Interview

Novel strategies of early phase drug development: RapidFACT, *iv*-Microtracer, and microdosing

— Interview with Dr. Lloyd Stevens —*

Lloyd Stevens
Senior Research Fellow, Quotient Clinical

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Abstract

This article is a record of interview with Dr. Lloyd Stevens, a clinical pharmacology and pharmacokinetics researcher at Quotient Clinical (Nottingham), a prominent CRO (Contract Research Organization) in the United Kingdom (UK). Quotient Clinical's position within the UK CRO marketplace is illustrated by the fact that of approximately 210 commercially submitted clinical trial applications (CTAs) reviewed by the MHRA (Medicines and Healthcare products Regulatory Agency) in UK in 2010, Quotient was responsible for in excess of 40, or 20%.

Dr. Stevens introduced new strategies for early phase drug development:

(1) "RapidFACT ™" a flexible manufacturing strategy designed to enable the accelerated selection and optimisation of drug formulation prototypes within a single clinical protocol. A process which is only made possible by integration of the GCP clinical with the GMP manufacturing facilities;

(2) "*iv*Microtracer ™", conducted to define the intravenous pharmacokinetics and determine absolute bioavailability in early clinical development programs;

(3) microdosing (Phase 0), conducted to characterize and select candidate drugs and backup compounds.

Quotient Clinical has the experience of dosing more than 50 compounds within *iv*-Microtracer or microdosing programs.

All clinical studies conducted in the UK have to be approved by the UK regulatory agency (MHRA), and all UK based clinical CRO facilities conducting clinical studies in healthy subjects have to be accredited by the MHRA according to UK GCP and GMP regulations.

All this information seems to be critical for those who are interested in early phase drug development in the UK and Japan.

Key words
microdose clinical trial, *iv*-microtracer, early phase drug development, pharmacokinetics, GMP (good manufacturing practice)

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1. “RapidFACT™”— a novel drug product manufacturing strategy

Interviewer　Thank you so much for accepting today’s interview. Recently in Japan early phase drug development has been promoted in several aspects. For example, following the guidelines of EMEA (European Medicines Evaluation Agency) on first-in-human (FIH) clinical trial [1], the Japanese government is developing the same kind of guidelines; and at the same time, a relatively large number of governmental grants promoting FIH trials have been provided to academic institutes. As you know, ICH-M3(R2) guidelines agreed in 2009 [2], including regulations on microdose clinical trial and other type of exploratory clinical trials, were introduced to Japan in 2010.

You have extensive experience of utilizing novel strategies in early phase drug development as a researcher working at a CRO (Contract Research Organization) in United Kingdom (UK), and I would like to ask you to introduce the new strategies introduced by Quotient in recent years. There would be many points to learn for Japanese researchers and companies who are interested in early phase drug development. So please can you describe the procedures and methodologies your company can provide to pharmaceutical companies across the world.

Stevens　Thank you for inviting me to talk to you. Within Quotient we introduced operational systems where we can integrate GMP manufacturing with GCP clinical studies. This we have called Translational Pharmaceutics and one of the main services we offer using this technology platform is called “RapidFACT ™” (Rapid Formulation development And Clinical Testing). This is the topic that I will talk about at the JSCPT (Japanese Society of Clinical Pharmacology and Therapeutics) meeting today in Hamamatsu [3].

Many drug development programs are put on hold due to the need to change formulation from that used in the Phase 1 studies to a drug product suitable to support Phase 2 and 3 studies. Using traditional methods this formulation development and evaluation process can take up to 18 months. Through integration of GMP and GCP processes RapidFACT ™ allows us to make a drug product just before it is administered and this strategy allows us to change the way we think about evaluating and screening new formulation prototypes. This is something that the pharmaceutical industry is very keen on doing, but they cannot do it for themselves because it means re-engineering their formulation development strategy and also changing their internal GMP processes. In order to meet the demands of the pharmaceutical industry Quotient Clinical has introduced the ability to manufacture drugs and dose them within a very short period of time; This relies on – small scale/batch sizes manufactured within 1 to 7 days of dosing, coupled with the requirement to provide stability data only covering the period between manufacturing and dosing, which means that we can screen formulations and we can introduce flexibility and precision into formulation development studies.

