BEST PRACTICE APPROACHES TO THE COORDINATION AND EXECUTION OF HUMAN CLINICAL TRIALS IN THE 'START-UP' SETTING

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OUTLINE

Disclaimer

1. **Biography**
2. **Introduction**
3. **Program Objectives**
4. **Agenda**
   a. **How do we define the ‘Start-Up’ setting and why is this important?**
   b. **How do we define ‘Best Practices’?**
   c. **What are the key challenges and common pitfalls faced when working in this setting?**
   d. **How do we address key challenges while upholding ‘Best Practices/Standards of Excellence’?**
   e. **Discuss the critical difference between negotiation and compromising integrity**
   f. **Review examples of real life issues and approaches to problem solving**
   g. **Recommendations**
   h. **Q & A**

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1. BIOGRAPHY

Pharmaceutical Industry professional with over 25 years' experience in large, mid-sized and start-up organizations; clinical trial Phases 1 - 4. Career appointments reflect the full spectrum of clinical operations roles from Quality Assurance oversight of a 42 bed in-patient Phase I clinic, to experience serving as a Clinical Research Associate, work in Project/Program Management, leading to Executive Management leadership positions in clinical operations and clinical affairs.

I also maintain my Board Certification and professional licensure as an Acute Care Nurse Practitioner with a practice focus in Internal and Emergency Medicine; and teach in the academic setting on request.

2. INTRODUCTION

The day to day pressure and challenges inherent to the management of a clinical operations department are amplified in the entrepreneurial world of the biotech **‘start-up’** organization.

In a vacuum of resources, time and finances, defining and delivering on a strategy for a scientifically sound plan of early to advanced phase trials that will yield robust safety, Proof of Concept (POC) and Mechanism (POM) data is critical to the future of the organization and the realization of product potential.

INTRODUCTION

Regardless of the size of the organization, there are many opportunities for error and few opportunities for second chances in the development of drug/biologic therapies.

This fact is only amplified in the ‘start up’ environment where VCs are anxious to realize appreciation of their investment, where every dollar is precious and every decision could make or break both the program and the company.

3. PROGRAM OBJECTIVES - KEY PRINCIPALS

With so much at stake, the following principals are critical:

- **Knowledge of the full scope and associated processes in the product development lifecycle**
- **A well designed, strategic program plan with a focus on the delivery of high quality data in support of protocol initiatives.**
- **Representation of each discipline by seasoned personnel; with clearly defined roles, responsibilities and strong leadership skills**
- **Concise lines of communication within and across disciplines**
- **An environment of mutual respect and collegiality**
- **Organizational alliance in addressing issues quickly and directly**
- **Recognition of the difference between negotiation, options and compromising integrity**

PROGRAM OBJECTIVES - KEY PRINCIPALS

The objectives of this presentation are as follows:

1. Define the ‘Start-up’ environment, highlight key differences between this and the ‘large pharma’ setting and discuss why this is important
2. Define ‘Best Practices’
3. Identify key challenges and common pitfalls of working in this setting
4. Review strategies for problem solving in the entrepreneurial arena while maintaining standards of excellence
5. Discuss the difference between negotiation, options and compromising integrity
6. Use case studies for illustrating ‘lessons learned’

3. AGENDA REVIEW

- How do we define the ‘Start-Up’ setting and why is this important?
- How do we define ‘Best Practices’?
- What are the key challenges and common pitfalls faced when working in this setting?
- How do we address key challenges while upholding ‘Best Practices/Standards of Excellence’?
- Discuss the critical difference between negotiation and compromising integrity
- Review examples of real life issues and approaches to problem solving
- Recommendations
- Q & A

A. HOW DO WE DEFINE THE 'START-UP' SETTING AND WHY IS THIS IMPORTANT?

Luke Timmerman of BioBeat online uses the following:

"I define a "newsworthy" biotech startup as one that has a big idea, a credible management team, and…at least $5 million from a first-time financing…"

He offers the caveat that $5 million is, *"…not much money."* – which is an understatement, but it's a start point.

The Biotech Startup Class of 2013: Don't Worry, It's a Short List
Luke Timmerman
November 18th, 2013
http://www.xconomy.com/national/2013/11/18/biotech-startup-class-2013-dont-worry-short-list/accessed 05AUG15

How do we define the 'Start-Up' setting and why is this important?

