
  - How much of the oral dose is absorbed (%F) ?
- It provides insights into the drivers of poor pharmacokinetics
  - Non-linear and variable PK
- Decision making
  - It empowers the clinical development team with equivalent data sets to the preclinical team

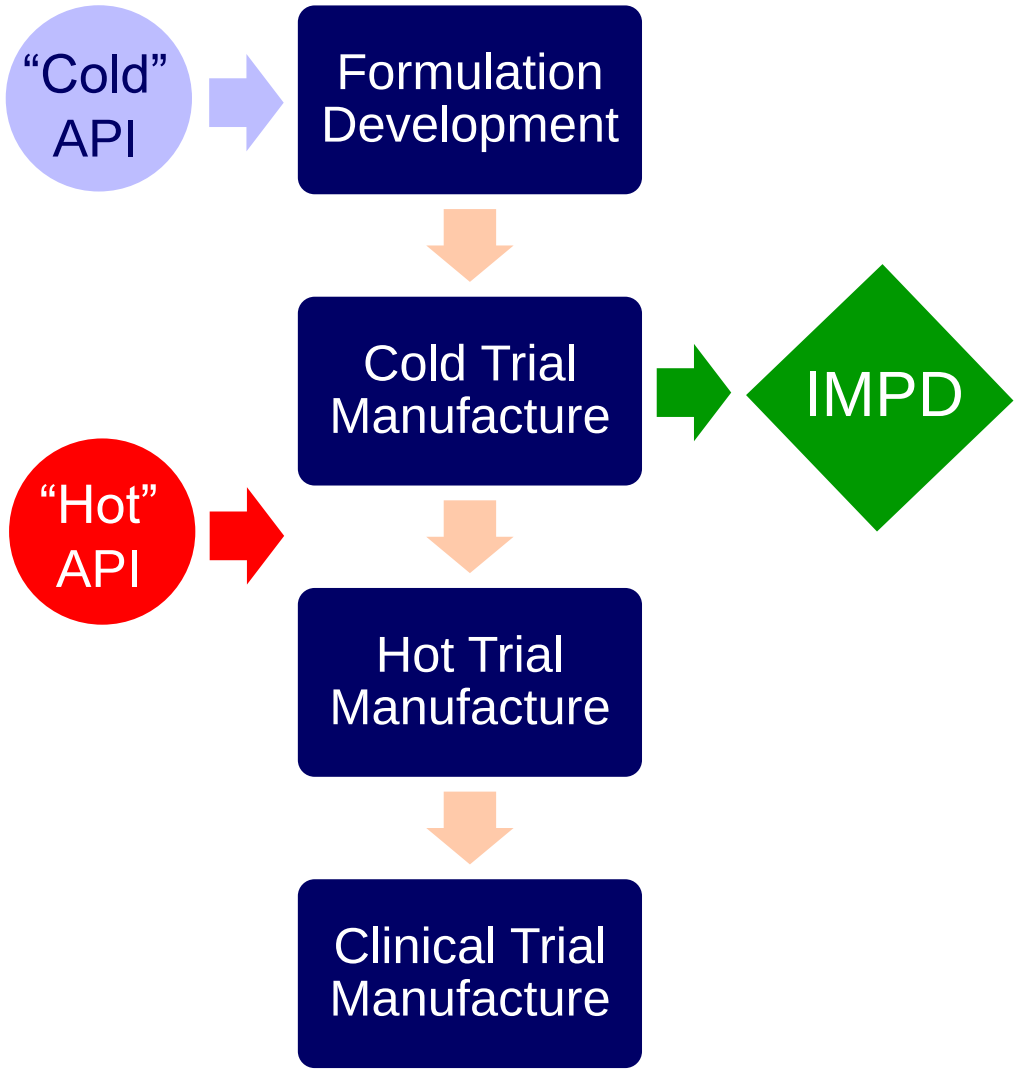
*iv*Microtracer study design

A rapid and cost effective approach to generate iv PK data

- Oral therapeutic dose
  - Measured by LC/MS:MS
- *iv*Microtracer dose administered when oral dose is at C_{max}
  - Measured by AMS
- *iv*Microtracer can be “piggy-backed” onto any standard development study
  - SAD, MAD, Food effect



Rapid development and manufacture of iv drug products



Our experience to date....

- >15 studies to date
  - Majority driven by customer drive for “early development insight”
  - Two studies in response to Regulatory Agency demands (FDA, Australia)
  - Approximately equal mix of big and small pharma

- *iv*Microtracer incorporated into a selection of study designs
  - Single period bespoke study
  - Single ascending dose
  - Multiple ascending dose
  - Enterion™ (IR control leg)
  - RapidFACT™ (IR control leg)

*iv*Microtracer™ case study

ABSOLUTE BIOAVAILABILITY OF CC-11050, A LOW WATER SOLUBLE NCE, USING AN IV MICRODOSE OF [^{14}C]-CC-11050 SOLUTION CONCOMITANTLY WITH AN ORAL UNLABELLED DOSE