Interviewer　Is your company the only one in the world to do such kind of strategy?

Stevens　As far as I am aware there are no other companies in the world offering the range of drug products that can be provided by Quotient using the RapidFACT ™ type of strategy. We have six manufacturing suites and can produce a very wide range of drug products (Table 1).

This has all come about because in our former life, “Quotient Clinical” was known as “Pharmaceutical Profiles” and at that time we developed the GMP capability to incorporate gamma- isotopes into a wide variety of oral and

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Lloyd Stevens gained a BSc in pharmacology and a PhD in biopharmaceutics in the early 1970's and has been involved in clinical pharmacology and pharmacokinetic aspects of drug development in both large pharmaceutical companies and CROs over the past 35 years. His expertise is in bringing new chemical entities into man and evaluating both pharmacological response and pharmacokinetic behavior early in the drug development process. Dr. Stevens is currently Senior Research Fellow with Quotient Clinical in Nottingham, UK where he is responsible for scientific aspects of study design, data analysis and interpretation. His particular interest at present is on the application of microtracers and enabling technologies to add value to studies in early drug development.

inhaled drug products, to define and correlate the *in vivo* deposition with pharmacokinetic profiles. We have further developed and built on that manufacturing capability and extended it to manufacturing of other formulations so that we can test formulations in man using our RapidFACT ™ make and test cycle.

Interviewer At that time of starting to employ RapidFACT ™ did your company or the sponsor pharmaceutical company discussed the regulatory issues with MHRA?

Stevens We developed the concept of just-in-time manufacture based on harnessing the potential rapidity of the United Kingdom's regulatory process for the release of drug products for clinical dosing. This release by an independent Qualified Person (QP) requires drug product stability data sufficient to cover the period between manufacture and clinical dosing. We presented a strategy paper to the MHRA, within a scientific review meeting in 2008 which I attended. The MHRA agreed in principle, that this was something that they would look favorably at, but every molecule is different and every CTA application is considered separately and not until we submitted the first 'real life' CTA were we sure that we would gain approval. In the 3 years since that meeting, we have completed 20 of these projects for sponsor companies distributed globally. We have received no qustions from the authorities regarding our CMC strategy and our average approval time with the MHRA is only 14 days.

Table 1 Range of drug products which Quotient Clinical can provide

- Inhaled products (metered-dose inhalers, nebulizers, dry powders).
- Intravenous formulations, either microdose, *iv*-microtracers or therapeutic dose.
- Solid and solution oral dosage forms (tablets, suspensions, solutions, including enabled drug products (SEDD, SMEDD, solid dispersions, hot melt extrusions etc.).
- Modified and controlled release systems (gastro-retentive, targeted delivery, controlled release etc.).

Interviewer　Could you explain the approximate timescale from the start of a project until the completion of the clinical report for a typical RapidFACT™ study designed to evaluate and optimise a novel formulation?

Stevens　The entire process is made up of four key phases (Fig. 1).

1. The initial phase is dedicated to formulation development and validation where we are identifying and selecting a prototype. This would also include obtaining the necessary CMC data to support a regulatory submission. This phase would also include providing a final clinical protocol and all supporting regulatory documents. It takes about 8-12 weeks depending upon the complexity of the formulation development required and the sponsor review cycle times,

2. The second stage involves the regulatory and ethics committee (IRB) submission and approvals. We allow 1 month for these.

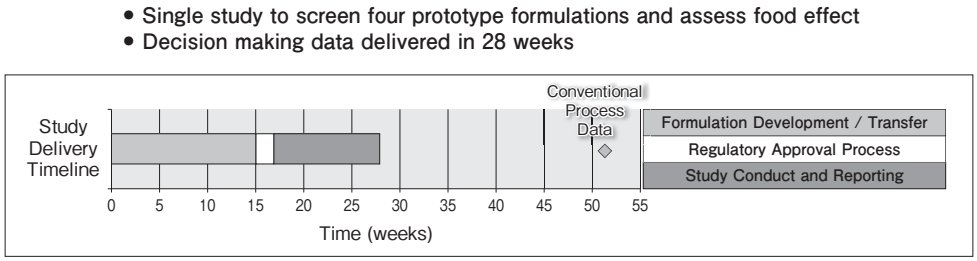
3. The third stage is the clinical conduct which includes subject recruitment and screening and running a 5 part crossover study (usually with a 7 or 14 day washout between doses). This takes 7 to 10 weeks according to the required washout period between doses

