

# Two Men and a Molecule

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# Biotech Industry Snapshot

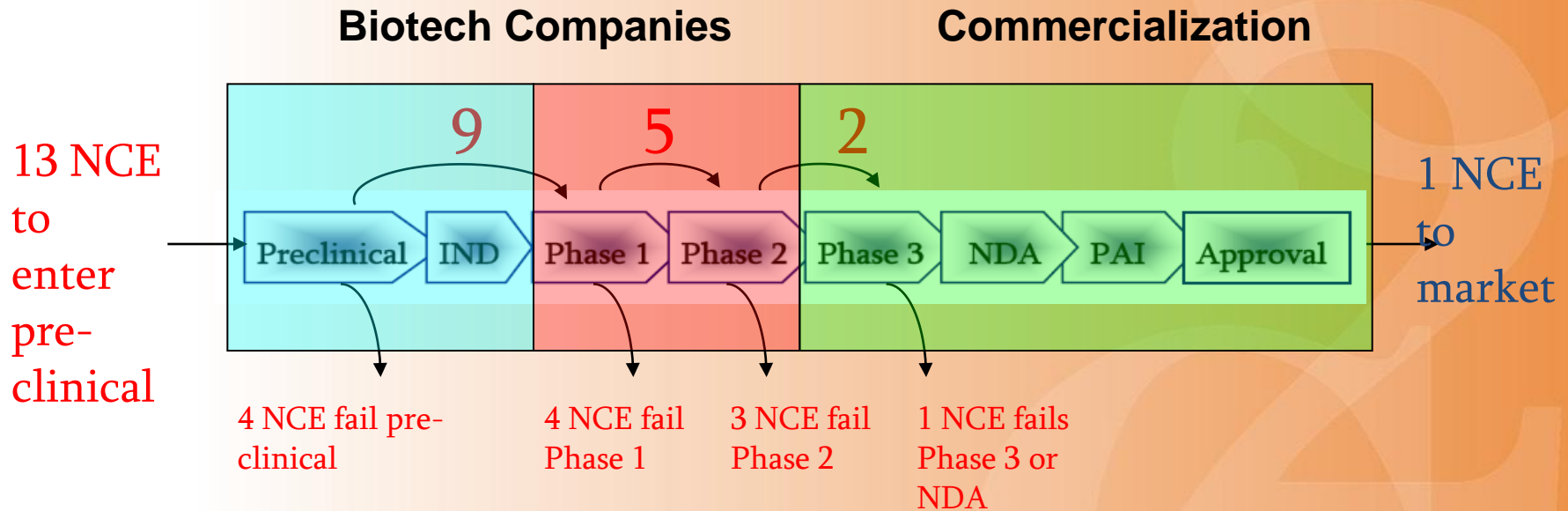
- With over 400 public and private companies, Canada has the **second largest number** of biotechnology companies in the world. (Resilience: *The Americas Biotechnology Report*, Ernst & Young and Statistics Canada)

## *Typical biotech company:*

- less than 20 employees
- virtual company with only executive leadership and board of directors
- leaders with little or no pharmaceutical development experience (e.g., financial, marketing, academic or medical background)
- one or two molecules (or technologies) in development
- less than \$one million cash on hand

# Pharmaceutical Product Development

# Pharmaceutical Development



(Ref: Data are published periodically in summary form by the Tufts University Center for the Study of Drug Development ([www.tufts.edu](http://www.tufts.edu)))

What cause the high attrition rate?

# Clinical Research

- Clinical Trial Material
  - Production, packaging (e.g., for blinded studies)
- Clinical Research

Pharmaceutical Research  $\neq$  Clinical Research

# Pre-formulation

- Characterize physicochemical properties of **Active Pharmaceutical Ingredient (API)**
  - Solubility
  - pKa (Dissociation Constant), logP (Partition Coefficient)
  - Intrinsic dissolution
  - Solid state properties (e.g., crystal form, water absorption, particle size and shape, etc)

# Pre-formulation - continue

- Stability
  - Chemical stability (stress test)
  - Excipient and packaging compatibility studies
- Early stage formulation
  - Design composition and dosage form (e.g., optimize drug release)

# Formulation Development

- Analytical Methods
  - According to International Conference on Harmonization (ICH) guidelines
- Prototype Formulations
  - Obtain a desirable drug release profile
  - Develop prototype batches
  - Optimize formulation

# Formulation Development - continue

- Manufacturing of Trial Batches
  - Scale up
  - Manufacturing process development (e.g., identify and optimize critical parameters)
  - Abbreviated stability program (e.g., up to 3 months at accelerated conditions)

