

Niklaus Stoecklin (1896-1982, Basel); Chemiebild - Die Neue Zeit; Image of Chemistry, The New Era; 1940; Forum 1, Novartis Campus, Basel

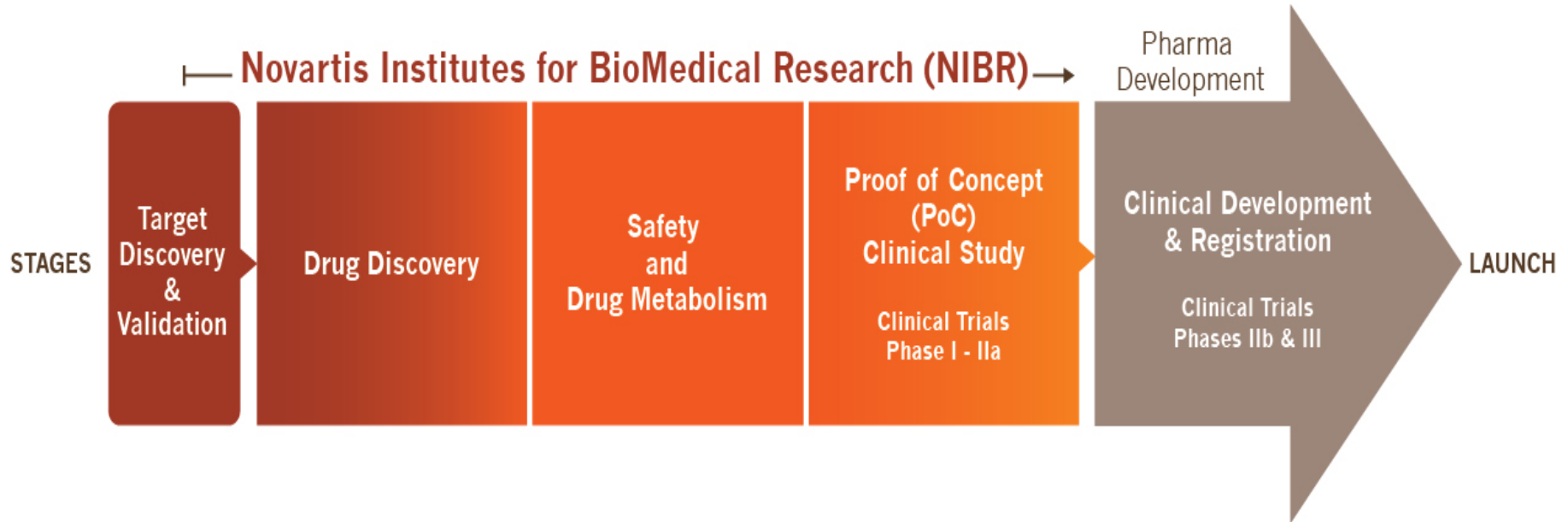
# An Overview of the Drug Discovery Process

**Presented by: Daniel F. Liberman, PhD;**  
**Director HSE and Global HSE Special Projects Manager (ret,)**  
**May 5, 2011 Spring Continuing Education Conference**