Anfan Wu[1], Lloyd A Stevens[2], Ishani Savant[1], Ying Ye[1], Xiaomin Wang[1], and Oscar L Laskin[1] Celgene Corporation, Summit, NJ, USA[1], Quotient Clinical Limited, Nottingham, UK[2]

INTRODUCTION

As an emerging methodology in the pharmaceutical industry, the absolute bioavailability of an oral dose can be assessed by administering the clinical oral dose first, with a simultaneous IV microtracer dose (microdose) of the same drug labeled with [^{14}C] at t_{max} of the oral dose. The analysis of the trace amount of [^{14}C] labeled parent drug is achieved by using accelerator mass spectrometry (AMS) following liquid chromatographic fractionation. Pairing the IV microtracer dose with the clinical oral dose allows the drug from IV microdosing to be processed by the body in a manner similar to that from the oral dose. By applying this technology, absolute bioavailability can be obtained without costly and extensive IV formulation development, toxicity testing, and initial First-Time-In-Man study to determine the safety and tolerability of the IV dosage form (Lappin and Stevens, 2008).
CC-11050 is a novel compound with anti-inflammatory activity and specific phosphodiesterase type IV (PDE4) inhibition activity.
The objective of this study was to evaluate the absolute bioavailability (F_{abs}) of CC-11050 capsule following a single oral dose of 100 mg CC-11050 and a concurrent IV microtracer dose of ~25 µg CC-11050 containing ~35 nCi [^{14}C]-CC-11050.

MATERIALS AND METHODS

Subjects
Six healthy male subjects between the ages of 18 and 55 years were enrolled in this study. All subjects were in good health as determined by a medical history, physical examination, 12-lead ECG, serum biochemistry, hematology, urinalysis and virology. Subjects were not permitted to take any prescribed systemic or topical medications within 30 days of the first dose administration or any non prescribed systemic or topical medication within 7 days of the first dose administration.

Study Design
This was a single-center, open-label, single period study in healthy male subjects. Each subject received a single oral dose of 100 mg CC-11050 at time 0, and a concomitant 1-minute IV bolus of 5mL of solution with ~25 µg CC-11050 containing ~35 nCi [^{14}C]-CC-11050 at the oral t_{max} (3 hrs and 10 min post oral dose). The 100mg oral dose was considered to be well tolerated in a previous healthy volunteer study.
The development and manufacture of the IV microtracer formulation and the clinical conduct of the study were performed by Quotient Clinical Ltd (Nottingham, United Kingdom). The protocol and Informed Consent Form were reviewed and approved by an independent ethics committee (ClREC, Chester, United Kingdom).

Safety and tolerability assessments
All subjects were evaluated for safety which included a series of adverse event monitoring, laboratory safety testing, vital sign and 12-lead ECG evaluation, and physical examination. AEs that began following the drug administration were defined as treatment-emergent adverse events (TEAE) and they were evaluated by the investigator for the intensity, duration, and relationship to the treatment.

Blood Sampling and Plasma Concentration Determination
PK blood samples for the analysis of plasma CC-11050 were collected at time 0 (pre-oral-dose), 0.5, 1, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72, and 96 hours post oral dose.

Plasma CC-11050 concentrations were determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at XBL, Plainsboro, NJ. USA. Plasma concentrations of [^{14}C]-CC-11050 were determined by a validated method by using HPLC fractionation followed by accelerator mass spectrometry (AMS) of the fraction corresponding to CC-11050 at Xceleron, York, UK. The limits of quantification are 0.5 ng/mL for HPLC-MS/MS and 0.7 pg/mL for HPLC-AMS, respectively.

Data Analysis

Safety data were listed and summarized using descriptive statistics.

Pharmacokinetic parameters (Table 1) were calculated from plasma concentration data using non-compartmental analysis (WinNonlin v 5.2.1). F_{abs} was calculated as the ratio of the oral $AUC_{0-\infty}$/intravenous $AUC_{0-\infty}$ corrected for dose. Descriptive PK summary data are presented in tabular and graphic forms.

Table 1: Definition of PK Parameters

Parameters	Definition
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
C_{max}	Maximum observed plasma concentration
T_{max}	Time to maximum plasma concentration
$t_{1/2}$	Terminal elimination half-life in plasma
Cl/F	Apparent total plasma clearance when dosed orally
Vz/F	Apparent total volume of distribution during the terminal phase when dosed orally
CV	Coefficient of variation
F_{abs}	Absolute bioavailability

RESULTS AND DISCUSSION

Pharmacokinetics
All six subjects received both the IV microtracer (25µg) and oral (100mg) doses and were included in the pharmacokinetic analysis. The mean plasma concentration-time profiles for both routes of administration are presented in Figures 1 and 2. The pharmacokinetic parameters are summarized in Table 2.