4. The final stage includes bioanalytical, pharmacokinetic and statistical analyses plus production of the draft and final clinical report. We usually allow 6-8 weeks for this process. Overall, it takes 6 to 7 months from contract signature to clinical report.

We are manufacturing drug product 'just-in-time' and submitting only the stability required to cover the period between manufacture and dosing, typically 7 days. This means that we are not required to manufacture large quantities of drug product in order to conduct long-term stability testing. By taking this approach we are reducing the amount of dosage units manufactured and also reducing the unnecessary waste of API (active pharmaceutical ingredients). This also shortens the time before the drug product can be dosed in the clinic. We have completed 20 of these programs for pharmaceutical companies. We have conducted a detailed review with those companies involved in the first 12 completed projects and in all cases when compared with traditional processes for prototype formulation development we have reduced the time from the start of the process to providing a new drug product and the overall cost by 50 percent.

We started doing this for small companies, but now most of our clients are top 20 pharmaceutical companies who see the clear advantages in terms of saving time and cost but with increased flexibility but are unable to change their internal manufacturing processes to achieve this. However, within 3 to 5 years, I think we will see a change in the way large pharmaceutical companies approach formulation support to early clinical trials particularly

Fig. 1　RapidFACT™ timelines



when addressing an urgent need to change formulation during a development program.

The pharmaceutical industry and the CRO sectors are organized into two clear types of function – the "Make" function (i.e. synthesizing API, developing formulations, manufacturing formulations, providing drug product on long-term stability) and the "Test" functions and organizations (pre-clinical or clinical testing). These two types of businesses or functions are very different, and are not integrated and as a consequence, time penalties are built between GMP manufacturing and GCP clinical testing. But by integrating manufacturing and testing as we have achieved, you can significantly reduce the time and the waste of API and in the process become more efficient and precise. But this is only possible where the national regulatory environment is permissive and where the sponsor company is willing to look again at the way in which drug products are supplied into these early stage clinical development programs. Those companies that are open to new ideas are benefiting considerably from application of RapidFACT ™ to the design of early clinical and formulation change programs.

2. Closed-door meeting with companies on microdosing

Interviewer Now we wish to move on the discussion to examine current thinking and application of microdose and microtracer techniques in early clinical development. We have been discussing microdosing since August 2009, when I visited your clinic in the UK. Could you please explain developments in this area over the past two years.

Stevens Before we go into further detail on microdosing I would like to clarify the difference between a microdose and a microtracer as they have very different applications.

The definition of a microdose we apply is that within the ICH M3(R2) guidance and is a dose $1/100^{th}$ of the predicted human pharmacologically active dose, up to a maximum of 100μg. A microdose may be administered as non-labelled or ^{14}C-labelled API.

Whereas, a microtracer is either a microdose or a therapeutic dose of API which contains a very small amount of a radiolabelled isotope (usually ^{14}C) and is used specifically to understand drug

Lloyd Stevens and interviewer: Chieko Kurihara

intravenous pharmacokinetics (*iv*-microtracer) or drug absorption/metabolism (oral-microtracer).

In June 2011we coordinated and hosted an "invitation only" one day, meeting in Washington with several key pharmaceutical companies that we knew had used microdosing and microtracers in various ways. The companies present were Bristol Myers Squibb, Novartis, GlaxoSmithKline, Pfizer, Merck, AstraZeneca and Takeda. Each one of the companies gave a 15-minute presentation on the microdosing and microtracer studies that they have conducted.

The focus of each presentation was on

- The design of the study,
- Why was the study conducted (objective and strategic purpose)
- The results obtained;
- Was it useful in terms of making decisions and moving molecules forward into further clinical development?