I offer the following definition and criteria in my characterization of a 'start-up':

- Venture capital or other privately funded research organization that is committed to the advancement of a portfolio of no more than 3 novel compounds/NCEs from pre-clinical development through Proof of Concept/Mechanism (POC)/(POM) with only the requisite resources needed to accomplish target initiatives.

WHY IS THIS IMPORTANT

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WHY IS THIS IMPORTANT ?

Because the pathway you follow in product development is the same, regardless of the organizational setting, but the resources available and the level of risk is vastly different.

There is a significant difference between great science and great potential

~ even the most innovative therapeutics will have no value or future if they cannot be manufactured, packaged, stored, shipped or stable to be marketable

In other words, buyer beware

WHY IS THIS IMPORTANT ?

You choose this setting:

- For the potential to be innovative and creative
- Explore novel approaches to problem solving
- Be ‘hands on’ and an integral part of the process
- Gain knowledge regarding other disciplines
- Experience interactions with Regulatory Agencies
- Work collaboratively with leaders in research development, clinical experts KOLs and organizational management
- Visibility
- Culture

WHY IS THIS IMPORTANT ?

While every company/employee is dedicated to upholding best practices and the highest standards of excellence in the execution of their organization's development plan, the limitations of budget and resources that define this environment will present a unique set of challenges that must be appreciated and understood.

Examples include:

1. Outsourcing – control, program management, reporting
2. Role Functions – multiple role responsibilities
3. Investor Commitments/Timelines – innovation/risk
4. Unity of Purpose – is everyone working towards the same goal?
5. Others?

WHY IS THIS IMPORTANT ?

1. Outsourcing – control, program management, reporting

The availability of resources in the start up arena demands outsourcing of many – if not all responsibilities.

✓ **Selection of CRO is critical** – consider:

- Size
- Specialty
- Previous therapeutic experience
- Competitive work
- Attrition
- Commitment
- Dedicated team
- References
- Cost/Contract

WHY IS THIS IMPORTANT ?

2. Role Functions – multiple role responsibilities

The availability of resources in the start up arena demands the wearing of many hats and oversight of multiple disciplines

✓ **Consider**

- Experience of leadership – striving for growth is vital to professional satisfaction but every staff member must have the expertise to deliver.
- The demands of this environment are significant. Commitment to work beyond job description is imperative.
- Willingness to be flexible, decisive, risk tolerant, manage stress and compromise are some of only a small handful of skills that are needed to be successful in this setting

WHY IS THIS IMPORTANT ?

3. Investor Commitments/Timelines – innovation/risk

Every organization has stakeholders –

- Large Pharma/Biotech's are beholden to their BOD
- In a privately funded organization, every action is directly tied to whomever holds the purse strings - VCs

✓ **Consider**

- The amount of funding immediately available and the milestones that must be met/timelines for future funding
- The culture of the VC/finance team
- The company's annual 'burn'
- Potential for success
- Status of competitors

WHY IS THIS IMPORTANT ?

4. Unity of Purpose – is everyone working towards the same goal?

- ❑ Small organizations provide both great visibility and no place to hide.
- ❑ In addition, the potential for success is directly correlated to the level of internal discord. The greater the internal discord, the greater the risk of failure.

✓ **Consider**

- A forum for the free flow of ideas will become a liability in the absence of strong leadership ~ not everything is a democracy and at some point, a determination must be made
- Every team member must be fully committed to the organization's goals and be willing to work through disagreements to achieve a unified plan
- Negativity is contagious and highly destructive – it is better to lose a resource than to allow an environment of discord to take root
- Be mindful and current with industry trends, regulatory updates and novel solutions – but do not be paralyzed by indecision

WHY IS THIS IMPORTANT ?

4. Others?

- What has been your experience ?
- What are your recommendations?

b. How do we define “Best Practices”?

This is not about Good Clinical Practices (GCPs)

Rather, this is about the ‘Best Practices’ for how we approach and execute the overall drug development process

b. How do we define “Best Practices”?