RESULTS AND DISCUSSION

Figure 1: Mean (+SD) CC-11050 Plasma Concentration-Time and Treatment Data with Standard Deviation (Linear Scale)

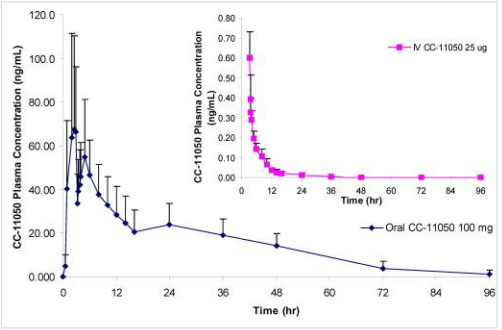


Figure 2: Mean (+SD) CC-11050 Plasma Concentration-Time and Treatment Data with Standard Deviation (Semi-Log Scale)

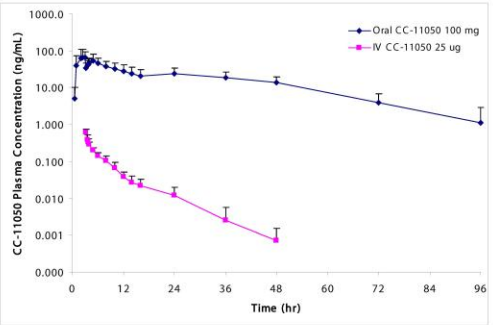


Table 2: Summary of CC-11050 Plasma Pharmacokinetic Parameters (Geometric Mean, Geometric CV

Treatment	t_{max}* (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{1/2}$ (hr)	CL/F** (L/hr)	Vz/F** (L)	F_{abs} (%)
Oral CC-11050	2.25 (2.00-5.00)	79.67 (44.6)	1383 (32.0)	1475 (26.8)	16.42 (66.1)	67.78 (26.8)	1606 (90.6)	24.59 (26.7)
Intravenous ^{14}[C]-CC-11050	0.08 (0.08- 0.33)	0.61 (20.3)	1.51 (23.3)	1.55 (23.3)	6.5 (19.7)	16.66 (22.2)	156 (29.4)	NA

*t_{max} is summarized by median and range (minimum – maximum)
**F=1 for intravenous dose
NA= Not applicable

Following intravenous microtracer and oral dosing, the disposition of CC-11050 was multiphasic and best described by a two-compartment model with initial rapid distribution phase followed by a slower elimination phase. The decline in the elimination phase was steeper following IV dosing compared to the oral dosing.

The absolute bioavailability of CC-11050 is low (24.59%). CC-11050 is a non-ionic compound with very limited solubility in water, which may explain the relatively low absolute bioavailability. This information is crucial for determining the feasibility of modified delivery oral formulations before significant resource is allocated to the effort.

Safety and Tolerability

There were no severe or serious adverse events reported. There were no withdrawals due to AEs. Four treatment emergent adverse events (headaches) were reported by 1 subject. No clinically significant findings were observed on vital signs, clinical laboratories, ECGs, or physical examination.

CONCLUSIONS

CC-11050 administered as an oral capsule exhibited a low absolute oral bioavailability of 24.59%. Despite its very low aqueous solubility it was possible to formulate and administer [^{14}C]-CC-11050 as an IV microtracer simultaneously with an oral dose of non-radiolabelled CC-11050 and thereby determine the oral absolute bioavailability early in development.