# Drug Discovery Process:

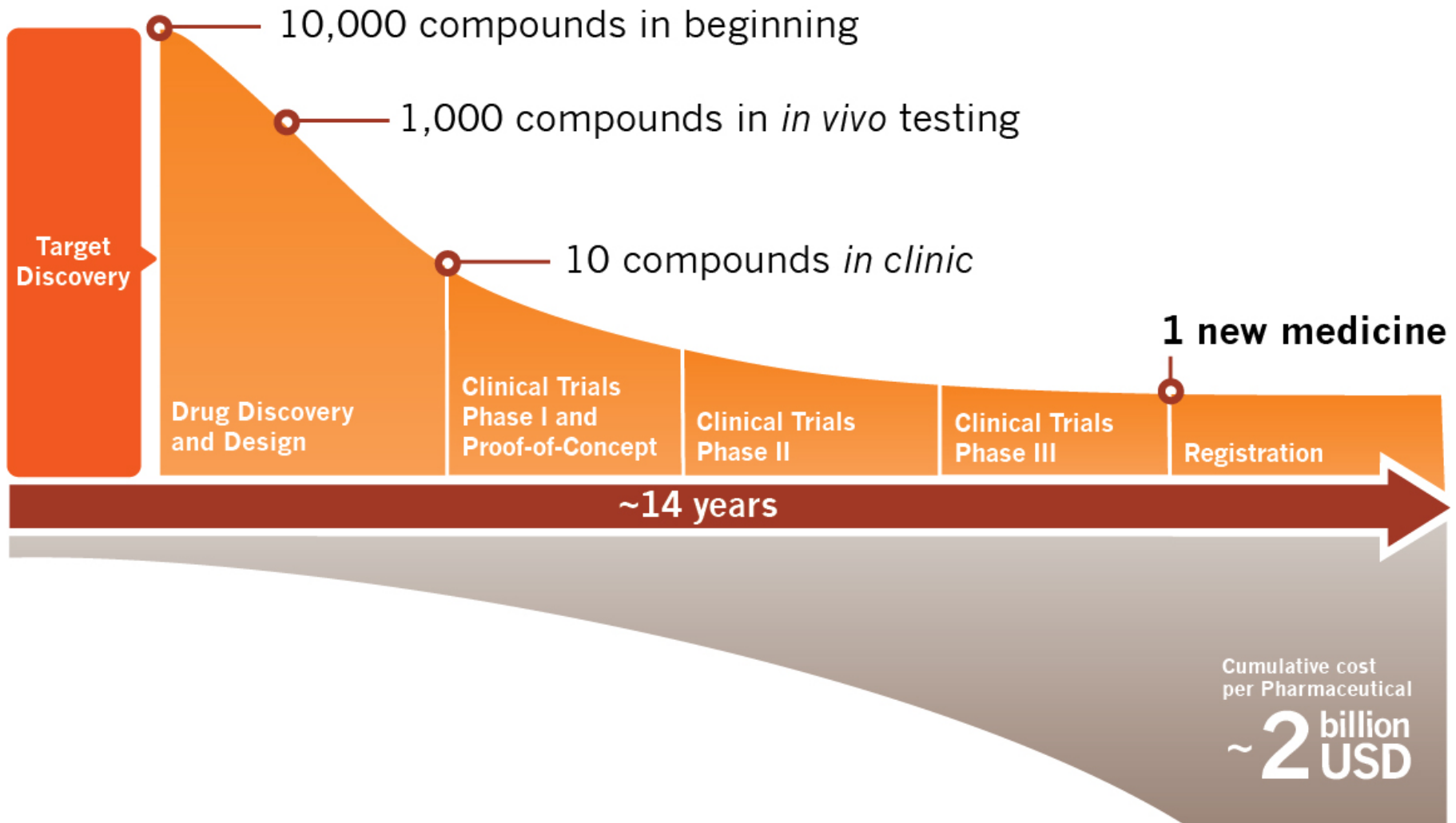
Preclinical (Target to Proof-of-Concept)

Clinical (Proof-of-Concept to Completion of Phase III)