For the record, domestic/international regulations and standards for ICH, ethical integrity and good clinical practice serve as the foundation from which the design, execution and analysis of human clinical trials must be conducted

I believe that failure to appreciate these principals is a key factor in the failure of products and programs in the development lifecycle

- True regardless of organization size
- Start up companies are at greater risk d/t in ability to absorb multiple setbacks, program reset…
- VC and investors may not tolerate

SO…

b. How do we define “Best Practices”?

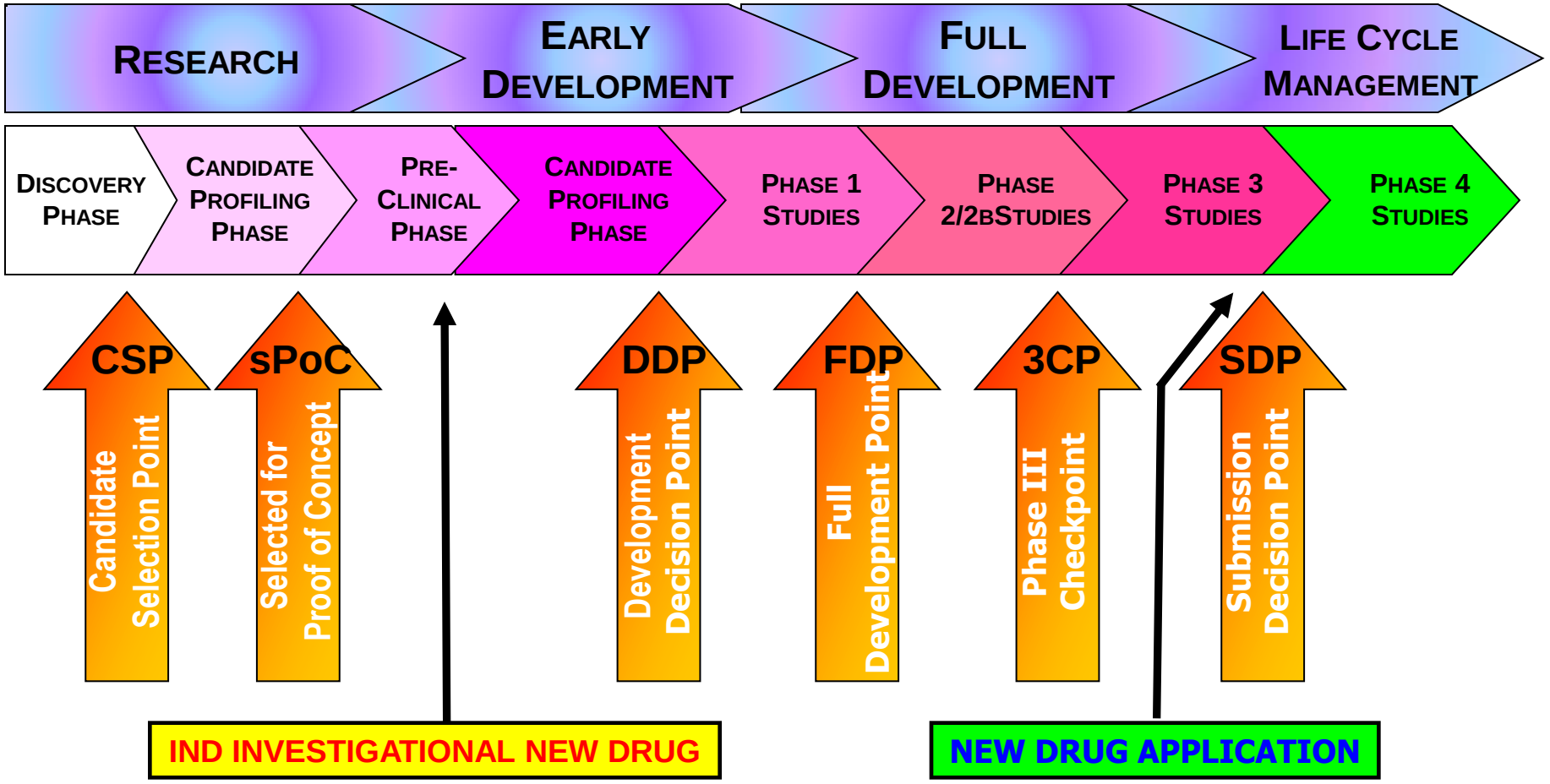
What is a ‘best practice’ approach to product development?