REFERENCES

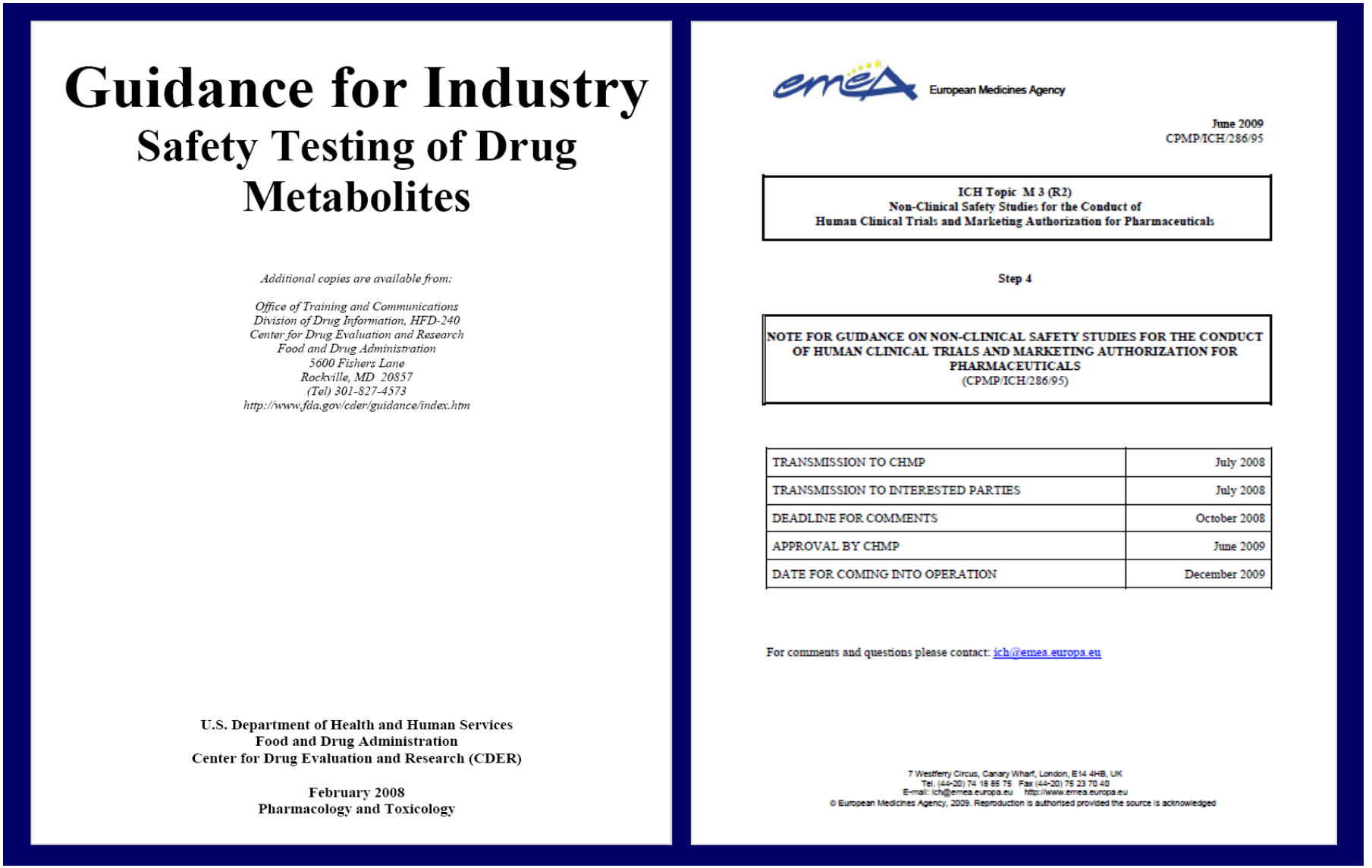
Lappin G and Stevens LA, Biomedical accelerator mass spectrometry: recent applications in metabolism and pharmacokinetics. Expert Opin. Drug Metab. Toxicol. 2008; 4:8: 1021-1033.

Poster: ASCPT Conference 2010, Atlanta, GA

Human Metabolism

Are the traditional paradigms changing?

Regulatory guidelines and perspectives



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February 2008
Pharmacology and Toxicology

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June 2009
CPMP/ICH/286/95

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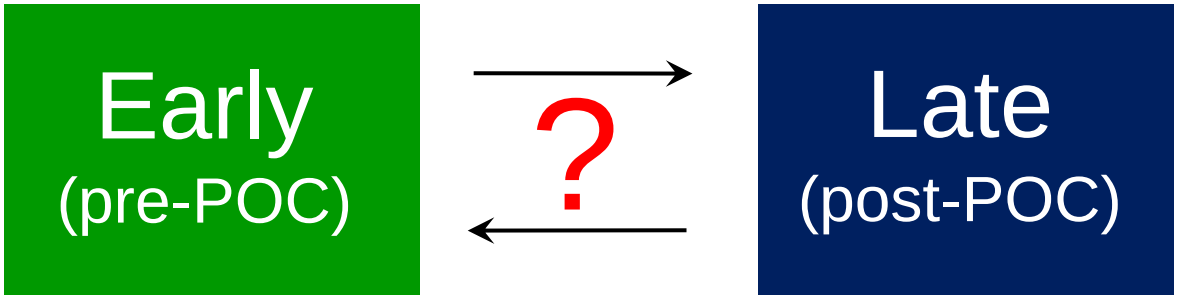
7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 85 75 Fax (44-20) 75 23 70 40
E-mail: ich@emea.europa.eu http://www.emea.europa.eu

Consistency in the guidance documents?

	MIST (FDA)	ICH Topic M3 (EMEA)
Direction	Metabolites at exposure levels >10% *parent compound*	Metabolites at exposure levels >10% *total drug related exposure*
Timing	"We encourage identification of differences in drug metabolism [.....] as early as possible during the drug development process"	"Such studies should be conducted to support Phase III clinical trials"

Placing metabolism in the Development plan

Sponsor perspectives



- Avoids surprises
- Identifies risks
- Increases costs

- Delays expenditure
- Increases metabolism risk?

Sponsor perspectives seem to be heavily influenced by past experiences which have been translated into current R&D strategy

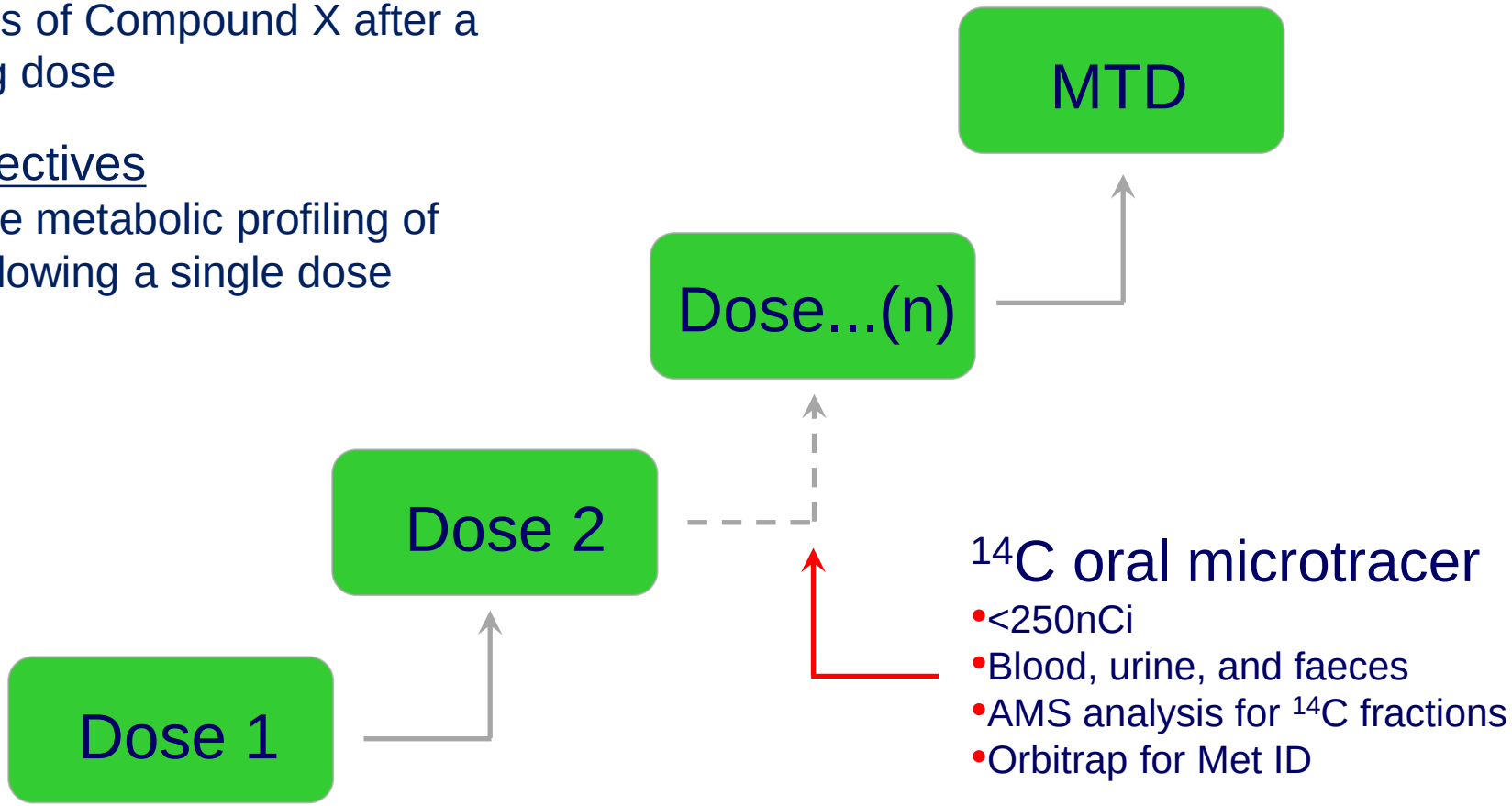
An example study design for metabolism investigations in the FIH study

Primary objectives

To assess safety and tolerability and pharmacokinetics of Compound X after a single ascending dose

Secondary objectives

To investigate the metabolic profiling of Compound X following a single dose



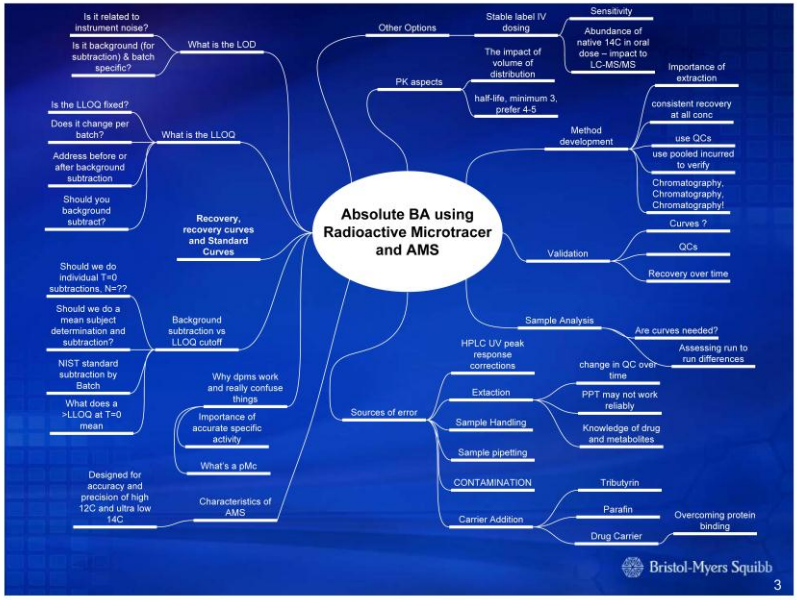
What about the bioanalysis?

Tracer applications have traditionally relied upon AMS analysis

Quotient has experience of working with all three commercial AMS providers

How do you validate an AMS assay ?

