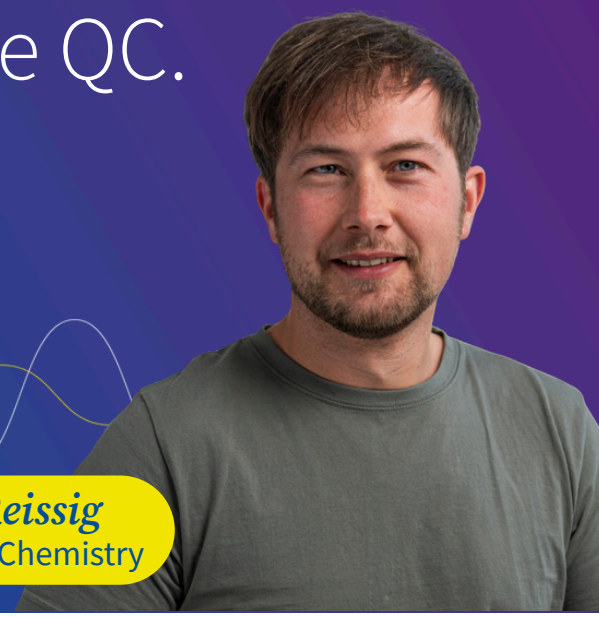
Radiolabeling Development.

From First Idea to Routine QC.

Why Radiolabeling fails in Practice – and How to make it GMP-Ready.



CUP contract labs

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Executive Summary

Radiolabeling represents a critical and highly sensitive step in the development of radiopharmaceuticals. While scientific concepts may demonstrate strong performance under controlled laboratory conditions, many programs encounter significant challenges during scale-up, technology transfer, and GMP execution.

Radiolabeling processes and quality control of labeled products are inherently complex and influenced by multiple interdependent factors, including radiolysis, precursor stability, formulation conditions, and analytical variability. As a result, insufficient process understanding or lack of early standardization may lead to batch variability, transfer failures, or delays in clinical development.

A structured, integrated development strategy—combining radiochemistry, analytical method development, and early consideration of GMP requirements — is therefore essential. Successful programs treat radiolabeling not as an isolated step, but as a system that must be understood, controlled, and reproducible across development stages and manufacturing environments.

Market Context and Regulatory Framework

The field of radiopharmaceuticals is experiencing rapid growth, particularly in targeted radioligand therapies and precision oncology. Increasing clinical activity, more complex molecular designs, and higher regulatory expectations are placing growing demands on Chemistry, Manufacturing and Controls (CMC) development.

Regulatory authorities require robust, well-characterized processes and reproducible analytical methods to ensure product quality, patient safety, and reliable clinical supply. At the same time, short half-lives and radiation protection requirements impose strict operational constraints on development and manufacturing.

Within this environment, radiolabeling becomes a central determinant of development success, influencing validation strategies, technology transfer, and ultimately GMP batch release.

Scientific Background

Radiolabeling involves the incorporation of radioactive isotopes into complex molecular structures under tightly controlled conditions. The resulting product must meet strict requirements for radiochemical purity, stability, and reproducibility.

However, radiolabeling systems differ fundamentally from conventional pharmaceutical processes. Radioactive decay induces radiolysis, leading to degradation pathways that directly impact impurity profiles and product stability. In parallel, precursor characteristics, buffer composition, and process conditions influence labeling efficiency and reproducibility.

Analytical methods play a critical role in this context. Techniques such as radio-HPLC, LC-MS, and ICP-MS are required to assess identity, purity, and stability. These methods must not only be scientifically sound but also robust across different laboratories, equipment, and development stages.

From Lab Success to GMP Failure

A critical gap in radiopharmaceutical development lies between early feasibility and reliable GMP execution.

Typical failure modes include:

- Inability to demonstrate process robustness during validation
- Unexpected variability during scale-up
- Technology transfer failures due to hidden dependencies
- Inconsistent analytical results across sites
- Batch failures driven by short shelf-life and unstable processes

These challenges highlight a fundamental issue: successful radiolabeling in early development does not guarantee GMP readiness.

Bridging this gap requires a systematic approach that integrates process understanding, analytical development, and manufacturing considerations from the outset.

Radiolabeling Development.

Structured, Integrated Development Approach

A structured, end-to-end development strategy is essential to ensure that radiolabeling processes are not only scientifically feasible, but also robust, reproducible, and transferable into GMP environments.
The following framework illustrates how early strategic decisions, process development, analytical methods, and validation are systematically aligned to enable reliable routine GMP testing and batch release.

Industry Perspective: Radiolabeling in Real-World CMC Development

Experience from early-stage radiopharmaceutical development highlights a recurring challenge: processes that perform well under laboratory conditions often fail to translate into robust GMP operations.