Then followed an open discussion to identify where these studies had given real benefit to compound selection or compound evaluation.

It was very clear that each company had used microdosing and microtracer studies for very different reasons that were driven by the need of the molecule, the strategy the company wanted to adopt, and the strength of the scientific and project management commitment behind it.

Interviewer Your company already had experience of working with these companies?

Stevens Yes, with most of them. We did invite other companies that we hadn't worked with as the meeting was not exclusive to our clients only. However as a result, only one of the participant companies had not worked with us in the past. We discussed the utilities, success and failures of the microdosing approach. There have been many scientists across the industry, including myself, saying what is possible through running a microdosing study but until that meeting in Washington, we haven't brought together a group of companies who have used it and asked specific questions concerning its usefulness in making key decisions concerning drug candidates.

Interviewer Can you give some examples where microdosing has been of significant benefit?

Stevens I'll give you 3 examples which are very different.

1. Potential Drug-Drug Interaction (Compound Screening). In this study the company wanted to assess whether back up molecules (all CYP3A4 substrates) when dosed as a microdose would show a similar degree of interaction already seen for a therapeutic dose with the lead compound. The company ran a ketoconazole interaction study where the victim drug was administered as a 50μg oral microdose before and during therapeutic dose ketoconazole at steady state. This was part of the candidate screening process before making a decision to take that molecule into Phase 1.

The data clearly showed that even at a microdose there was a 10-fold increase in the AUC of the victim drug in the presence of ketoconazole and that this was similar to the extent of interaction for a corresponding therapeutic dose of the lead molecule.

2. Evaluation of Pre-clinical Screen (Animal Species). Another example is a company that was using rat and dog to screen for PK data that could be incorporated into physiological modeling software to predict human bioavailability and pharmacokinetics. The problem they had was that the animal data was inconsistent and could not be used with confidence to predict human PK. The company undertook a microdose study, not to select a drug candidate but to identify which animal species was predictive of human pharmacokinetics. The microdosing study was conducted using non-radiolabelled drug and parent drug concentrations were deter-

mined using LC/MS/MS (Liquid Chromatography / Mass Spectrometry / Mass Spectrometry) assay which had an LLOQ approaching 1pg/mL. The study was very quick to perform as there was no requirement for either ^{14}C drug synthesis or AMS (Accelerator Mass Spectrometry) based determination of drug concentrations.

This work has been published as part of the article by Harrison, et.al. [4].

3. Screening Molecules for Compound Selection. A third example was a top 5 pharmaceutical company who had taken a lead molecule into Phase 2 but the pharmacokinetics did not fully comply with the target product profile. They wished to select the back-up molecule, but wanted to include human pharmacokinetics as a key part of that selection process. There were four potential candidates from a similar chemical scaffold. The microdose study was designed as a 5 compound comparison where the lead molecule already in Phase 2 was again dosed at a microdose and provided a micro and macro-dose benchmark against which the four candidate back-up molecules could be compared. Each molecule was administered in an intravenous/oral crossover design to the same subjects. This study was conducted at Quotient using ^{14}C-labelled drug candidates. However, the company first of all, looked at the pharmacokinetic data using LC/MS/MS bioanalytical methods (LLOQ=1pg/mL) and were able to obtain all the required pharmacokinetic data without the need to use AMS methods. . This perhaps is an example of the ideal study design for candidate selection where it is possible not only to compare candidate molecules at a microdose level but also to be able address the issue of dose extrapolation by comparing the micro and macro dose pharmacokinetics for the lead molecule.

Interviewer Do all microdosing studies rely on the administration of ^{14}C radiolabelled drugs and is LC-MS/MS capable to support a microdosing study with non-labeled candidates?

