How to Bring an Agent to the Market

Translating a new MRI pulse sequence, acquisition/processing scheme, or RF Coil into the clinic involves a certain level of clinical trials and regulatory approval. However, to translate an MR molecular imaging agent requires a great deal more since both the agent and the imaging must be tested. As a result, the overall translational pathway is much longer, complicated, and costly;

1) The following highlights some of the major concepts of the path to clinical translation. It is not comprehensive and, although presented linearly, represents an iterative process.

1) An Idea is Born
   a) Pertinent Clinical Need is vital. A great idea “looking for an application” is not sufficient.
   b) The Clinical Need drives development and, ultimately, the clinical use (i.e., market).

2) Formulating the Agent
   a) Always think forward about “drugability” (the ability to be developed, produced and used commercially as a pharmaceutical agent considering the technical, clinical, and financial aspects) and technology transfer (see below).
   b) From the beginning, consider the impact of manufacturing and sterilization processes, shelf life (both for stability and sterilization), number of API’s (active pharmaceutical ingredients – as defined by FDA), number of possible enantiomers, etc.
   c) Consider overall cost (not just of materials, but also of manufacture, QA and analysis).

3) Preclinical Testing – Where the concept is demonstrated
   a) Both in vitro and in vivo testing demonstrate feasibility that the agent works and that images can be acquired using realistic doses, timing and other parameters.
   b) Additional in vivo testing, often in multiple species, provides data about PK (pharmacokinetics), organ distribution and clearance, and toxicity.
   c) Preclinical testing provides opportunity to identify challenges and obstacles, i.e.:
      i) How will the images be processed and quantified? What data/result is the clinically-important information?
      ii) Are there any MRI Hardware / Software limitations to overcome (e.g., Resolution, Sensitivity/SNR, Coils, Motion, etc.)?
      iii) Does the combination of Agent & Acquisition require unique acquisition techniques that may not be clinically available?
   d) QUANTIFICATION: Images alone are likely inadequate.
      i) Beyond basic post processing, what information is derived, how is it quantified and reported?
      ii) Are QA/QC processes required?
      iii) Are “special” techniques required (e.g., mapping of $B_0$, $B_1$) for accurate quantification?

4) Company to Commercialize – Once preliminary testing indicates a potential product, a company must be formed (or recruited) to commercialize it.
   a) If creating a company, the following must be considered:
      i) Incorporation  iv) Personnel
      ii) Business Plan  v) Facilities
      iii) Funding  vi) Intellectual Property

5) Technology Transfer – Conveying the manufacture, characterization, and imaging of the agent to the new company is far from trivial.
   a) What works in the lab will need to be adjusted for commercialization, but must still work equal to or better than original.
   b) Adjustments include:
      i) Product Ingredients
      ii) Manufacturing Procedures
         (1) rework, e.g., from milliliter volumes to liter batches
         (2) must be under cGMP (current Good Manufacturing Practices)
(3) yield from ‘benchtop’ methods may be unacceptable for commercial purposes, and/or the process may have too many steps

iii) May need to reduce number of API’s or possible enantiomers

c) Analytical Methods

i) If not transferred, must be developed.

ii) Each API requires analytical test for characterization for release, dose confirmation, and in biological fluids for PK.

iii) Some drugs may require more than 20 different parameters to be characterized.

d) Once transfer is “finalized”, efficacy studies should be repeated with the “new” agent for confirmation.

6) From Research to Development – Once tech transfer is complete, product development begins

a) Pharmacology / Toxicology Studies – conducted under GLP, typically on multiple species

b) Historically, approx. only 1 in 50 candidates makes it beyond this point.

c) If the agent is ready to move to human studies, an IND must be filed for a specific indication.

7) Investigational New Drug (IND) Application[3]

a) An IND is an exemption for a marketing permit and allows experimental agent to be tested in humans.

b) There are various IND types, and the IND must be filed with the FDA division that applies to the chosen clinical indication.

c) An IND Application includes information in three broad areas:

i) Pharmacology and Toxicology Studies

ii) Manufacturing

iii) Clinical Protocols and Investigator Information

d) FDA has 30 days to review and either grant the IND or respond with questions to be addressed.

8) First-in-Human Clinical Trials

a) Depending on product, may be in healthy normal volunteers or patients with the disease indication

b) Primary purpose is to establish safety (minimal risk) in humans

9) Four Phases of Human Clinical Trials[4]

a) Phase I – new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

b) Phase II – larger group of people to verify effectiveness and to further evaluate safety.

c) Phase III – large groups of people to confirm effectiveness, monitor side effects, compare to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

d) Phase IV – done after the drug or treatment has been marketed to gather information on the drug’s effect in various populations and any side effects associated with long-term use.

10) Making it to Market

a) Business plan is updated to marketing, selling and distributing.

b) Exit Strategy – Is the company capable of “going it alone”? If not, partnering or purchase may be required.

For Further Reading:

- http://www.fda.gov/nanotechnology/
- http://imaging.cancer.gov/clinicaltrials/

Bibliography:


