14C enabled drug development:
From gold standard clinical ADME studies to emerging innovations

Lloyd Stevens PhD
Quotient Clinical, Nottingham, UK
Synthesis-to-Clinic enables seamless delivery for all study types
“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
- Microdose, microtracer, human ADME

14C API synthesis
Preclinical Data
Regulatory affairs
Drug product
Clinical conduct
Bioanalysis/met profiling
Biometrics/Reports
Study Design
• Single period, open label, human metabolism study
• N=6 to 8 healthy male volunteers

Deliverables
• Mass balance recovery from urine, faeces and expired air
• Routes and rates of elimination
• Metabolite profiling and ID

Time and cost benefits
• Single protocol & submission
• Single radiochemistry program
• Enabling non-clinical program
• Single radio-dilution & CMC program
• Condensed timelines
Assumes $^{14}$C API available and enabling non-clinical studies completed

* Clinical residency is dependent on the individual characteristics of the drug
Recent Study Metrics – Mass Balance

Data from our 15 most recent studies:

• In all studies the objectives of the study were met completely.

• Where recovery was "lower" this was entirely predictable and expected

• Target recovery of >90%

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<tr>
<th>Study</th>
<th>Recovery</th>
<th>Main Excretion Route</th>
<th>Volunteer Nos</th>
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Absolute bioavailability and intravenous microtracers
What is an \(\text{iv} \)Microtracer?

**Study design**
- Single period
- Oral therapeutic dose + \(\text{iv} \)Microtracer administered at oral Tmax
- Oral PK via LC-MS/MS
- IV PK via LC-AMS

**Deliverables**
- Absolute bioavailability
  - Regulatory driver (Australian regulatory agency – TGA)
- IV and PO PK
- Add to any early development study
3. Products for which biopharmaceutic studies need to be submitted

Biopharmaceutic data as indicated below should be submitted, unless otherwise justified, for any new medicinal product which is an oral tablet, capsule or suspension, intramuscular or subcutaneous injection, topical medicine, product for inhalation or transdermal dosage form where the product has a systemic action.

Unless otherwise justified, studies should be carried out for each strength of a product.

3.1 New innovator medicine containing a new chemical entity

- Absolute bioavailability (compared with that of an intravenous injection or infusion);
- Relative bioavailability (with that of an oral solution or suspension of defined particle size where the absolute bioavailability of the new finished product has not been determined but that of a solution or suspension has been determined);
- Bioavailability studies to determine the relative bioavailabilities of the individual enantiomers in racemic drug substances;
- Effect of food studies;
- Bioequivalence of the market formulation(s) compared with the different formulation(s) used in pivotal dose-defining and efficacy studies.
Micro-Tracer Approach for the Determination of the Absolute Bioavailability of Saxagliptin

Dave Boulton, PhD
Director
Discovery Medicine and Clinical Pharmacology
Bristol-Myers Squibb R&D
QBR106186: Onglyza  absolute bioavailability

Study design
• Single period
• 8 subjects
• 5mg oral dose; 50µg $^{14}$C-IV dose
• LC-AMS & LC-MS/MS assays
• PK sampling for 24h

Deliverables
• IV PK of Onglyza
• Absolute oral bioavailability
• Completion of regulatory package
Impact

- Data accepted by TGA and saxagliptin was approved shortly thereafter
  - Confirms Health Authority acceptance of microtracer absolute bioavailability study
- Significant Cost and Time Savings vs Historical Approach
  - $800-900K and ~18 months
  - Avoidance of iv tox studies and traditional iv formulation development
- Serves as a model for future absolute bioavailability studies
  - Succeeded along tight timelines through close collaboration between many functions of the Sponsor, Formulation Lab/Clinical Site (Quotient) and the AMS Lab (Vitalea Science, Ltd)
Optimal use of $^{14}$C-API to address metabolism and pharmacokinetic questions
Single\textsuperscript{14}C study to deliver IV PK and ADME

**Study design**
- Two period crossover/parallel groups
- N= 6 or 8 subjects

**Deliverables**
- Absolute bioavailability
- Mass balance recovery
- IV and PO PK
- Routes and rates of elimination
- Metabolite profiling and ID

**Time and cost benefits**
- Single protocol & submission
- Single radiochemistry program
- Enabling non-clinical program
- Integrated radio-dilution & CMC program
- Condensed timelines
Case Study: Combined IVMT/ ADME for a targeted oncology molecule
Molecular-targeting molecules

- Review all available preclinical and clinical safety data to provide detailed “risk assessment”……. As for every other molecule