Stevens Microdosing studies do not always have to use ^{14}C radiolabelled drugs. We are currently doing a study for a company where they're conducting a traditional microdose study of 4 molecules where candidate selection will be based on clearance and half-life as the main differentiating factors. So we're only giving the drug intravenously. We are administering ^{14}C drugs but the primary PK data will be obtained using LC/MS/MS and AMS will only be used if the MS method does not give adequate sensitivity. When we started that program, we asked both the AMS and LC-MS/MS providers to define the LLOQ for their assays. Both came back with default LLOQs of 1pg/mL. When challenged on this the LC-MS/MS LLOQs were reduced to 500fg/mL and therefore we have a cold assay which is more sensitive than AMS. The analytical strategy therefore was to first look at the LC-MS/MS data and again only use AMS if the MS assay failed for whatever reason. One of the things that we always say to companies is, if you want to do a true microdosing study, the first thing to do is to push your LC/MS method. If you have good ionization; if you can take bigger volumes of blood; if you can push your assay sensitivity down to less than 1pg/mL then you should consider doing a cold microdose study. However, if you also want to have metabolism data, then you have to do a ^{14}C microdose study. Therefore, one of the key aspects for any microdosing study is to be very clear on the data you want to produce as this will determine whether or not to use ^{14}C or non-radiolabelled drug.

Interviewer It is very nice and do you have any plans to publish the meeting report or to have a similar meeting in the future?

Stevens We are planning another meeting with smaller companies. It just happened that the companies which agreed to meet in Washington were

from the top 10 pharmaceutical companies.

So there's been a lot of talk about microdosing, and we have condensed all of this information into a presentation that we are giving in the American Society of Clinical Pharmacology and Therapeutics next March. This is a poster presentation in collaboration with the companies that were involved.

3. World trend of microdosing

Interviewer　So what do you think is the situation regarding the conduct of microdosing studies in Europe, USA and the rest of the world?

Stevens　Europe does more microdosing studies than anywhere else in the world and I think this is because the GMP regulatory environment is much better defined and as a consequence there is more experience in conducting microdosing in Europe. In Europe, we have a process of regulatory approval where the national authority, particularly in the UK, can delegate certain GMP manufacturing responsibility to a qualified person (QP). This means that the QP takes responsibility for assurance of the quality control of that process and the QP will then be responsible for release of the drug product. That's not a situation that occurs in U.S. and in Japan.

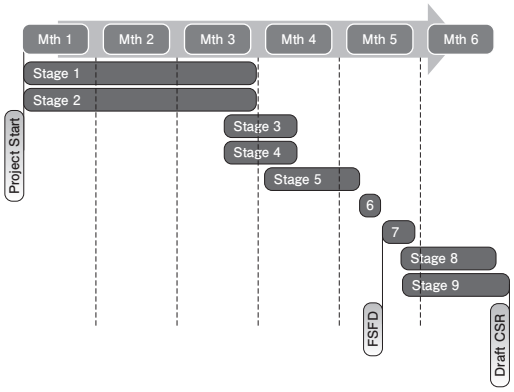
In the U.S., there is a process called "compounding". As I understand "compounding", this is a responsibility that can be taken on by the physician at the bedside, which is okay for dispensing drugs and dissolving drugs. But it won't allow you to undertake full GMP style manufacturing of intravenous drug product.

We've done 20 pure microdosing studies within the UK and with close integration of GMP with GCP in Quotient approximately seventy five percent of that business comes from the USA. For 1 project, it takes about 6 months (Fig. 2). Currently, most microdosing studies are set up by large pharmaceutical companies; not from smaller pharmaceutical and biotechnology companies.

I think one of the factors that help us provide different services in the UK is that we have an open regulatory environment which is very flexible. For example, we can put together multi-part protocols where a single protocol may include single and multiple ascending doses in healthy volunteers and a safety/PK/pharmacodynamics part in patients. That's three parts of one protocol. We have one regulatory submission, and at Quotient we can support that protocol with just-in-time GMP manufacturing.

Interviewer　Are there any successful exam-

Fig. 2　Microdosing: illustrative timelines



Stage	Activities
Project start	Contract execution: exchange of materials and information
1	Synthesis of ^{14}C API
2	Preclinical toxicology studies (rat)
3	CMC program: oral / iv formulation development / validation
4	Transfer of bioanalytical method
5	Clinical protocol development, EC and CTA preparation, submission and approvals
6	Volunteer screening (1 - 2 weeks)
7	Clinical conduct (1 - 2 weeks)
8	AMS analysis (7 - 10 weeks)
9	Biometrics, PK analysis, metabolite profiling and ID, clinical reporting (7 - 10 weeks)

ples of genuine microdosing that reached marketing authorization?