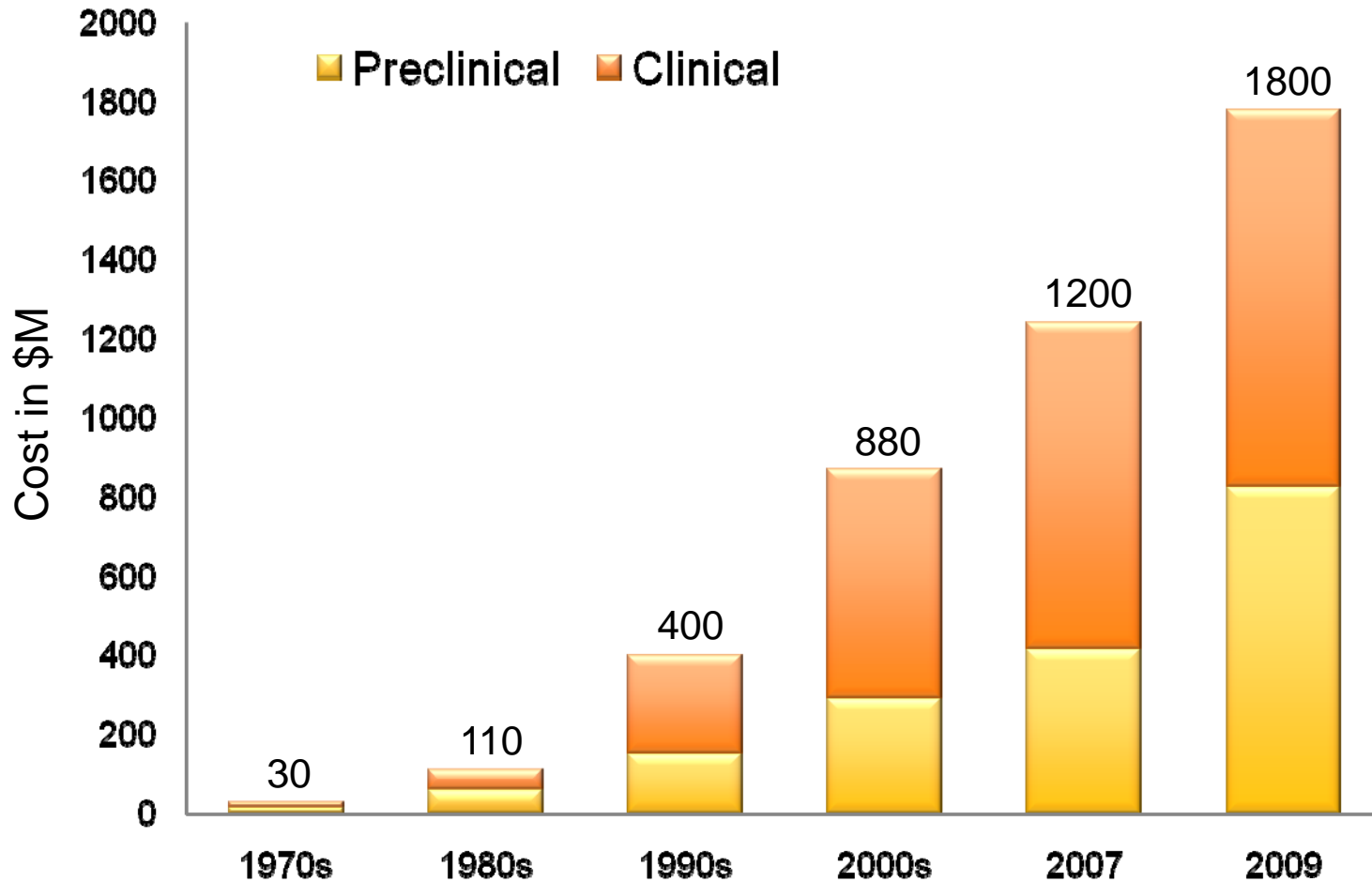
# 14 years and 2 billion CHF to develop one drug