- Design options could include
  - Parallel or crossover designs
  - Specific safety assessments driven by a priori experience
  - Use of a sentinel group
  - Dose escalation element with interim safety decision
  - Crossover design with interim safety review between periods
Study background

• Human ADME data to support regulatory submission for their candidate drug, a molecular targetted molecule, for treatment of various oncology indications

• The drug candidate had not previously been dosed to healthy volunteers

• A thorough safety review confirmed that a sub-clinical dose could be administered to healthy volunteers

• The available pharmacokinetic data indicated dose dependent variability which complicated final dose selection for the ADME period
Single $^{14}$C study to deliver IV PK and ADME

**Study design**
- Three period study
- N= 6 subjects per period
- Sentinel dosing on Periods 1 & 2

**Deliverables**
- Absolute oral bioavailability
- First safety & tolerability information in healthy subjects
- IV and PO PK
- Mass balance recovery
- Routes and rates of elimination
- Metabolite profiling and ID

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**Period 1**
Absolute bioavailability vs dose A

**Period 2**
Absolute bioavailability vs dose B

**Period 3**
Human ADME at dose B
The key highlights of this study were as follows:

- First administration of the drug substance to healthy volunteers
- Regulatory and ethical approvals were obtained in standard timeframes
- ADME dose was administered at a sub-clinical level
- Dosing completed with no safety concerns or issues
- Mass balance recovery achieved
- Key AMS analysis completed
Inhaled ADME
Inhaled human ADME: The challenges

Traditional approaches involve IV and/or PO dosing of $^{14}$C-API

- Difficult/impossible to formulate and administer inhaled $^{14}$C-IMP
  - Dry powders often require micronisation

- High risk for contamination of GMP and Clinical ward environment

- Health and safety risk to clinical staff from exhaled $^{14}$C-API
Inhaled ADME study design: Novel design

- Inhaled administration of therapeutic dose of “drug X” by dry powder inhaler
  - Inhaled PK by LC-MS/MS

- Immediately post inhalation, an intravenous infusion of $^{14}$C microtracer
  - $^{14}$C detected by LC-AMS technology

Study design reviewed with FDA prior to initiation
Inhaled ADME using $^{14}$C-IVMT

Study enables/delivers

- Mass balance recovery of $^{14}$C
- Assessment by inhaled route of delivery
- Metabolism profile and ID for inhaled drug
- Absolute bioavailability for inhaled product

LC-AMS radiochromatographic profile determines LC retention times for putative metabolites

Same LC conditions applied to same plasma/urine extract allows $^{14}$C detection of all drug derived product by AMS and parallel structural identification by MS/MS
Summary

• Conventional ADME remains the benchmark for regulatory submission

• There’s more to $^{14}$C than traditional ADME

• IV-microtracers will change our approach/strategy for obtaining intravenous pharmacokinetic data

• Regulatory authorities have accepted absolute bioavailability data derived from IV-microtracer dosing

• Combinations of AMS and MS/MS methods will facilitate ADME studies with inhaled drugs

• Watch this space… there’s more to come….. All driven by the molecule!
Thank you
lloyd.stevens@quotientbioresearch.com
$^{14}$C-enabled studies with cytotoxic drugs
Recruitment of suitable cancer patients is very challenging
  • Cohorts are virtually impossible
  • Single subjects as and when available

Preparation of $^{14}$C-drug product (IV or PO) is achievable

IVMT and ADME studies are possible in certain circumstances in healthy subjects

Cytotoxics:
  • Not possible to administer a therapeutic dose to healthy subjects
  • IV /PO microdose mass balance with potential for fingerprint radiochromatographic profiling using LC-AMS
Molecular-targeting molecules

- Review all available preclinical and clinical safety data to provide detailed “risk assessment”........ As for every other molecule

- Design options could include
  - Parallel or crossover designs
  - Specific safety assessments driven by a priori experience
  - Use of a sentinel group
  - Dose escalation element with interim safety decision
  - Crossover design with interim safety review between periods
<table>
<thead>
<tr>
<th>ADME</th>
<th>IVMT &amp; ADME</th>
<th>IV-PO</th>
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<tbody>
<tr>
<td>HSP-90 inhibitor *</td>
<td>HSP-90 inhibitor **</td>
<td>Tyrosine kinase inhibitor</td>
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<tr>
<td>Histone deacetylase inhibitor *</td>
<td>Anti-metabolite ** &lt;br&gt; pyrimidine analogue *** &lt;br&gt; Cytotoxic (microdose)</td>
<td>CDK inhibitor</td>
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<tr>
<td>ROCK2 inhibitor *</td>
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* Traditional ADME  
** First time administered to healthy subjects  
*** Mass balance data requested by FDA