Stevens Yes. One of the very first microdose studies was not the study that we conducted, but it was conducted for a company called Speedel who screened three candidate renin inhibitors in a microdose study They selected one molecule that was put into development. I think that molecule has now achieved registration. Speedel was acquired by Novartis.

Interviewer How many microdosing and microtracer studies have you conducted so far?

Stevens I think in terms of microdosing and microtracer, we've probably dosed more than 50 different molecules over the past 6 years.

Interviewer How many are genuine microdose studies?

Stevens Genuine microdose molecules, about 25. The other 25 would be "*iv*Microtracer™". Most of the *iv*Microtracer™ studies have been to support formulation development programs. However, at present we are conducting less microdosing and more *iv*Microtracer™ studies.

Interviewer Are most of the Phase 1 studies conducted in the UK first-in-human?

Stevens It is difficult to answer that question accurately. As I think a high number of the 210 MHRA Phase 1 applications in 2010 would be multi-part protocols. There would be various stand-alone or combinations of first-in-human single and multiple ascending dose, bioavailability, biosimilars, drug/drug interaction, gender, age, food effect study designs.

Among the 210 or so phase 1 protocols that the MHRA reviewed in 2010, Quotient submitted approximately 50 of those. So the regulatory authorities are very familiar with our GMP approach to formulation screening, just in time manufacture, intravenous products, ^{14}C-products, etc.

Interviewer How about Japanese companies? Do many Japanese companies conduct studies at your laboratory?

Stevens Yes of course. We have conducted *iv*Microtracer™ or microdose for approximately 10 Japanese companies. For one company we have done a pure microdose study, but that wasn't compound selection. In fact it was a specific example of a drug which had species differences in toxicology which was associated with one metabolite. And the question, "Is that metabolite produced in man?" was answered using a microdose design.

We have done intravenous and oral microtracers for other companies in Japan, studies that had been set up directly with the Japanese office or through the European and U.S. offices of the company. We have done one study which was unique to a Japanese company, where the same group of subjects received an *iv*Microtracer™ to determine the absolute bioavailability and after a suitable washout period, the same group of subjects received a full radiolabelled dose to determine the human metabolism for regulatory purposes.

4. On the issue of cassette dosing

Interviewer Do you think that if you were to conduct a cassette microdosing study that the toxicology studies required would be for each compound individually or for a mixture of all the compounds?

Stevens I see two main issues with conducting cassette microdosing studies. The first of these concerns the toxicology requirements to support administration of a drug cocktail. I have had "off the record" conversations with several members of two regulatory authorities in Europe and all agree that a cassette dose to humans must be supported by a cassette dose in the toxicology studies. The second main issue is all to do with the chromatography

used to separate the drugs and their metabolites. It is a much greater chromatographic challenge when fractionating samples for AMS than when using MS to identify and quantify analyses. The only example I am aware of where a cassette dose has been administered to humans is the work from Professor Sugiyama in Tokyo who administered a cassette of marketed drugs and used LC-MS/MS to provide the PK data. I am not aware of any ^{14}C-drug cassette dosing requiring AMS detection.

The other method to compare the pharmacokinetics of two NCE drugs is to use the same subject for the cross-over design. At present, if you look at the scope within the ICH-M3 regulations, they do not allow you to use the same volunteers in a cross-over basis looking at different NCE molecules (unless the preclinical toxicology has been conducted with both molecules in the same animals). So if you want to compare molecule A with molecule B, the most practical way is to use two separate cohorts of subjects. You can't put both drugs into the same subject for a cross-over.

Interviewer But there is no description about it in the ICH-M3. It does not directly prohibit such kind of study.

Stevens If you have the appropriate supporting toxicology then a cassette or cross-over design study could be conducted in healthy subjects. Until now I am not aware of any company doing this.

Interviewer So you don't have any project experience with PET?