## Overview of drug development process



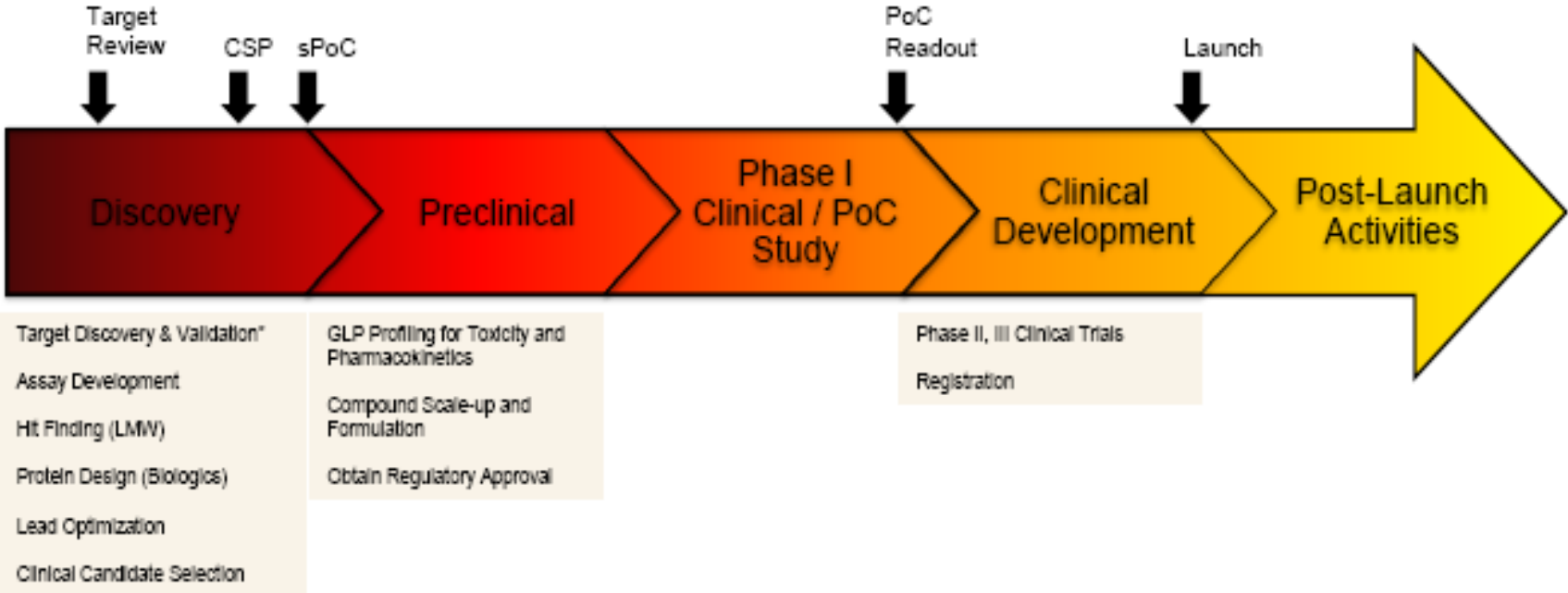
# Increasing R&D Costs per Drug

## *Total Capitalized Cost per Approval*



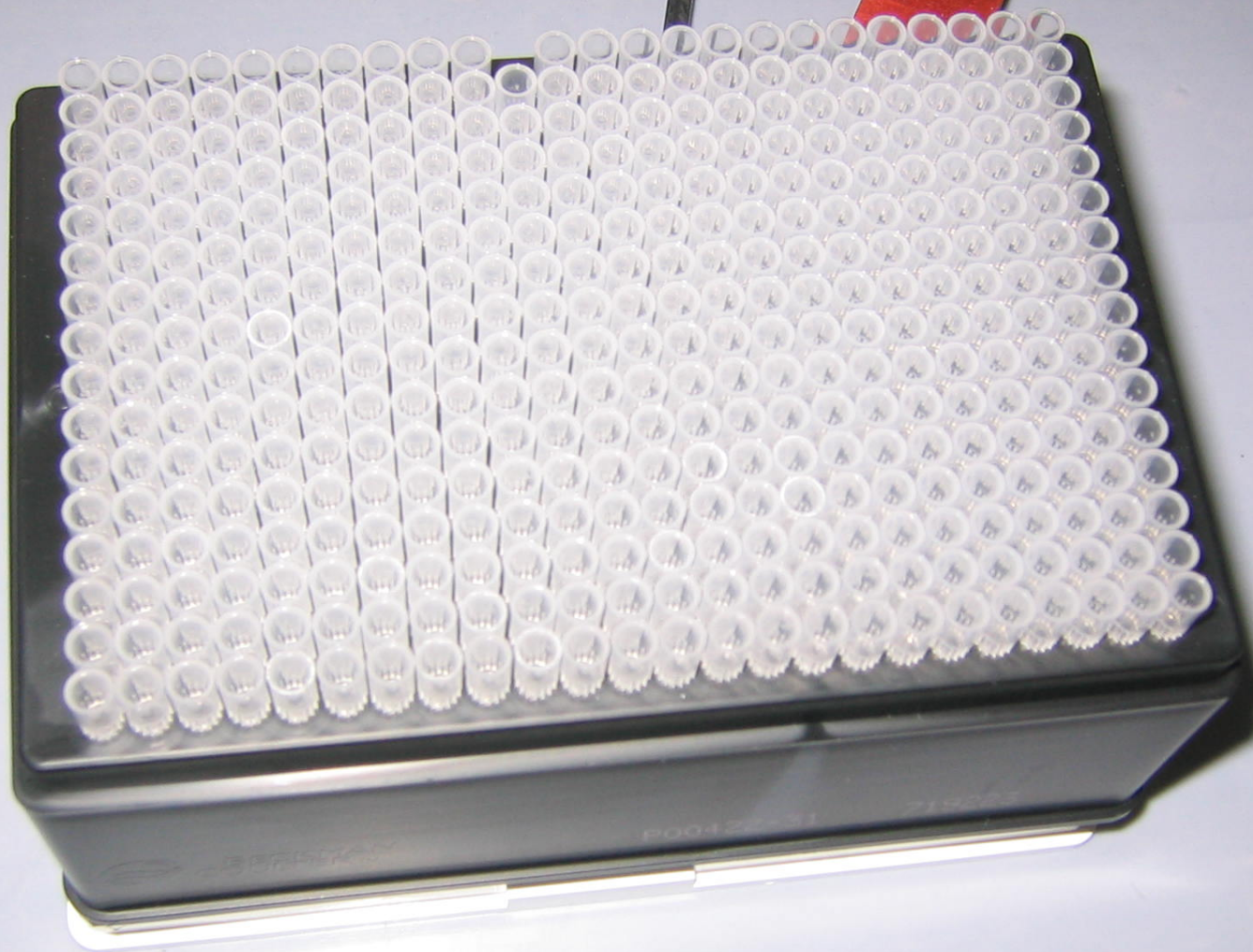