- Critical factor for studies where AMS data is pivotal to study outcome
- Specifically to studies generating absolute bioavailability data for regulatory submission
- Topic at CPSA, Oct 2010
- Standardization of Validation for AMS Microtracer Studies: Absolute Quantitation without Reference Standards
- Future progress through subgroup for AMS validation within the Global Bioanalysis Consortium

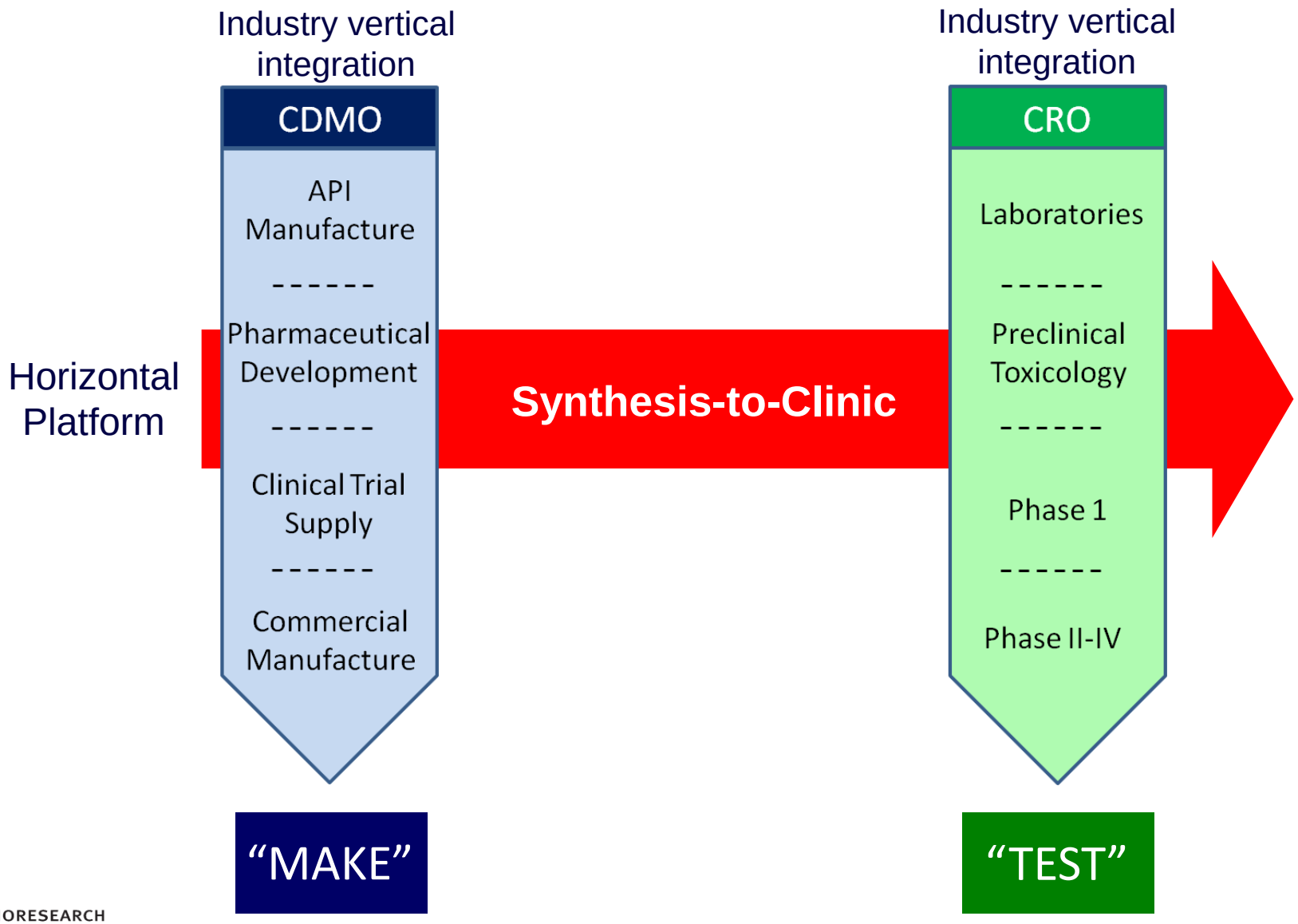


Ref: Thoughts on using AMS for Absolute BA Studies, Mark E Arnold, BMS (CPSA 2010)

Closing comments

- The medical science being applied in Early Development is continually evolving
- Seeing an increased utility of ^{14}C radiolabeled molecules in drug development
- Driving new and more complex early development protocols
- Makes efficient and robust testing of 14C compounds in the associated bioanalysis pivotal to the outcome of these applications

How do we differentiate ourselves?



AAPS 2010 poster publication

Quality standards for ^{14}C API for use in human clinical studies

QUOTIENT BIORESEARCH

I Shaw, G Johnston, K Dare, D Dams

1. Quotient Bioresearch, Newmarket Road, Fordham, Cambridgeshire, CB7 5WW, UK

Overview

The Good Manufacturing Practice (GMP) guidelines[1] state that the active pharmaceutical ingredient (API) intended for use in early stage clinical trials should be of 'suitable quality'.