Stevens We explored it about 3 or 4 years ago. But the UK clinical environment at that time was not set up for commercial PET studies. Most of the PET machines are supported by the NHS (National Healthcare Service), and these machines are in place mostly for patient diagnostic purposes. I know one is in Imperial College, and it's supported by GSK. In Europe, there are some places in which PET machines are set up, but they tend to be supported by individual pharmaceutical companies.

5. Understanding drug pharmacokinetics through *iv*Microtracer™

Stevens One thing that has been changing the last year (2010) is that a lot of companies will now use an *iv*Microtracer ™ in Phase 1 to determine absolute bioavailability and intravenous pharmacokinetics. We find that one of the departments in the company that's driving this more than anybody is Formulation Development because they use the *i.v.* data to simulate and model an input function to support development of modified delivery formulations.

Interviewer Could you explain about the "*iv*Microtracer ™"?

Stevens In terms of the regulations, the "*iv*Microtracer ™" is a microdose and therefore conforms with ICH-M3 definition of a microdose. In this case, we are administering an intravenous microdose of the drug which contains no more than 250 nano curies of ^{14}C. This amount of radioactivity is very low and we did not need any supporting dosimetry or tolerance and safety data. The formulations that we use are manufactured using pharmacopoeial grade materials.

The concept behind the *iv*Microtracer ™ is that the intravenous dose is given at the t_{max} of the oral dose. For example, the oral dose could be a hundred milligrams; so the intravenous dose would be not more than 100 micrograms which is a thousand times lower. Now the intravenous dose is ^{14}C-labelled. The oral dose is cold at a therapeutic dose level. So the oral cold pharmacokinetic profile would be determined using LC/MS/MS, but the intravenous profile would be determined using chromatography to give you specificity coupled with AMS (accelerator mass spectrometry) to give

you the required sensitivity. This means that you can determine intravenous and oral pharmacokinetics in the same subject at that same time. So you could administer this *iv*Microtracer ™ dose on top of any one of your doses in a single ascending dose, in a multiple ascending dose, in any oral bioavailability study. You can conduct *iv*Microtracer ™ in any other oral study. This can be achieved in volunteers and in patients. The introduction of an *iv*Microtracer ™ into any other bioavailability or dose escalation study does not add to the timelines for the study providing that ^{14}Cdrug is available. It takes about 5 months for whole the process (Fig. 3).

Interviewer Do you have experience in conducting successful *iv*Microtracer ™ study – to support marketing authorization?

Stevens Yes, we do. We're doing some work with Bristol Myers Squibb. BMS has a product called Onglyza® (saxagliptin). And they plan to more fully develop and sell this product in collaboration with AstraZeneca. However, the Australian regulatory authorities insisted on having absolute bioavailability data and as a consequence BMS came to us to conduct and absolute bioavailability study using the *iv*Microtracer ™ approach. This study has been completed and the data has been reviewed and accepted by the Australian authorities.

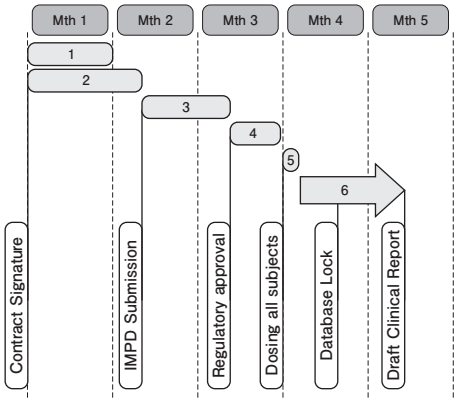
Interviewer In your presentation slide at the JSCPT, there is also the case of conduct of *iv*Microtracer ™ according to the requirement by United States FDA (Food and Drug Administration).

Stevens Yes there was. Absolute bioavailability data was requested by the FDA and the US west coast company asked us to conduct an *iv*Microtracer ™. This was completed in 4 months and successfully submitted to the US FDA.

Interviewer Do companies use oral microtracer studies in the place of the traditional human ADME study?