# Biotech Companies – Two men and a Molecule - Examples

# Examples from our clients

- Company 1:
  - Company of one, CEO
  - Wall Street analyst turned into CEO
  - One development program (drug delivery technology)
  - >\$1 million budget
- Company 2:
  - Zero employees in company
  - Government research institute and academic joint venture
  - Part time “acting” CEO, financial background
  - One development program
  - \$350,000 cash on hand

# Examples from our clients

- Company 3:
  - Zero employees in company
  - Government research institute and academic institution joint venture
  - One technology platform development program
  - \$450,000 cash on hand
- Company 4:
  - National Research Council (NRC) spin out
  - One development program
  - Company of three
  - \$\$ Unknown

Do the right thing at the right  
time

# Challenge?

- How do you convince inexperienced CEO to spend on analytical method validation?
  - \$40,000 is a big piece of a \$350,000 budget!
- How do you convince someone to spend on feasibility batches or excipient compatability?
  - Batches they can't use for clinical studies (i.e., not official), but cost significant % of their cash on hand?
- How do you sell a pilot toxicology screen or a cytochrome P450s screen?
  - No regulatory requirements
  - Minimum data package versus mitigating risk that will increase asset value at time of exit

# Things that you just can't budge on

- What constitutes method validation for pilot batch or phase 1 CTM?
  - Method validation for the current stage of development
  - Precision : day-to-day variation versus lab-to-lab variation
- What are essentials upon technology transfer?
  - Critical process parameters, validated analytical methods
  - You can't take short cut – otherwise things will go wrong

# Things that you just can't budge on - continue

- How much stability data do you really need?
  - Do you always need 12 months stability data ?
  - Concurrent stability program to minimize lead time
- How many batches do you really need to run?
  - Early phase clinical research – prototype formulation
  - Late phase clinical research – use final formulation
- Minimal phase 1 clinical designs?
  - 3+3 model versus Continual Reassessment Method (CRM) for dose finding study
  - Patient numbers

# No more, No less

- Company 1:
  - Proprietary drug release technology
  - Dissolution pH@ 6.0, 6.5, 6.8 – too many combination?
  - Residual solvents tests for finished products – not necessary
  - N=12 in Phase 1 clinical study?

# No more, No less

- Company 2:
  - Use “whole blood” versus “leukapheresis” for immuno-cell therapy
    - Leukapheresis is a laboratory procedure in which white blood cells are separated from a sample of blood.
    - White blood cell counts may be high enough to cause hemostasis and "sludging" in the capillaries
  - Whole blood – for feasibility study
  - Leukapheresis - for development
  - These processes are not comparable, start over again.

# No more, No less - continue

- Company 3:
  - Where to draw the GMP line in API synthesis?
    - Only the final step under GMP environment – too risky?
  - Pilot drug product stability assessment
    - # of pH conditions in nasal spray formulation
    - CMO inflates the project scope?
- Company 4:
  - Investigate 4 chemo-therapies using their delivery system
  - Only one of them will be selected for further development
  - Xeno model – transplantation of living cells from one species to another
    - Too costly, reduce the number of run

# No more, No less - continue

- Company 5:
  - Impurity – ester in blood or plasma, not stable, easily hydrolyzed
  - Too costly to develop a meaningful bioanalytical assay for toxico-kinetic study
  - Instead, write justifications to explain why it is not necessary, supported by in-vitro stability data

Why do you need to spend  
\$40,000 on method  
validation?

# Analytical Procedure – Research

- Scientist writes down the procedures in his/her lab notebook
- Sufficient for publications and research purposes
- Procedures are always “modified” or “adapted” based on analyst-to-analyst or lab-to-lab preference

# Analytical Procedure – GMP

- GMP – Good Manufacturing Practices
  - Set the standards for regulatory requirements in pharmaceutical industry
- Steps:
  - Develop the analytical procedure (similar to research environment)
  - Draft the method validation protocol (e.g., procedure, parameter such as precision, acceptance limits, ICH requirements)
  - Execute the method validation experiments
  - Quality review and approval
  - Publish method validation report
  - Publish analytical procedure
  - Significant change to the procedure – method re-validation

How difficult it is to make the  
“pills”?

# Manufacturing – for Clinical Research

- Develop the formulation and manufacturing procedure (e.g., critical parameters)
- Issue and approve “manufacturing ticket” (e.g., technical, management, quality)
- Qualify and test all raw-materials (e.g., active ingredients, excipients, packaging)
- Validate all analytical methods for the drug products
- Execute the manufacturing and packaging process
- Perform in-process and drug product testing
- If necessary, handle deviations and out-of-specifications results
- Issue and approve batch record
- Conduct ongoing stability test.....

Do the right thing at the right  
time – key for success

# Thank you

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