Source: Boston Consulting Group, 2001 & *Journal of Health Economics*, 1991 & Tufts CSDD DiMasi 2003, 2007, NRDD 2010

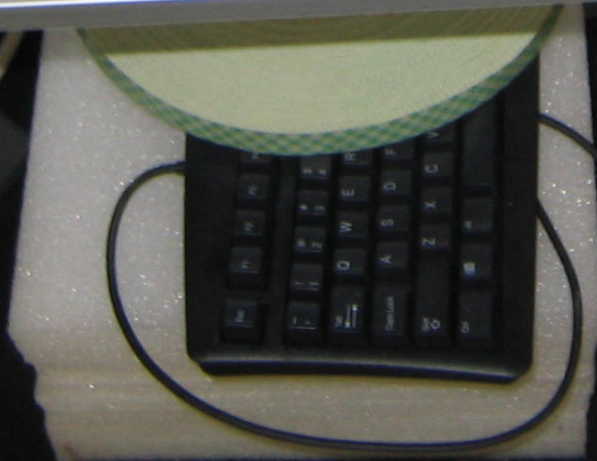
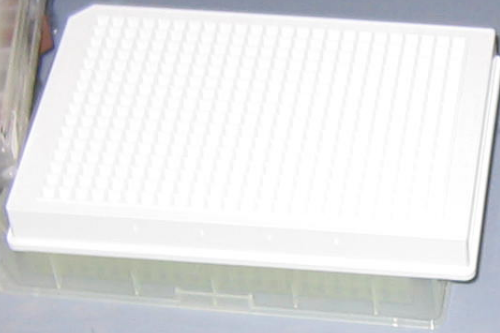
# Drug Discovery and Development