You must START

With where you want to FINISH

b. How do we define “Best Practices”?

Both US and International Regulatory Agencies have established standardized pathways for NCEs



The “Standard” Approach

Identify Research Target

Discovery of Lead Compound

Candidate Selection

Off to the races!

DEVELOPMENT

- Complicated, time-consuming and costly process
  - 2-20 years
- Hundreds to thousands of chemical compounds/biologics/botanicals must be screened
  - Up to 10,000 screened
- No standard route through which drugs are developed
- Some major sources of new drugs:
  - Synthetic compounds
  - Discovery of a new use for an old-drug
  - Natural chemical

Pre-Clinical Research

- Animal pharmacology/toxicology testing – "Is it safe to proceed to human trials?"
  (The Nuremberg Code)
- Approximately 2-3 yrs development
  - 20-30 substances
- Minimum FDA requirements:
  - pharmacological profile
  - Determine acute toxicity in at least 2 species of animals
  - Conduct short-term toxicity studies (2 wks – 3 mos)

Investigational New Drug Application (IND)

- Documentation that allows investigational clinical testing of a new medicine
- Must be filed with FDA before drug administered to humans
- Studies may begin within 30 days of application…..if no response from the FDA
- An IND contains the following sections
  - Table of contents
  - Introduction
  - Investigator's Brochure
  - General investigational plan
  - Previous human experience
  - Pharmacology & toxicology
  - Protocols for each planned study
  - Investigator
  - Facilities and IRB
  - Manufacturing and control
  - Additional information

21 CFR 312.23

Clinical Trials

- IND filed first
- 3-5 years
- Process:
  - Clinical Trials - Phase I – Phase III
  - On-going Biological tests (safety)
  - On-going formulation work

Clinical Trials - Phases

Phase	Purpose	Subjects	Scope	Length (per phase)
I	Safety, ADME, bioactivity, drug-drug interaction	Healthy volunteers or subj. w/ indications	20-80	6-12 mos
II	Short-term side effects & efficacy	Subjects with indications	Several hundred	1-2 yrs
III	Safety & efficacy Basis for labeling, new formulations	Subjects with indications	Hundreds-thousands	2-3 yrs
IV	New indications, QoL, surveillance	Subjects with indications	Hundreds-thousands	1-5 yrs

21 CFR 312.21

Phase I

- First time in human subjects
- Small number of healthy volunteers or severely ill patients
- Safety profile and dosage range
- Single and multi-dose studies
- Pharmacokinetics / pharmacodynamics
- Open label, often single center
- Not always performed in the U.S.

Phase II

- Safety, side effects
- Efficacy – dose response
- Double-blind, positive control or placebo, multi-center utilizing a limited number of subjects (100-300); often the first time drug is used in population for which it is intended
- Phase IIa – proof of concept, pilot, feasibility, usually healthy volunteers
- Phase IIb – well-controlled in target population
- Following completion of Phase II, meet with the FDA to pave the way for "pivotal trials"

21 CFR 312.47

Phase III

- 2 or 3 studies are pivotal (critical) studies
  - To prove safety and efficacy of primary endpoints
  - Double-blind, positive or placebo control, multi-center
  - Study population resembles the intended population
  - Support package labeling
  - New Drug Application (NDA)
- Special population, concomitant medications, multiple illnesses, etc.
- IIIb studies – post NDA-submission trial looking at additional indications
- Pre-NDA meeting with the FDA near conclusion of Phase III

21 CFR 312.47

New Drug Application (NDA)

- The average NDA is 100,000 pages or longer
- Must provide all relevant data collected during R&D
- Consists of:
  - **Index - non-clinical pharm - clinical data**
  - **non-clinical pharm - human toxicity - CRF's**
  - **safety update - case report tabulations**
  - **pediatric data - statistics**
  - **PK / Bioavailability - patent information / certification**
  - **ISES (Integrated Summary of Efficacy and Safety)**
  - **CER (Clinical Expert Report – summary of drug impact, how data supports)**
  - **CSR (Clinical Study Reports)**
- Can now be filed electronically
  (a CTD = Commercial Technical Document) 21 CFR 314.50
- Review process: Target 10 months (but often longer)

