



Drug Development Overview

Bernard Ravina, MD

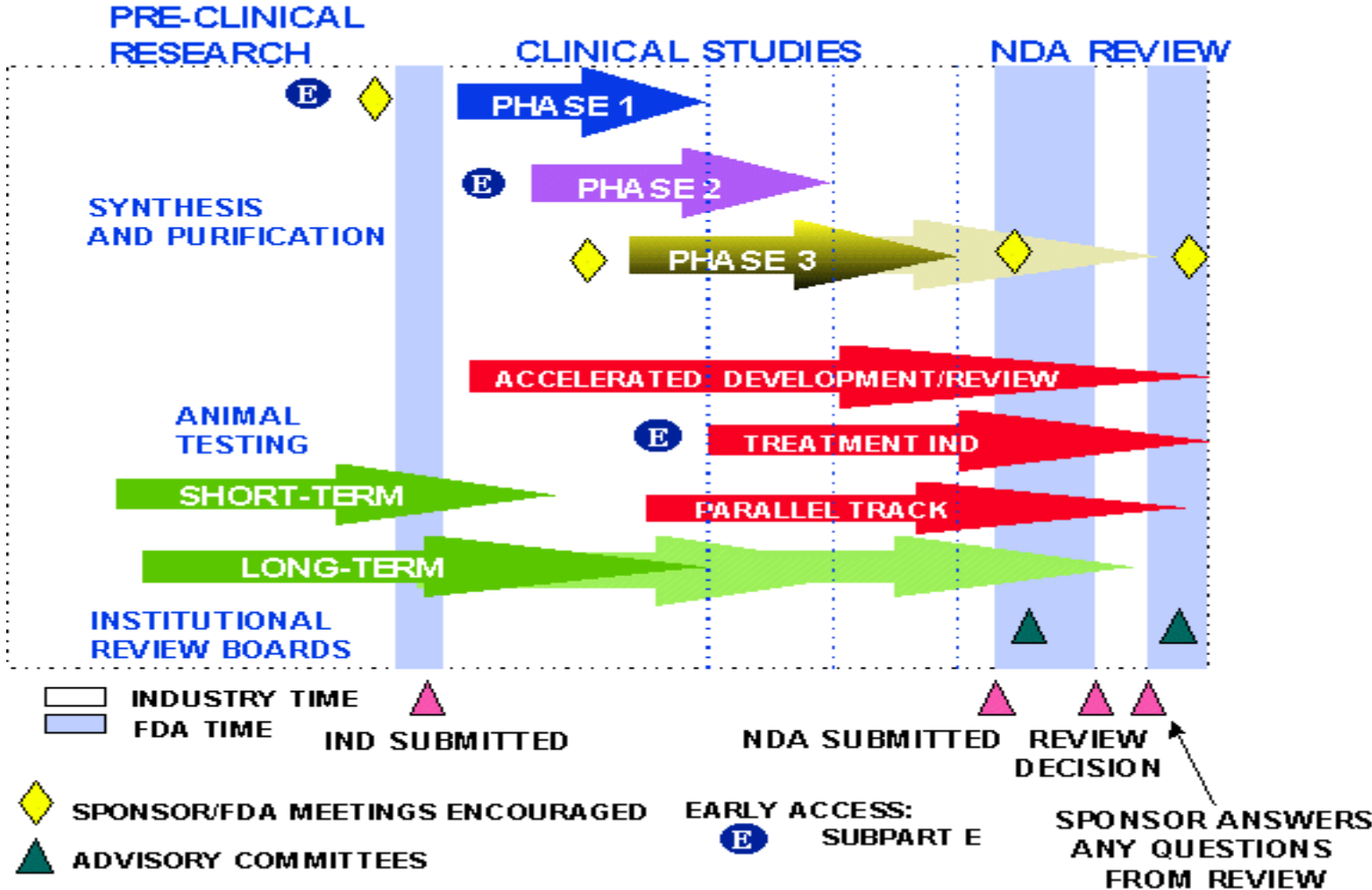
Tim Hackett

Cornelia Kamp, MBA

Wednesday, November 19, 2008

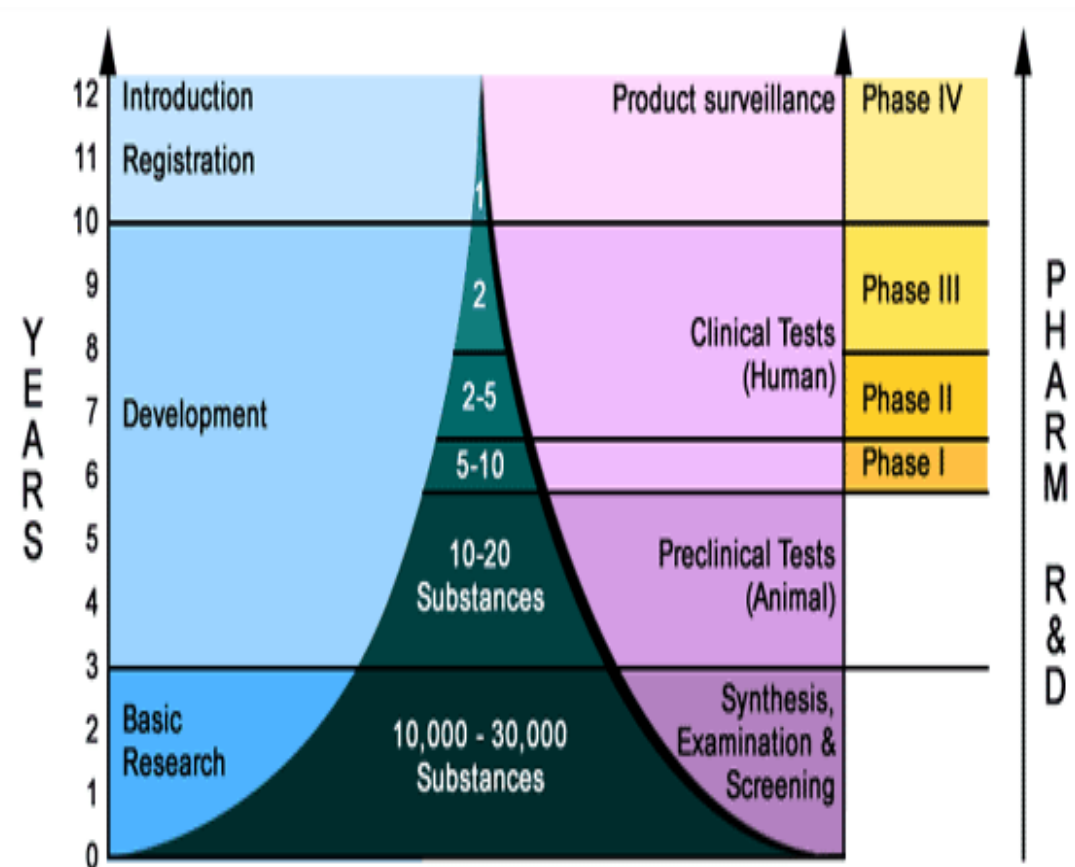
12-1:30pm ET

Drug Development Process

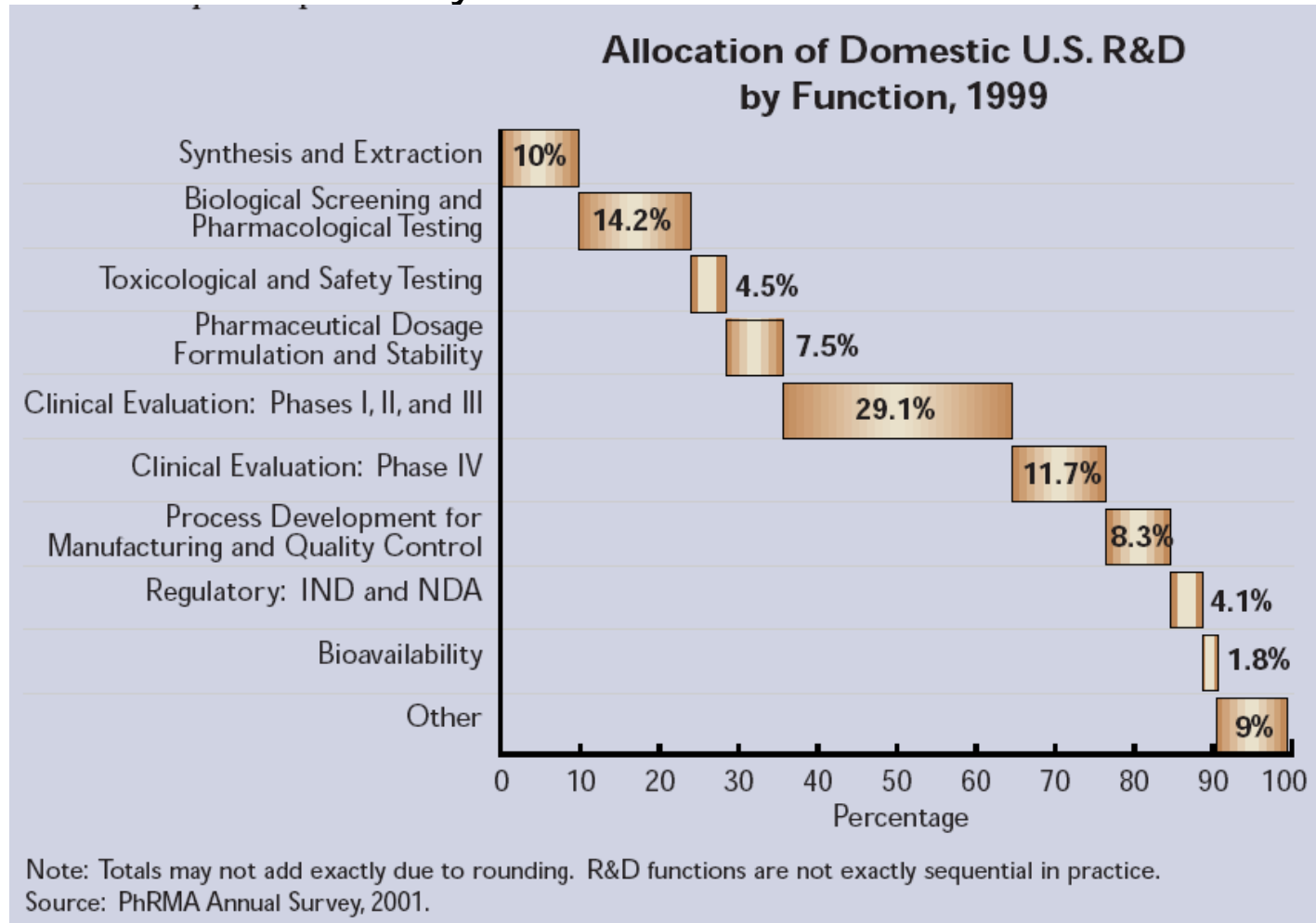


Drug Development Process

- It costs about \$800 million over 12 years to bring one medicine from discovery in a laboratory to the patient.
- For everyone one medicine that reaches the marketable stage, between 10,000-30,000 compounds must be screened.



Because most of the money spent on drug development occurs late in the cycle...



...it is critical to identify compounds that will eventually fail as early as possible.



Aside From Funding the two biggest rate limiting factors in the drug development process are:

- Drug Supply
- Drug Supply
- Drug Supply

- Enrollment
 - 81% of studies have enrollment delays of 1 to 8 months



21 CFR 312 IND requirements

includes:

- FDA form 1571
- Table of Contents
- Introductory Statement and General Investigational Plan
- Investigator's Brochure
- Protocols
- FDA form 1572 for participating investigators
- Chemistry, Manufacturing and Control Information (CMC)*
- Pharmacology and Toxicology Information
- Previous Human Experience with the Investigational product



Studies conducted under an IND must comply with GCPs, GLPs and GMPs

- GCPs:

- 21 CFR parts 11, 50, 54, 56, 312 and 314

- cGMPs:

- 21CFR parts 210 and 211

- GLPs:

- 21 CFR part 58



Applicable cGMP Guidance Documents

**Guideline on the
Preparation of
Investigational
New Drugs**

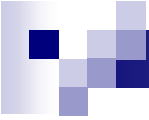
March 1991

[http://www.fda.gov/cder/guidance/
old042fn.pdf](http://www.fda.gov/cder/guidance/old042fn.pdf)

**Guidance for
Industry CGMP
for Phase 1
Investigational
Drugs**

July 2008

[http://www.fda.gov/cder/guidance/
GMP%20Phase1IND61608.pdf](http://www.fda.gov/cder/guidance/GMP%20Phase1IND61608.pdf)



Main Differences between the guidelines:

1991 Guidance :

- Did not discuss all manufacturing situations
- Did not address FDA's expectation for an appropriate approach to manufacturing controls during different phases of product development



July 2008 Guidance applies to Phase 1 drugs in either small or large scale environments.

July 2008 Guidance does not apply to the following investigational products:

- Human cell or tissue products regulated solely under 361 of the public health services act
- Clinical Trials for products subject to device approval
- Investigational products manufactured for phase 2 and 3 Clinical Trials
- Already approved products being used in phase 1 (new indication)
- PET drugs subject to 501(a)(2)© of FD&C Act



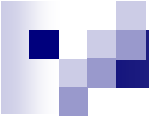
Recommended CGMP for Phase 1:

- Personnel
- QC Function
- Facility and Equipment
- Control of components, and containers/closures
- Manufacturing Records
- Laboratory Controls
- Packaging/Labeling/Distribution
- Record keeping



Applicable Phase I guidance documents

- Guidance for Industry, Investigators and Reviewers: Exploratory IND studies (January 2006):
<http://www.fda.gov/cder/guidance/7086fnl.pdf>
- Content and format of Investigational New Drug Applications (INDs) for phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products: 11/20/1995;
<http://www.fda.gov/cder/guidance/clin2.pdf>
- Q&A: Content and format of Investigational New Drug Applications (INDs) for phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products (October 2000);
<http://www.fda.gov/cder/guidance/3591fnl.pdf>



Special Protocol Assessment Process (SPA) (May 2002)

- FDA will evaluate within 45 days three types of protocols are eligible for this SPA under PDUFA goals:
 1. animal carcinogenicity protocols
 2. final product stability protocols, and
 3. clinical protocols for phase 3 trials whose data form the primary basis for an efficacy claim if the trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the review division, or in some cases, if the division agrees to such a review because the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.
- SPA's may be requested even if an Investigational New Drug (IND) has not been filed with the FDA, however, if such a request is granted FDA will need to be informed of the overall development plan for the drug or biologic.
- <http://www.fda.gov/cder/guidance/3764fnl.PDF>




Top 10 mistakes Biotechs Make

Stephen Ferruolo

Partner in the Business Law

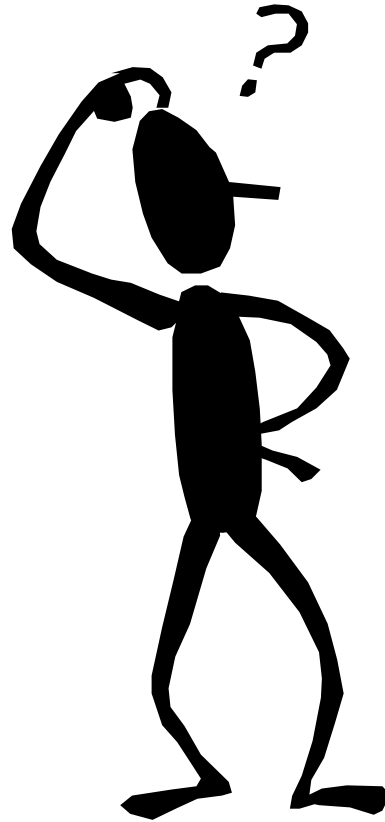
Department at Goodwin Procter

<http://www.fiercebiotech.com/special-reports/top-10-mistakes-biotechs-make-and-how-avoid-them>