In practice, in the UK this requires the Qualified Person (QP) to decide what is meant by 'suitable quality'. Quotient Bioresearch has developed a CLINIC READY quality standard[2] for ^{14}C drug substance (the API) that is suitable for use in GMP Investigational Medicinal Product (IMP) manufacture.

The CLINIC READY quality standard ensures that the API is synthesised with all the appropriate documentation to facilitate QP release of the final IMP for human clinical dosing.

Introduction

Pharmaceutical companies can undertake numerous radiosynthesis campaigns during a drug development programme to satisfy the requirements for non-regulatory development studies, non-clinical metabolism studies and ultimately, clinical metabolism investigations. With the MIST guidelines[3] encouraging metabolism investigations early in drug development, it is more efficient to consider whether a single radiosynthesis campaign can be performed that will enable all the potential studies required in the development programme.

The Synthesis Process

We have developed a step-wise approach to ^{14}C API synthesis to support non-clinical and clinical investigations. ^{14}C labelled CLINIC READY API synthesis is carried out as described below:

Step 1

The ^{14}C labelled starting material for the CLINIC READY ^{14}C API synthesis is prepared. The ^{14}C labelled starting material is released to a pre-agreed specification. A Certificate of Analysis (C of A) and BSE/TSE certificates are provided.

Step 2

The analysis method for release is transferred to and established at Quotient Bioresearch.

Step 3

Some of the material from step 1 is used in a trial synthesis of ^{14}C API. This is required for dosimetry studies to calculate the permitted radioactive dose to a volunteer in a human mass balance study and can also be used in non-clinical ADME and *in vitro* studies.

Step 4

The determined radioactive dose and the intended clinical dose are used to calculate the required specific activity of the CLINIC READY ^{14}C API. Unlabelled GMP API is added to the batch of 14C API from step 2 in a trial preparation of a homogeneous batch of CLINIC READY ^{14}C API. Homogeneity is ensured by co-crystallisation or freeze-drying of an aqueous solution.

The trial batch provides materials for use in:

- Assessment of storage stability
- Trial manufacture of the ^{14}C IMP

Data from steps 3 and 4 are used in the preparation of regulatory documentation and draft batch manufacturing record (BMR) documentation for the synthesis of the final batch.

Step 5

The manufacture of the final batch using a final BMR is coincided with the needs of the planned clinical study. The final batch is released to pre-agreed specifications by Quotient Quality Assurance (QA) and provided with a C of A and BSE/TSE certificate.

Quality Assurance and Monitoring

The Quotient QA group responsible for monitoring the radiosynthesis is involved throughout the step-wise process:

Step 1

Ensuring that the Quality Agreement is in place and current

Step 2

Auditing and releasing of method transfer. Documentation confirms that the method is acceptable to the client.

Step 3

Assessing the provenance of any starting materials for ^{14}C API synthesis to ensure BSE/TSE statements are in place

Step 4

Co-authorising the final BMR with the responsible chemist

Step 5

Reviewing the clean status of the room/defined area and associated equipment for CLINIC READY synthesis . Line clearance is authorised and documented.

The QA group:

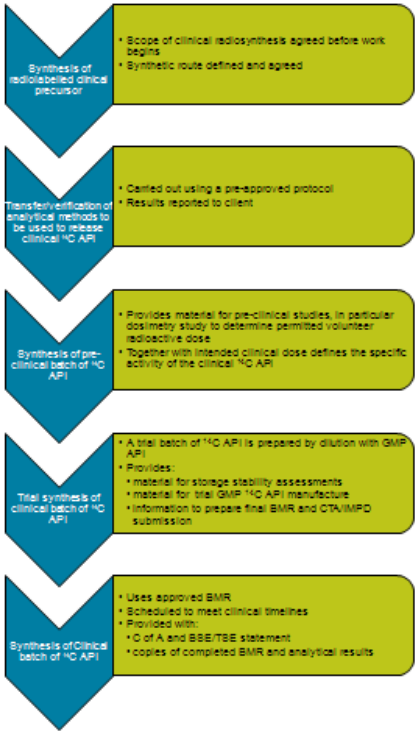
- Review the completed BMR (i.e. after completion of the manufacture) incorporating authorisation of the in-process and analytical results of the manufactured item.
- Check that the ^{14}C API has been manufactured in accordance with the BMR, Quality Agreement and the product specification details
- Co-authorise the C of A for the CLINIC READY ^{14}C API once all criteria have been met and state on the C of A that the material has been manufactured "in accordance with the Quality Agreement dated XXXX"

The QA BMR statement page is signed followed by formal QA release of the CLINIC READY ^{14}C API.

The QP and IMP Release

There is no regulatory requirement for an active ingredient in an IMP to be manufactured to GMP. In fact, there is no recognised standard to be applied and the emphasis is with the QP certifying and releasing the finished IMP to determine acceptability of the active ingredient. Determining which 'GMP principles' can be applied appropriately in the synthesis of the ^{14}C API has been key to developing an agreed quality standard, which is defined in a quality agreement between the sites of ^{14}C API synthesis and MP manufacture.