Key challenges observed in real-world development include:

- Radiolysis-driven degradation affecting impurity profiles over time
- Sensitivity of precursor quality and formulation parameters
- Limited reproducibility when moving from small-scale to clinical batches
- Variability between laboratories, CROs, and CDMOs
- Analytical inconsistencies due to differences in methods and equipment

These factors demonstrate that radiolabeling is not a fixed or universally transferable process. Instead, it is highly context-dependent and must be adapted to specific development and manufacturing conditions.

As a result, many failures are not caused by fundamental scientific limitations, but by insufficient process understanding and lack of standardization across development stages.

Radiolabeling success therefore depends less on initial performance and more on the ability to understand, control, and reproduce the system across different conditions, scales, and environments.

Practical Lessons from CMC Development

Experience across multiple development programs shows that successful radiolabeling strategies share common characteristics:

- Early definition and locking of analytical methods and process parameters
- Testing under clinically relevant conditions from early stages
- Development of methods with transferability in mind
- Systematic evaluation of formulation stability
- Parallel testing across different laboratory environments
- Structured experimental design and data-driven decision making

These principles transform radiolabeling from an experimental activity into a controlled and predictable development process.
A key success factor is the early alignment between process development and analytical strategy. Without a clear analytical framework, critical parameters and potential risks often remain undetected until late-stage development or technology transfer.
In addition, robust radiolabeling programs are characterized by a strong focus on reproducibility under real-world conditions. This includes not only controlled laboratory environments, but also variability across equipment, operators, and sites—ensuring that processes remain stable and reliable throughout the entire development lifecycle.

Our Analytical toolbox:

Radio-TLC · HPLC (UV / Radio)
LC-MS/MS · GC-MS · ICP-MS

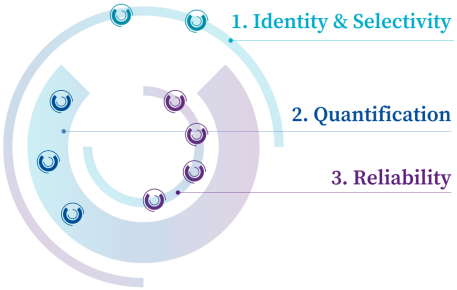
Comprehensive analysis of identity, radiochemical purity, impurities, and stability across development stages.

Broad radionuclide handling capabilities within licensed facilities, ensuring analytical reliability under GMP-relevant conditions.

Radiolabeling Development.

From development to validated performance

Method validation ensures that analytical methods are fit for GMP use, in accordance with ICH Q2 guidelines.
We follow a structured validation approach to obtain GMP-compliant analytical methods ready for routine use and reliable batch release.



This includes the evaluation of key validation parameters such as specificity, linearity, range, accuracy, precision, limit of quantitation, robustness, and stability, ensuring reliable and reproducible analytical performance.
A particular focus is placed on impurity control and method performance under stress conditions, enabling robust results even in the presence of degradation products, matrix effects, or minor process variations.

Regulatory Insight

Validation requirements depend on the clinical development phase.
For early-phase trials, analytical method suitability must be demonstrated, including defined parameters and acceptance criteria.
In later phases, structured validation data is required in summarized form, in line with IMPD and similar expectations.

By integrating these parameters into a structured framework, analytical methods become both regulatory-compliant and suitable for routine GMP use across different laboratories and environments.

Strategic Value

A structured and integrated radiolabeling strategy significantly reduces development risk and improves the likelihood of successful GMP implementation.

Early process understanding enables:

- Reduced risk of late-stage failures
- More efficient technology transfer
- Increased reproducibility across sites
- Improved batch release reliability
- Faster and more predictable clinical development timelines

Collaboration with experienced analytical partners allows companies to establish robust processes and generate regulatory-ready data without building extensive in-house infrastructure.

Conclusion

Radiolabeling is a central and highly sensitive step in radiopharmaceutical development. Its complexity extends beyond chemistry and requires a deep understanding of interconnected process, analytical, and operational factors.
Programs that treat radiolabeling as an isolated step often encounter significant challenges during validation and GMP execution. In contrast, an integrated development strategy—combining early process understanding, robust analytical methods, and structured validation—enables predictable and reproducible outcomes.
In an increasingly demanding regulatory and competitive environment, such an approach is essential to ensure reliable product development, successful technology transfer, and consistent GMP performance.

EXPERT VOICES

"I am fascinated by radiolabeling because it combines radiochemistry and state-of-the-art analytics.
I can see the results immediately, optimise methods and thus ensure that our radiopharmaceutical products **meet the highest quality standards right from the start** – for the safety of patients."

Dr. Konstantina Makrypidi
Expert Scientist

Any questions?
Let´s talk.

CUP contract labs
Leading the way in Complex Pharmaceutical Analysis.

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