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Specialty area: Molecular & Cellular Imaging: From the Bench to the Bed

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Highlights

- Molecular imaging agents regulatory approval complex, time consuming and costly

- Many molecular imaging agents reply on the use of nanoparticle as a platform for contrast label generation and targeting

- Guidance from the FDA is evolving

Title: Regulatory Challenges

Target Audience: attendees interested in molecular and cellular imaging and its translation to human.

Objectives: After the talk, attendees should be able to understand the safety and regulatory issues in molecular imaging and nanotechnology.

Purpose: Development of a new molecular imaging agent will undergo the same degree of regulatory oversight as the development of a new drug. As expected the regulatory process is complex, time consuming and costly (Buxton D et al. Circ 2011; 123:2157-2163). In the USA, the process for approval is dictated by the FDA. The reimbursement is approved by the Center for Medicare and Medicaid (CMS) and insurance carriers. The discovery and development of molecular imaging agents is similar to the current therapeutic drug development process (see Figure 1). It is estimated the time and cost to bring a therapeutic to the market is 10-17 years and 0.8-1.7 billion dollars, respectively. In contrast, the cost to bring new imaging agents to market has been estimated to be $100-$150 million (see Table 1 and Frangioni J Nature Biotechnology 2006; 24:909). Many of the newer molecular imaging agents are expected not to have the broad markets for sales compared to the typical contrast agent. Therefore, the development process may even be slower and more complicate and thus costlier (Chapter 76 Hoffman JM from "Molecular Imaging Principles and Practice" Eds. Weissleder R; Ross BD; Rehemtulla A; Gambhir SS 2010 PMPH-USA).

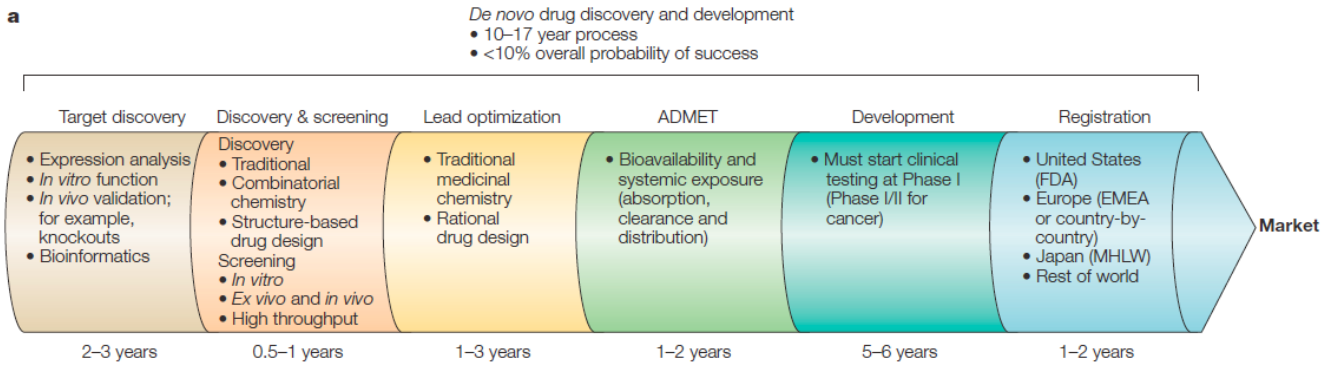

Figure 1: Timeline of de novo drug discovery and development (Ashburn TT and Thor KB Nature Reviews Drug Discovery 2004;3:673).

	1999	2000	2001	2002	2003	2004
Amersham						
R&D costs (£)	74	74	83	95	102	—
% sales*	10	9.5	9	10	10.5	—
Schering						
R&D costs (€)	67	105	121	137	134	125
% sales*	6.4	7.7	8.3	9.7	10.2	9.6

*Sales of imaging and radiotherapy products. Radiotherapy sales are a small percentage of this total. Systemic radiotherapy research, if performed, is included but is a small percentage.