- 
1. Not Thinking Strategically About IP
 2. Not Understanding The Target Market
 3. Not Raising Enough Money
 4. Not Having a Regulatory Strategy
 5. Not Listening to FDA
 6. Designing Trials Poorly
 7. Not Properly Powering Studies
 8. Not Being Ready For Success
 9. Not Knowing When to Partner
 10. Relying Heavily on Third Parties,
Especially CROs and even consultants



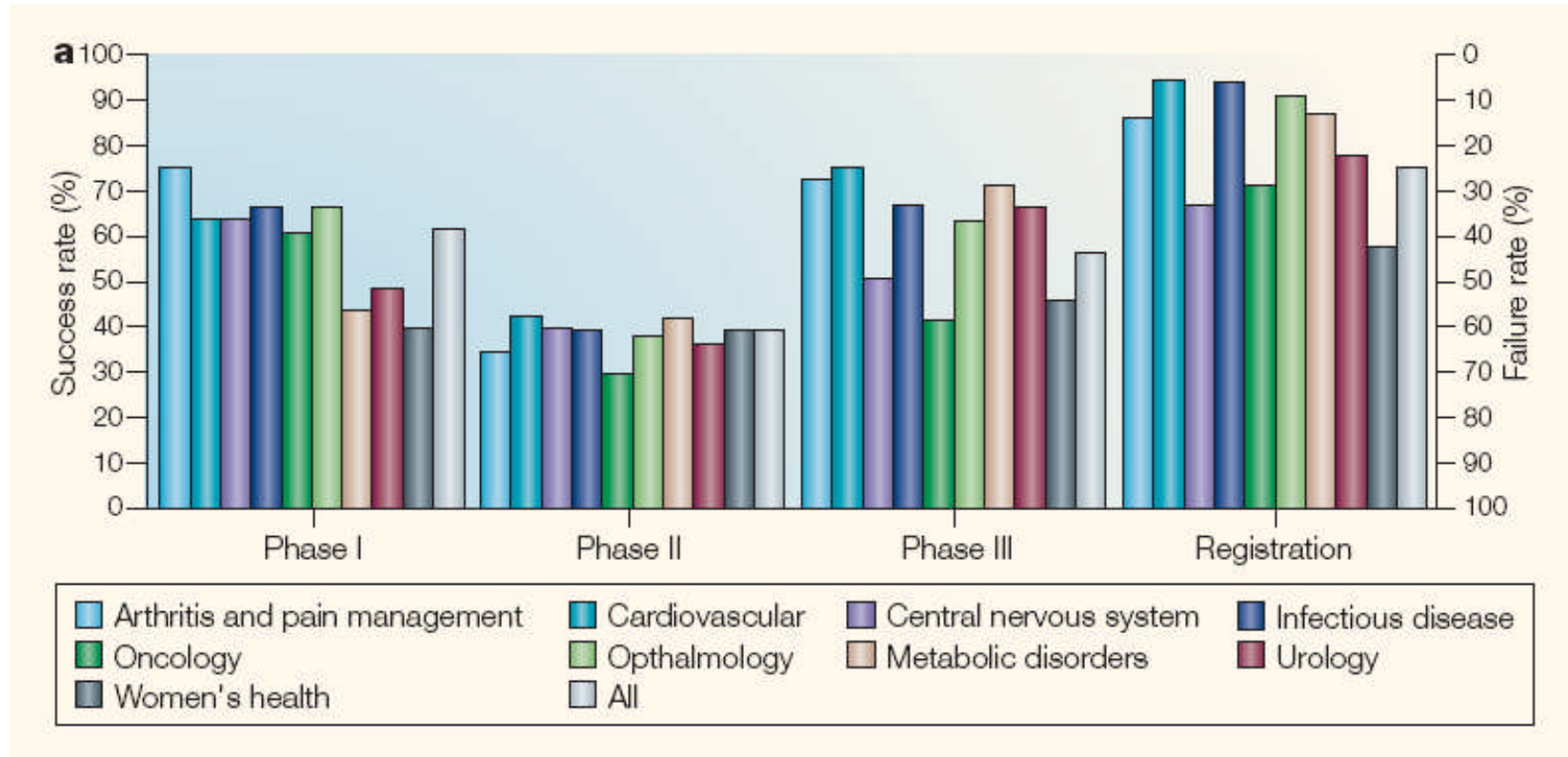
QUESTIONS?





