How to Succeed in Science

How to Develop a Clinical Product

Ultrasound Molecular Imaging: How to Develop Clinical Products

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Learning Objectives:

- Identify the various steps to be followed between an early development stage to a final product to be used in humans
- Raise the specific issues to be considered when developing a new agent
- Identify possible causes of failure when developing a new agent

The introduction of targeted contrast agents among agents eligible for ultrasound molecular imaging (USMI) has reinforced the interest for this method and significantly broadened the scope of CEUS but in the same time, has raised significant issues with regard to the agent to be used clinically (1,4-8,11-14,16). When entering the USMI domain, the need to add a ligand to target a specific molecular marker/signature implies the validation of the targeting moiety and more precisely, the compatibility with regulatory requirements for a human use. The bubble size is not significantly modified by the presence of a ligand meaning that the specific characteristic of these agents as strict markers of the vascular bed is still a property which can be considered as a great advantage for quantification in some indications, such as therapeutic treatment monitoring. The specific issues considered for such agents are strictly related to the nature of the ligand itself and the mode of attachment to the shell membrane. Whereas preclinical tests have been performed with a biotin-streptavidin linker, the impossibility to translate this construct into clinics due to possible immunogenicity has conducted scientists to propose alternative methods compatible with human use. From a regulatory point of view, the gas microbubble is considered as the active entity meaning that each of the microbubble components should be fully characterized. The manufacture of clinical material should be carried out in compliance with the GMP guidelines. With respect to the formulation characteristics, the selection of the ingredients is of paramount importance since the use of specific components should be validated for these new drug delivery systems for parenteral administration. In that perspective, the retained formulation for clinical trials must be challenged before finalization as changing any of the components at a late stage could be difficult and costly, even impossible. Once the formulation is finalized, many steps must be accomplished before any clinical use: robustness of the manufacturing process, stability of the product, validation of the test methods. Another requirement is completing a pharma-toxicology package according to the International Conference on Harmonization (ICH) guidelines. These different steps are time-consuming and relatively expensive. Finally, when the steps above have been completed, the agent is suitable for clinical testing pending Investigational New Drug (IND) submission and Institutional Review Board (IRB) or ethical committee approval for the selected indication. At present, literature is rich of papers reporting good results with targeted UCAs in many animal models. However, only one agent BR55 (Bracco Imaging, Milan, Italy) entered clinical testing so far. This illustrates the difficulties to develop a suitable approach for clinical use. The development time of such agents does not differ significantly from what is currently reported for therapeutic drugs, i.e. at least 10 years. The translation to clinics targeted agents requires high level expertise to develop suitable agents according to the various constraints.

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