Table 1: Annual R&D spend on imaging agents and % of imaging agent sales (Nunn AD Invest Radiol 2006;41: 206–212).

Unlike small molecules, which often have limited effect size, NPs can produce high signal to background ratios, can provide simultaneous contrast for multiple imaging modalities, and can carry a therapeutic payload along with contrast agents. Because a large majority of molecular imaging agents are based on nanoparticles (NPs) formulation, we will focus our attention to these classes of molecular imaging (nano)agents. The regulatory issues are summarized in **Table 2** (Choi HS and John V. Frangioni J). Information on FDA and its regulation of nanotechnology products is evolving and can be viewed at the FDA website (http://www.fda.gov/nanotechnology).

Category	*Issue*	*Considerations*
Synthesis and physicochemical characterization	Structure, morphology, and formulation	Solubility, size and size distribution, morphology, structural arrangement, spatial distribution, density, geometric features, composition (organic vs inorganic), shape (nanoemulsions, nanocrystal colloid dispersions, or liposomes), surface charge, and drug combination (drug-device, drug-biologic, drug-device-biologic)
	Stability	Short- and long-term stability in various environments, such as in serum and under different pH, temperature, and salt concentrations
	cGMP synthesis	Residual solvents, processing variables, impurities, and excipients
	Scale-up process	Critical steps in the scale-up and manufacturing process for NP products
	Tools	Standard characterization tools of NP properties such as NMR, MS, DLS, SEC, CE, SEM, TEM, AFM, DSC, and XRD
Safety and toxicity	Size-specific effects on activity	1. Will NPs gain access to tissues and cells that normally would be bypassed by larger particles? 2. Once NPs enter tissues, how long do they remain there? 3. How are they cleared from blood, tissues, and the body? 4. If NPs enter cells, what effects do they have on cellular and tissue functions (transient and/or permanent)? 5. Do different cell types exhibit different effects?
	Route specificity	1. Inhalation: local respiratory toxicity and bioavailability 2. Subcutaneous: sensitization 3. Dermal: bioavailability, follicular retention, local lymph nodes, and phototoxicity 4. IV: hemocompatibility, sterility, different tissue distribution and half-life of API (with targeted delivery and liposomes) 5. Oral: bioavailability 6. Ocular: intravitreal retention
	ADME	1. Absorption: how readily can the NP cross biologic barriers (eg, skin, cell membranes, and BBB)? 2. Distribution: how easy is it for the NP to travel to other locations, and what organs do the NPs tend to target? 3) Metabolism: does the nanomaterial get degraded into further constituents? 4. Excretion: do the particles get excreted, or do they accumulate in various tissues? This ADME framework provides a structure that can be used to address the potential biologic effects of nanomaterials. 5. What are the differences in the ADME profile for NPs versus larger particles of the same drug? 6. Are current methods used for measuring drug levels in blood and tissues adequate for assessing levels of NPs? 7. How accurate are mass balance studies, especially if levels of drug administered are very low; ie, can 100% of the amount of drug administered be accounted for? 8. If NPs concentrate in a particular tissue, how will clearance be assessed accurately? 9. Can NPs be successfully labeled for ADME studies?
	Blood tests	CBC, electrolytes, hemolysis, platelet aggregation, coagulation time, complement activation, and leukocyte proliferation
	Toxicity	1. Developmental and reproductive toxicity 2. (Sub)chronic toxicology 3. Immunotoxicity 4. Neurotoxicity 5. Genotoxicity 6. Respiratory toxicity 7. Carcinogenicity 8. Histopathology
Environmental	Toxicity and elimination	1. Can NPs be released into the environment following human or animal use? 2. What methodologies would identify the nature and quantify the extent of NP release into the environment?

Conclusions: The development of new molecular imaging agents undergo the same degree of regulatory oversight by the FDA as the development of new drugs. This is a complex, time

consuming and costly process. In addition, when based on nanoparticles, these molecular agents need to be evaluated according to FDA guidance and regulation on nanotechnology.