Stevens This is a key question regarding oral microtracers. To be clear, an oral microtracer is where you have a therapeutic dose of drug which contains a very small amount of radioactivity. We have conducted these studies for a Japanese company where an oral microtracer was administered as part of a single ascending dose study in healthy subjects. The purpose was to determine the metabolic fate of the drug early in clinical development. However, one question we are always asked is – would the oral tracer approach replace the full regulatory high-dose ^{14}C? Scientifically it could. There's no reason why it could not; but at present

Fig. 3 *iv*Microtracer: illustrative timelines



Stage	Activities *(assumes safety package and ^{14}C material is available)*
1	Protocol drafting, regulatory preparations (4 wks)
2	Receipt of supplies - *In vitro* program - iv formulation / validation (4 - 5 wks)
3	EC & CTA Submissions (4 wks)
4	Recruitment & Screening (2 - 3 wks)
5	Clinical Conduct (1 day)
6	Bioanalysis, Data Management & Reporting (7 wks)

the industry and the regulatory authorities do not have the experience or the volume to be confident in saying, "Yes, I can guarantee if you use an oral tracer approach this will satisfy the regulatory requirements. The main barrier to using microtracers for all metabolism studies is more to do with the logistics of turnaround times for the AMS assay and being absolutely sure in the chromatographic separation of the various metabolites. With traditional human ADME studies you use high amounts of ^{14}C and can use radiochemical detection to monitor changes in the chromatography and get your results almost instantaneously. With AMS detection following sample fractionation you may have to wait a week for each chromatographic run, so logistically, it is more challenging from a technological view and also more expensive.

Here is a good example of a company using the *iv*Microtracer™ approach to define the intravenous pharmacokinetics of a drug. This example is from a company that had a drug which had been through Phase 1, Phase 2 – oral administration – but wanted an intravenous drug product to be used in an intensive care setting where patients would have blood flow related changes to drug clearance. With this in mind the company wanted intravenous PK data for modeling and simulation in order to determine the appropriate intravenous infusion regimen which accounted for reduction in drug clearance.

6. Influence of EMEA and MHRA policies on first-in-human study

Interviewer There is another topic that I would like to discuss. What has been the impact of the EMEA's guideline on first-in-human study and MHRA's policy on phase 1 studies conducted in the UK?

Stevens The MHRA have introduced a method of risk analysis for new chemical entities going into first-in-human studies. If your compound is classified as "high risk" it is reviewed through a different regulatory process where you would base your dose calculation on pharmacological activity via MABEL (Minimum Anticipated Biological Effect Level) principles and not toxicology. That's one aspect.

Another key change we have seen is that, under the MHRA policy, all CROs in the UK have to be accredited to conduct studies in healthy subjects and if you are conducting a study with a "high risk" molecule it could only go to a site which has "supplementary" accreditation. But I think most of the clinical CROs in the UK that are serious about first-in-human studies have supplementary accreditation. At Quotient we have supplementary accreditation. This higher level of accreditation relates to procedures for safety and resuscitation; emergency support.

The other consequence that we've seen in changes in Phase 1 environment is that we would employ sentinel dosing for a very first-in-human study. . So if you have 8 subjects – 6 are active, 2 are placebo – we will dose two subjects one day ahead of the main cohort, and those two subjects will be one active and one placebo. There will be an initial assessment of safety and if everything is OK then the next day we will dose the remaining six subjects. This has become a standard procedure now within all first-in-human studies with new chemical entities in the UK I don't know in other countries in Europe.

Interviewer Is there any increase in the cost of running such kind of study?

Stevens Of course, because if you are running two subjects a day ahead of the rest, that does add to the cost. It's not that much, but it does add to the cost.

Interviewer As you said, there is real change in the required preclinical data – particularly from

toxicology data towards pharmacology for the "high risk" molecules as defined by the MHRA?

Stevens Yes, I think there's a general trend to generate much more data on the pharmacology. We certainly see much more information in the Investigator's Brochure for biomarker responses, that is, wet biomarker, and pharmacological responses. There's a lot more. Certainly when we are reviewing investigator's pre-clinical data, we are seeing more data on defining receptor occupancy, target concentrations, target effective dose levels more so than we did ten years ago.

Interviewer Thank you so much for your precious time and very informative discussion. In Japan, first-in-human studies are promoted now and we will be able to learn which direction we should go from your plentiful experience.

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