BACK-UP SLIDES

Significant attrition continues late in development...



Kola I, Landis J. Can the Pharmaceutical Industry Reduce Attrition Rates?
Nature Reviews/Drug Discovery Volume 3, August 2004, pg 711

Clinical Trials

	Preclinical		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5-6.5		1-1.5	2	3-3.5		1.5-2.5	15 Total	
Test Population	Laboratory and Animal Studies		20-80 healthy volunteers	100-300 patient volunteers	1,000-3,000 patient volunteers				
Purpose	Assess safety and biological activity	File IND with FDA	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions for long term use	File NDA with FDA	Review process / approval		Additional post-marketing testing
Success Rate	5,000 compounds evaluated			5 enter clinical trials			1 approved		



1. Not Thinking Strategically About IP

- licenses and patents--both what you own and what you'll have to license from others
- Ask yourself this: If I were a buyer or partner doing IP due diligence, where would I poke holes and see issues? Identify them and fix them now.



2. Not Understanding The Target Market

- Think about the commercial viability of the end product
- Don't treat the R&D process as just a research project
- Ask yourself these questions:
 - Is there a reasonable and timely path to approval?
 - Can the drug be differentiated?
 - Will it be reimbursed?
- A super-expensive drug--even an effective one--may not be worth pursuing if there are alternatives on the market



3. Not Raising Enough Money

- Drug development inevitably takes more money and time than anticipated, so raise as much money as you can, when you can
 - Often, the decision is made to raise just enough money to the next development milestone, with the assumption that the company will then be able to raise a new round at a higher valuation. This is Not an ideal strategy
- Pick experienced VCs with deep pockets



4. Not Having a Regulatory Strategy

- Chose an advisor **EARLY ON** that is well-versed in current FDA requirements and issues so that he or she can recommend the best strategy for clinical development and regulatory approval



5. Not Listening to FDA

- Engage FDA through-out the development cycle
- Request a Pre-IND meeting, end of phase II etc.
- When the FDA says ‘we think you ought to consider’ something”, that should not be viewed as a suggestion, but as a mandate
- Consider the Special Protocol Assessment (SPA) method if you want to get FDA to agree on your pivotal protocol



6. Designing Trials Poorly

- Pull in needed experts to help with the trial design
- Have answers to the following questions before spending millions on a poorly designed trial:
 - Do you have the right endpoints?
 - Are they appropriately defined?
 - Are you pursuing the right indications?



7. Not Properly Powering Studies

- Big pharma's typically power studies at 80%
- If you are an emerging biotech designing pivotal trials for the drug candidate that is going to make or break you, you should consider powering the trials at 90%.



8. Relying Heavily on Third Parties, Especially CROs

- Small biotech companies typically get lower priority within a CRO than the large repeat clients
- Work to find a practical balance between outsourcing and in-house work
- The more you can do in-house the better:
 - Do as much as you reasonably can do with people who live, die, sleep and eat thinking about nothing but your program. What they lack in experience may be made up in commitment.



9. Not Being Ready For Success

- Once NDA approval is obtained many biotechs are not ready to scale up manufacturing and supply sources
- Being unprepared to commercialize wastes valuable time and can substantially reduce the ROI. If it takes a company a year to get up to speed, that is one year of lost sales-and a year of patent protection squandered.
- Once the NDA is submitted begin efforts to scale up



10. Not Knowing When to Partner

- Partnering too early or too late; both has negative consequences
- Think strategically about partnering:
 - Are you a platform company?
 - Are you a product company?
 - An indication company?
 - What indications are you targeting?
 - If chronic indications, like diabetes, that require large, long-term trials and a large sales force to market the drug?
 - If targeting a rare or fatal disease with no approved therapy that will require smaller trials with clearer endpoints and drugs that need only be marketed to a defined number of specialized centers.
- Each situation is unique so companies shouldn't follow generalized trends about when and how to partner.