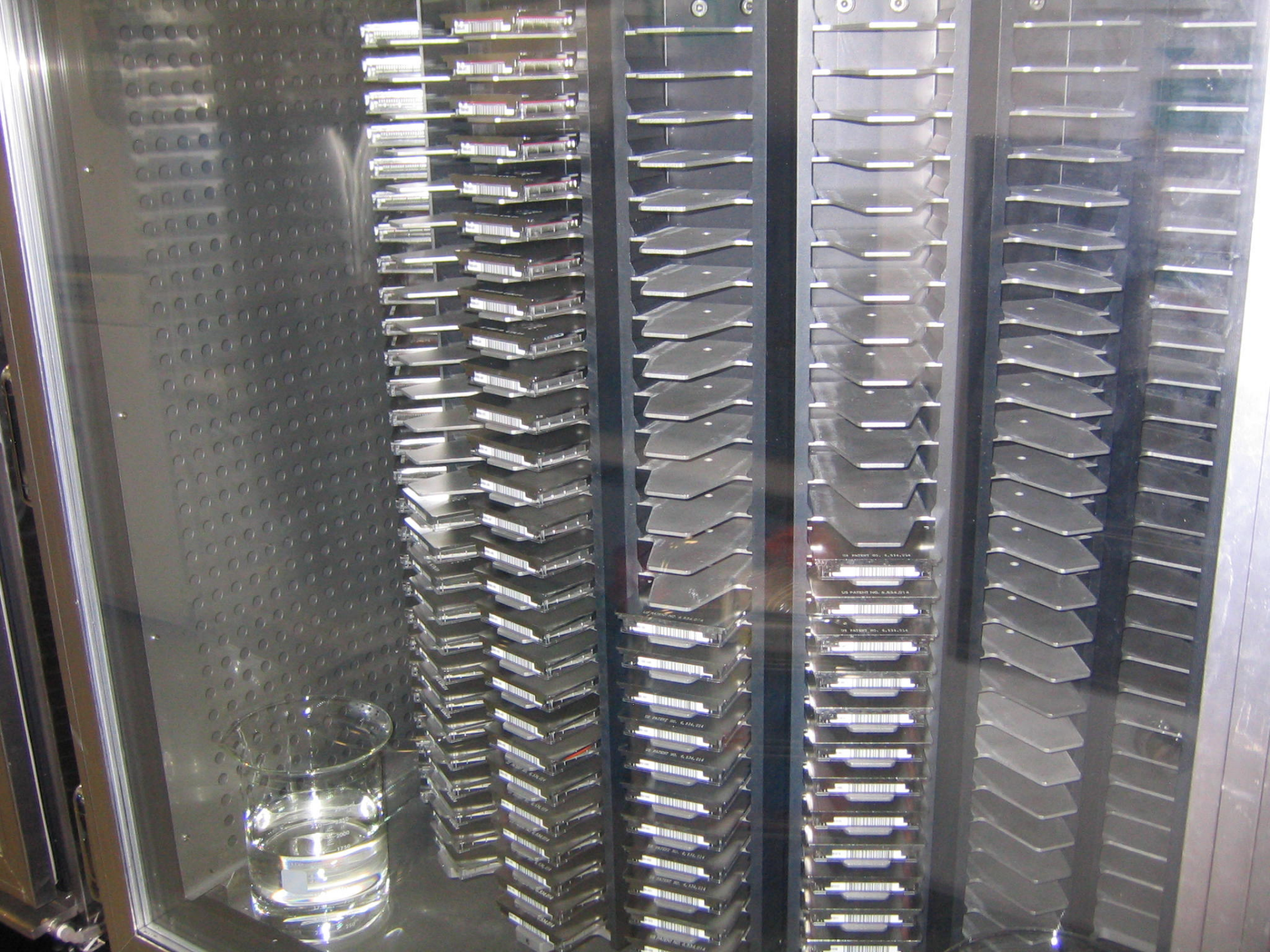


\*Target validation continues through PoC readout

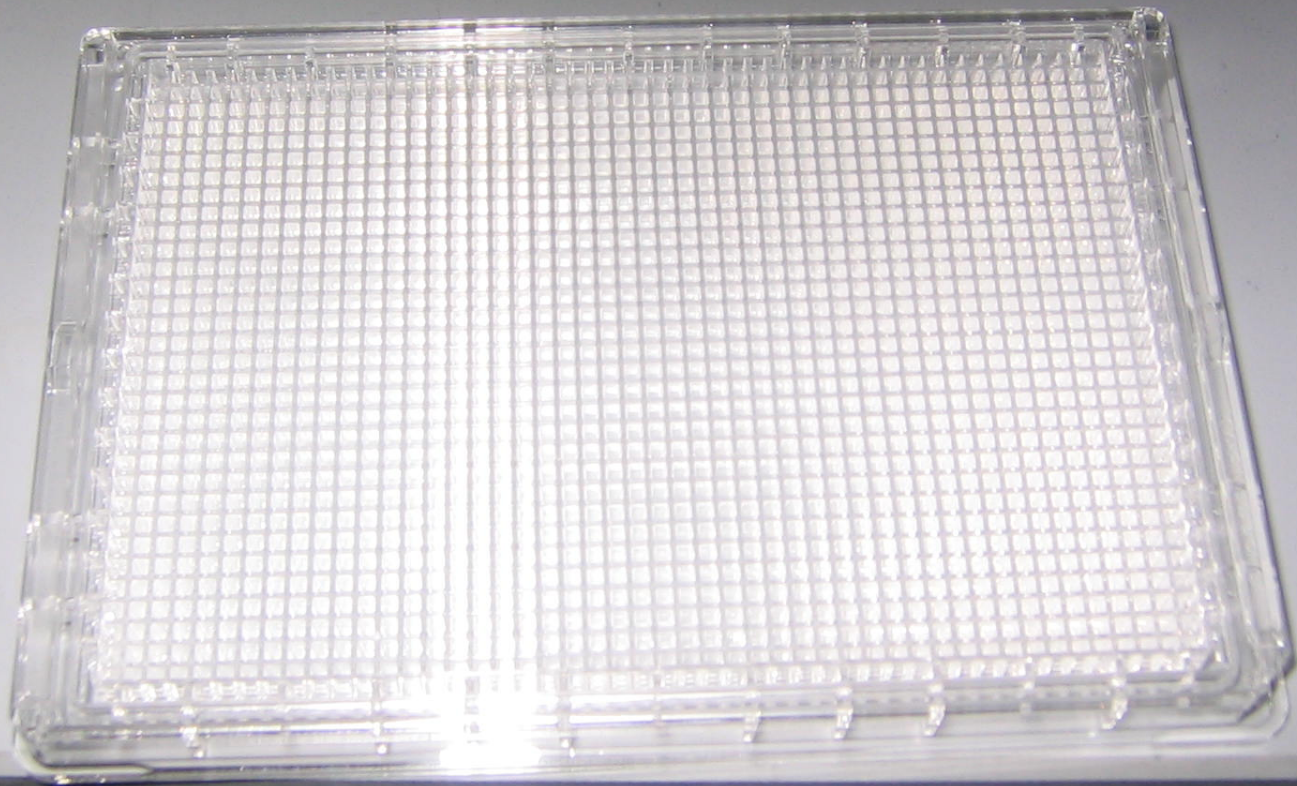
CSP: Candidate Selection Phase
LMW: Low Molecular Weight
PoC: Proof-of-Concept Study
sPoC: Selected for Proof-of-Concept Study