Step-wise Radiosynthesis for CLINIC READY ^{14}C API



Determining which 'GMP principles' can be applied appropriately in the synthesis of the ^{14}C API has been key to developing an agreed quality standard, which is defined in a quality agreement between the sites of ^{14}C API synthesis and MP manufacture.

Knowledge of the synthesis process for ^{14}C molecules resulted in an understanding of any risks to API quality from the processes typically employed.

Involvement of technical and QA personnel at both the synthesis and IMP manufacturing sites ensured agreement on how the requirements would be met, what documentation would be generated and responsibilities for data review and release of the ^{14}C API. Audits of the synthesis site by the releasing QPs are regularly conducted against the requirements of the Quality Agreement.

This has ensured quick acceptance of ^{14}C API into the IMP manufacturing process for clinical studies.

Quotient Quality Agreement

We have established a Quality Agreement defining responsibility for 35 quality tasks to assure every batch of ^{14}C API synthesised for IMP manufacture. It confirms that the required documentation will be provided with each batch of ^{14}C API as well as specifying the monitoring that will be performed to ensure the paperwork will meet requirements for IMP manufacture.

Documentation provided with each batch is as follows:

- C of A for ^{14}C API batch
- BSE/TSE certificate
- Certification that ^{14}C API is manufactured in accordance with agreement and approved specifications.

Conclusions

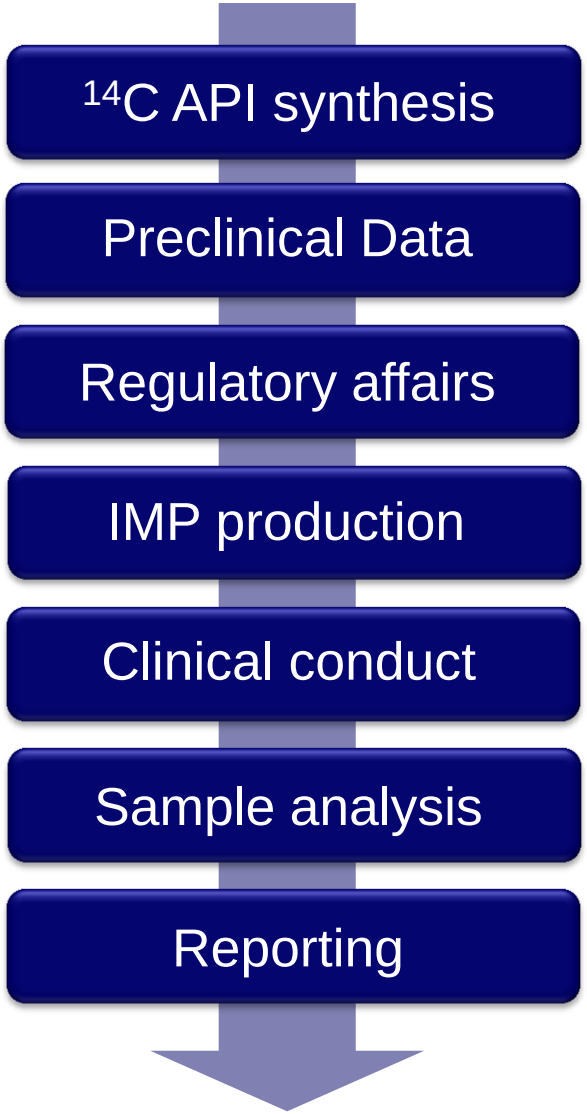
The step-wise approach described above enables the application of a single radiosynthesis campaign to serve all the likely development requirements with only the step from final intermediate or a re-purification of final product being repeated to ensure CLINIC READY status for clinical investigations. By ensuring the quality and provenance of all starting materials and intermediates and by ensuring adequate controls at critical steps of the synthetic process with thorough monitoring by QA, Quotient Bioresearch has developed an efficient procedure that minimises wastage of ^{14}C API and facilitates the optimal application of ^{14}C API to address metabolism issues effectively at a time of more demanding regulatory requirements.

References

1. Eudralex Volume 4 (especially Annex 13) and Directives 2001/20/EC and 2003/94/EC
2. Quotient Bioresearch Quality Agreement 'Synthesis of 14C radiolabelled Active Pharmaceutical Ingredient for subsequent investigational medicinal product manufacture and administration in a human study at Quotient Clinical' Nov 2009
3. FDA Guidance for Industry 'Safety Testing of Drug Metabolites' Feb 2008

Tel: +44 (0) 1638 720500 Email: info@quotientbioresearch.com www.quotientbioresearch.com

Synthesis-to-Clinic



- Tightly integrated supply chain
  - ✓ Single vendor
  - ✓ Single project manager
  - ✓ Integrated Quality process
  - ✓ Continuity of the science
  - ✓ Removal of management burden
- Relevant to all ^{14}C containing study types

Thank You

iain.shaw@quotientbioresearch.com