NDA Review Process

- Review Process
  - standard
  - expedited (in the case of life threatening diseases for which the only medications available are of little or limited effectiveness, e.g. ALS).
- Results of Review
  - Approvable
  - Approved
  - Denied
- Negotiation of the labeling process

www.fda.gov

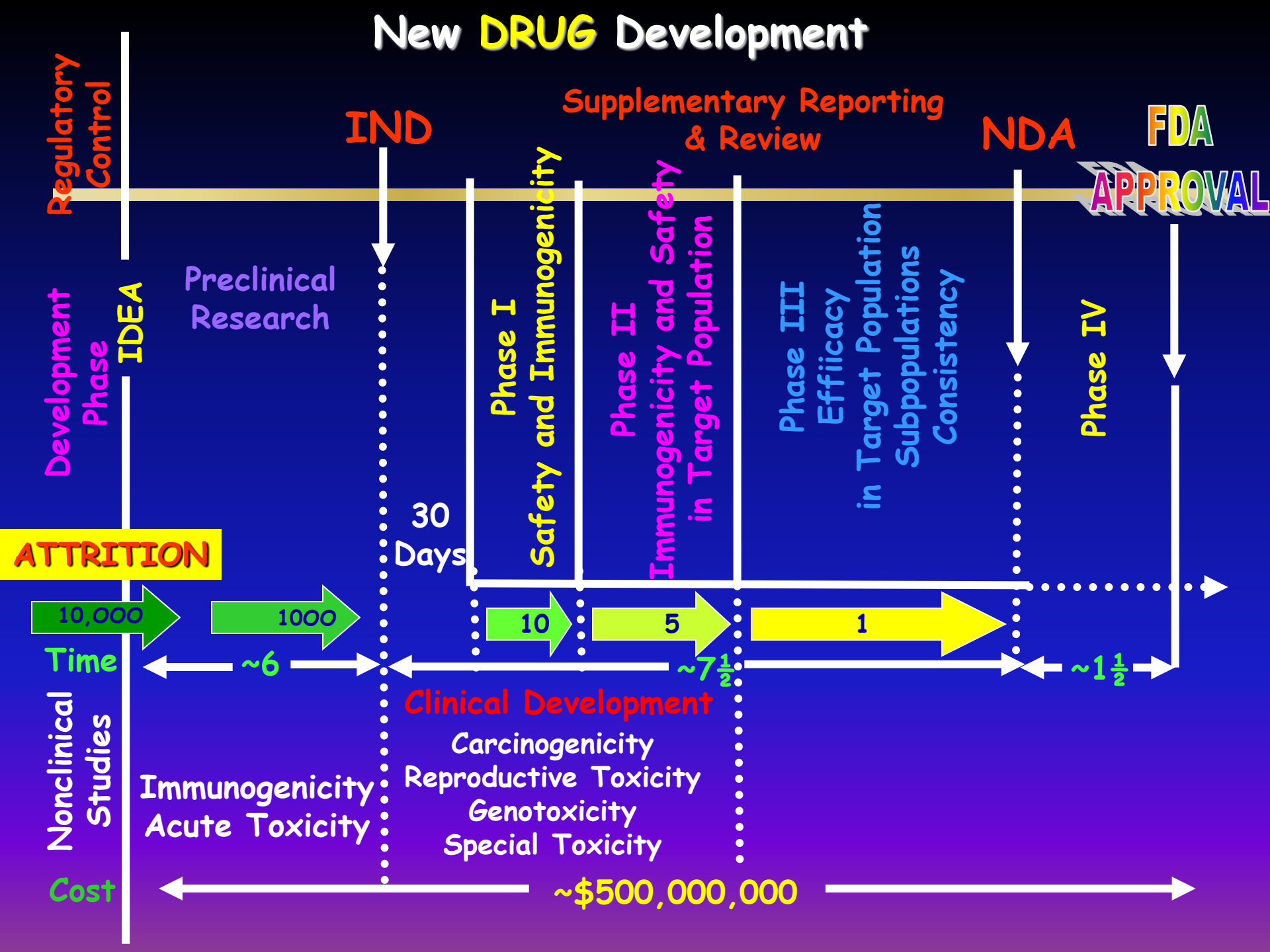
Registration & Launch

- Product Registration and Launch
- 2 - 3 years
- Process:
  - Register Product with Health Authorities (FDA)
  - Prepare Sales Teams

