Roundtable Session – Table 1 – Targeted Radiopharmaceuticals – Raising Awareness of the Regulatory CMC Challenges and Approaches to Harmonising Regulatory Expectations

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Abstract:

Targeted radiopharmaceuticals are a relatively new class of modality that can potentially change the way cancer is treated by enabling precise targeting of tumours at the molecular level and delivering cancer cell killing doses of radiation. This includes the exciting area of theranostics, where diagnostic (imaging) and therapeutic radiopharmaceuticals are co-developed. There are a large number of clinical trials ongoing using such modalities that vary in terms of radionuclide used and the nature of the targeting scaffold (large or small molecules).

In the last year, there has been an increase in the number of guidance released, across both the clinical and CMC related topic areas. This demonstrates the momentum building in this class of new modality, and the push to provide greater clarity in agency expectations. Recent examples from the CMC field include the QWP draft guidance for radiopharmaceuticals, CDE guidance on antibody-based radiopharmaceuticals and Radiopharmaceuticals EU-IN scanning report, with additional guidance due in 2026 like the BWP draft guidance (Radiopharmaceuticals based on Monoclonal Antibodies, 3AQ21a).

Based on cross-industry discussions on some of the above draft guidance, a number of CMC-related challenges are emerging that could slow patient access to these new modalities, especially if requirements and regulatory pathways are not harmonised across global markets. These include ensuring flexibility in the CMC information we provide in clinical and marketing dossiers, where scientifically justified on a risk-based approach, categorisation of radionuclides/precursors and appropriate control strategies for radiopharmaceuticals.

Discussion Questions:

1. What are the unique CMC challenges that industry faces, in the development and manufacture of targeted radiopharmaceuticals and which have regulatory components?

2. What are the common regulatory CMC cross-industry challenges, with regards to clinical and marketing phase dossiers?

3. From an agency perspective, what are the challenges in the review (and approval) of clinical and marketing dossiers of a radiopharmaceutical?

2 – Agency, 3 – Industry

- QWP & BWP Guidance is pending, current EU guidance recognized as out of date
- Expertise is not ubiquitous

Notes:

1. What are the unique CMC challenges that industry faces, in the development and manufacture of targeted radiopharmaceuticals and which have regulatory components?

- Terminology needs to be aligned. Even the language becomes confusing. E,g, definition of “intermediate” vs “radionuclide”, “precursor”, or others…
- Definition of “active substance” and the fact that this is not isolated
- Difference between “kit” use and ready-to-use therapies. Predominant experience is with kit products and changing perceptions could be difficult.
- Focus on radionuclides as these are novel and critical to the safety and efficacy of the radiopharmaceutical, in combination with the targeting vector”

Manufacturing challenges:

- Point of control is tricky to define. What is necessary for release?
- Supply of the radionuclide is critical. This means in practice that many more suppliers are required than would be normal for a more standard therapy. Managing these suppliers and the consequent regulatory information presents a challenge. The masterfile concept could drive efficiencies in this context.
- What can be learned from ATMPs? Some things can be thought about, but the flexibility that comes from the variability of the patient is not relevant. However the use of rapid sterility methods, common in ATMPs, could be applied to these products.
- Appropriate control strategies for both kit and ready-to-use products is key. These should be distinct and reflect the needs of both product types.
    - Kits: more emphasis on upfront control on precursors/validation of process
    - Ready-to-Use: more traditional end-product testing, but still a need to reduce this by e.g. using RTRT approaches, especially in cases where the half-life of the radionuclide is relatively short
- The half-life of the radionuclide is key to the appropriate control of the project
- Because of the length of the standard sterility test, it may not be possible to do this before the patient is dosed. Use may be made of rapid sterility testing, commonly used in ATMPs.
- Industry needs flexibility in operations to cover a multitude of different use scenarios. It may be necessary from an occupational exposure perspective to use multi-use vial, where product will be extracted by repeated piercing, rather than a single use vial.
- Multi-pierce vial closures are typically used to minimize handling exposure, and are an important option in radiopharmaceutical manufacturing processes

- There may also be occupational exposure considerations applied to QC testing which have an impact on the testing of radiolabelled finished product.
- In all cases, the method of manufacture and testing would be supported by an appropriate control strategy to minimize the risk to the manufacturing personnel, handlers and the patient, whilst maintaining appropriate levels of quality, safety and efficacy.
- Assessment of impurities is a major factor
    - Free radionuclide (safety issue)
    - Free precursor (more for quality)
- Typically, only ~1% of the conjugate is "active". The excess is necessary – it's not an impurity. Probably something to describe in the characterisation section. Context is key. The excess precursor is added by design for safety reasons to ensure that the amount of free radionuclide is minimized. By this, the excess is neither an impurity nor an overage, but does need discussion.
- This should be covered in the formulation design section and some thought given to whether there is a need to optimize the free precursor. Questions of the therapeutic effect of the precursor should be also be considered (similar to free mAb in ADCs), but it was discussed about the sub-therapeutic level typically administered.
- Again, the imaging paradigm becomes key to understanding suitable pathways
- Isotopic purity is key. Different isotopes will introduce new decay pathways and potentially vastly different half-life. This must be considered as part of the control of the radionuclide.

3. From an agency perspective, what are the challenges (opportunities) in the review (and approval) of clinical and marketing dossiers of a radiopharmaceutical?

- Greater use of the masterfile concept will be very important. This was used successfully for a recent filing (^{131}I radionuclide) and the expansion of the Masterfile concept in the NPL is a welcome development and should facilitate efficiencies.
- The control of multiple manufacturers of radionuclide presents a challenge from a GMP perspective. Adequate control of these sites should be assured by the manufacturer, including control of the use of masterfiles and appropriate disclosure of information.
- Need to ensure disclosure for safety reasons of certain parameters, maybe around the isotope balance
- Inspection is probably centred on the facility doing the fill finish. How might this be facilitated isn't clear.
- Comparability of the precursor, from the perspective of ICH Q5E, may still be a factor. Point of control is still key.

- Theranostics is a very important concept – though this breaks into the "companion diagnostic" sphere and adds a further level of complexity.

- The ability to select patients based on scanning may shorten clinical trials significantly and to shorter development timelines
- Could mean that there is less time for CMC development and a need to use more creative regulatory strategies to match clinical timelines (e.g. greater use of tools in the PRIME toolbox).