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

I Shaw[1], G Johnston[2], K Dare[1], D Dams[2], Quotient Bioresearch

1. Quotient Bioresearch, Clinical Sciences, Nottingham, UK
2. Quotient Bioresearch, Chemistry and Metabolism, Rushden, 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"

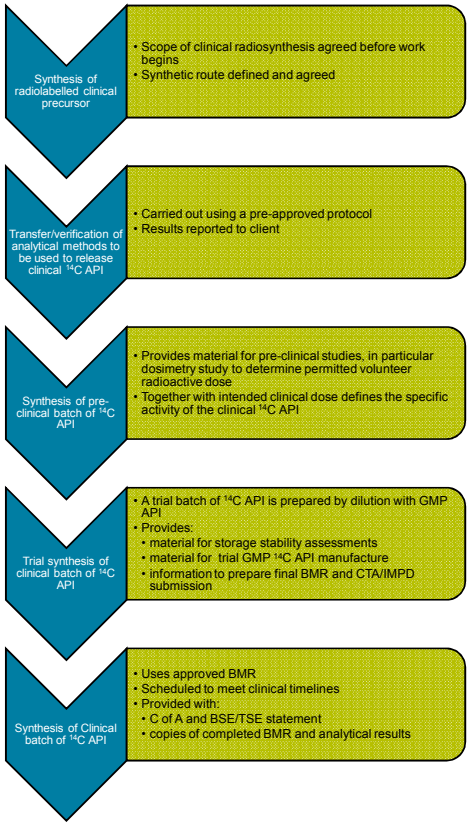
The QA BMR statement page is signed followed by formal QA release of the CLINIC READY ^{14}C API.

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