Phase IV

- Post-licensure studies to confirm the safety in large population (after NDA is filed)
- Phase IV commitments
- Possible types of studies
  - Compared versus competition
  - Post-marketing surveillance
  - Special population
  - Rare event incidences
  - Additional long-term usage safety data
  - Pharmacoecomonic and Quality of Life (QoL)

21 CFR 312.85


New DRUG Development
Regulatory Control
IND
Supplementary Reporting & Review
NDA
FDA
APPROVAL
Development Phase
IDEA
Preclinical Research
Phase I
Safety and Immunogenicity
Phase II
Immunogenicity and Safety in Target Population
Phase III
Effiicacy in Target Population
Subpopulations
Consistency
Phase IV
30 Days
ATTRITION
10,000
1000
10
5
1
Time
~6
~7½
~1½
Clinical Development
Nonclinical Studies
Immunogenicity
Acute Toxicity
Carcinogenicity
Reproductive Toxicity
Genotoxicity
Special Toxicity
Cost
~$500,000,000

CASE STUDIES

1. Identify key challenges and common pitfalls of working in this setting
2. Review strategies for problem solving in the entrepreneurial arena while maintaining standards of excellence
3. Discuss the difference between negotiation, options and compromising integrity

TODAY…..

- Success rates in bringing a drug from discovery through to commercialization are low and getting worse.

- Recent Tufts Center for the Study of Drug Development (CSDD) research indicates that only 11.3% of drugs that enter clinical testing will be approved in the United States, down from a 16.4% success rate ten years ago.

- Since at least 10 years are required to bring a single molecular entity through R&D and approval, the total average capitalized cost to successfully introduce a marketed drug — including the shared cost of compounds that fail in development — now exceeds $2.6 billion.

A Tufts Center for the Study of Drug Development White Paper

- **Mary Jo Lamberti, PhD, Senior Research Fellow**
- **Kenneth Getz, MBA, Director of Sponsored Research Programs and Research Associate Professor**
  May, 2015

FOR YOUR CONSIDERATION…..

1. Have a clear understanding of your objectives and plan – if you are striving to build an organization to successfully achieve POC and preliminary PH 1 and 2 studies, then embrace this strategy and start off with the goal of executing these studies with excellence and to yield the highest quality data to support the sale of the company once these initiatives are complete
2. Know your capabilities and limitations. - This sounds so simple, but it is critically important. If you refuse to acknowledge what you do and don't know, you will realize pitfalls that could easily be avoided
3. Know the skills and expertise of your staff and capitalize on this
4. Unless they are the biotech industry's answer to Mark Zuckerberg, resist the temptation to hire your friends or other's friends/relatives.
5. Focus on quality vs quantity – clinical study protocols should be limited to no more than 4 endpoints and, I would argue that 3 is better. Studies that are designed to attempt to answer more questions than can possibly be accomplished create excessive data that is meaningless.

FOR YOUR CONSIDERATION…..

6. Never compromise your ethics, the regulations or standards for GCP. There is a big difference between efficiency and integrity. If you start to question the regulatory appropriateness of what you're doing, it's probably not the approach to take.
7. Resist the temptation to purchase large, complex and expensive systems that have every bell and whistle and far more 'stuff' than you will ever need. Company 'road shows' may sound tremendous, but in the smaller, entrepreneurial setting, efficient, validated systems are all that are needed.
8. Don't be afraid to be creative and to listen to the ideas of everyone on your team, regardless of experience. You never know where a great idea will come from.
9. Address problems quickly, directly, and thoughtfully. It is always wiser to acknowledge issue up front then to try to sugar coat them. Eventually, everyone finds out the truth.

QUESTIONS

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7th Annual Global Pharma Summit

On

June 20-22, 2016 at New Orleans**, USA**

http://american.pharmaceuticalconferences.com/


Thank You!