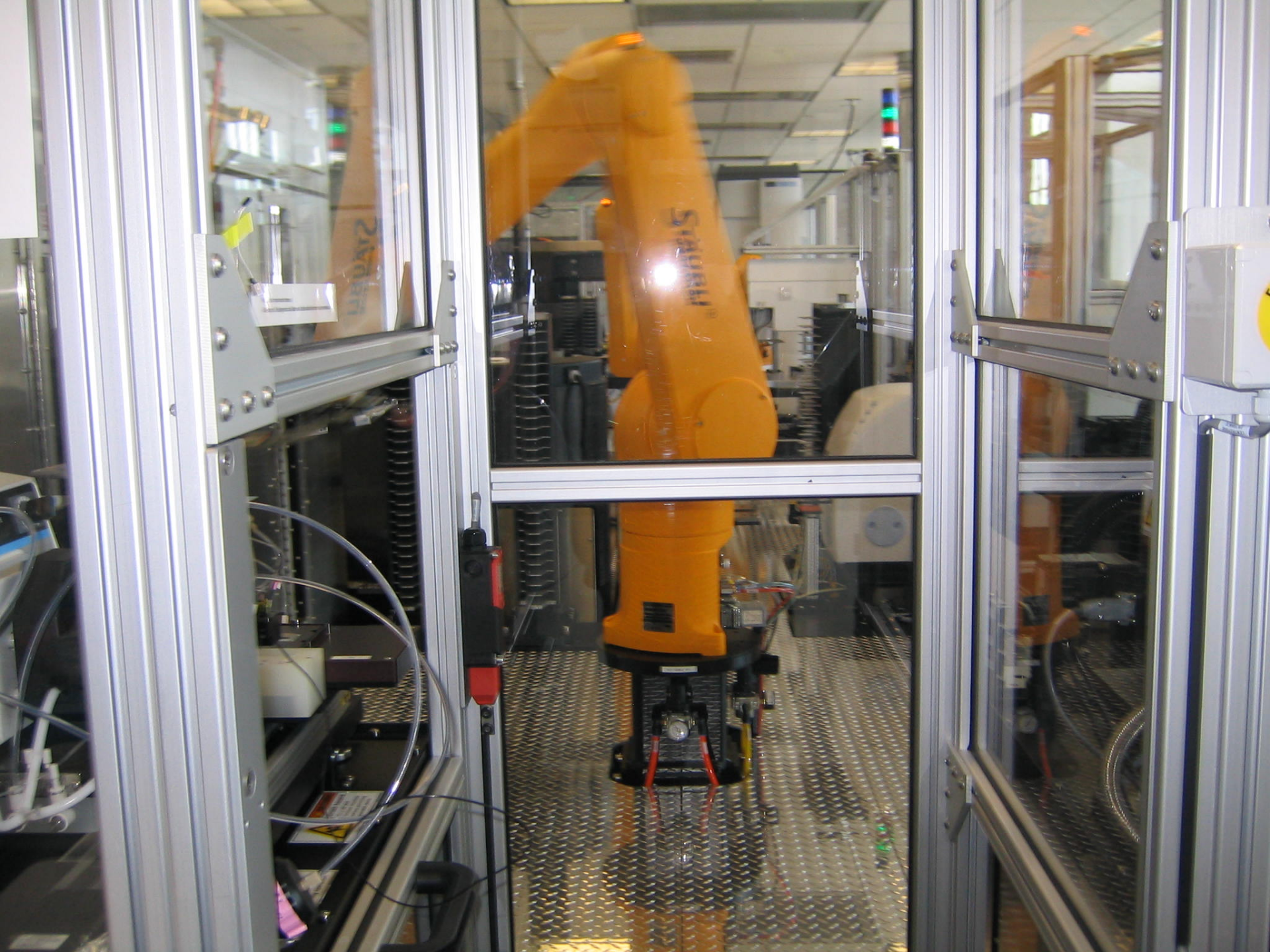


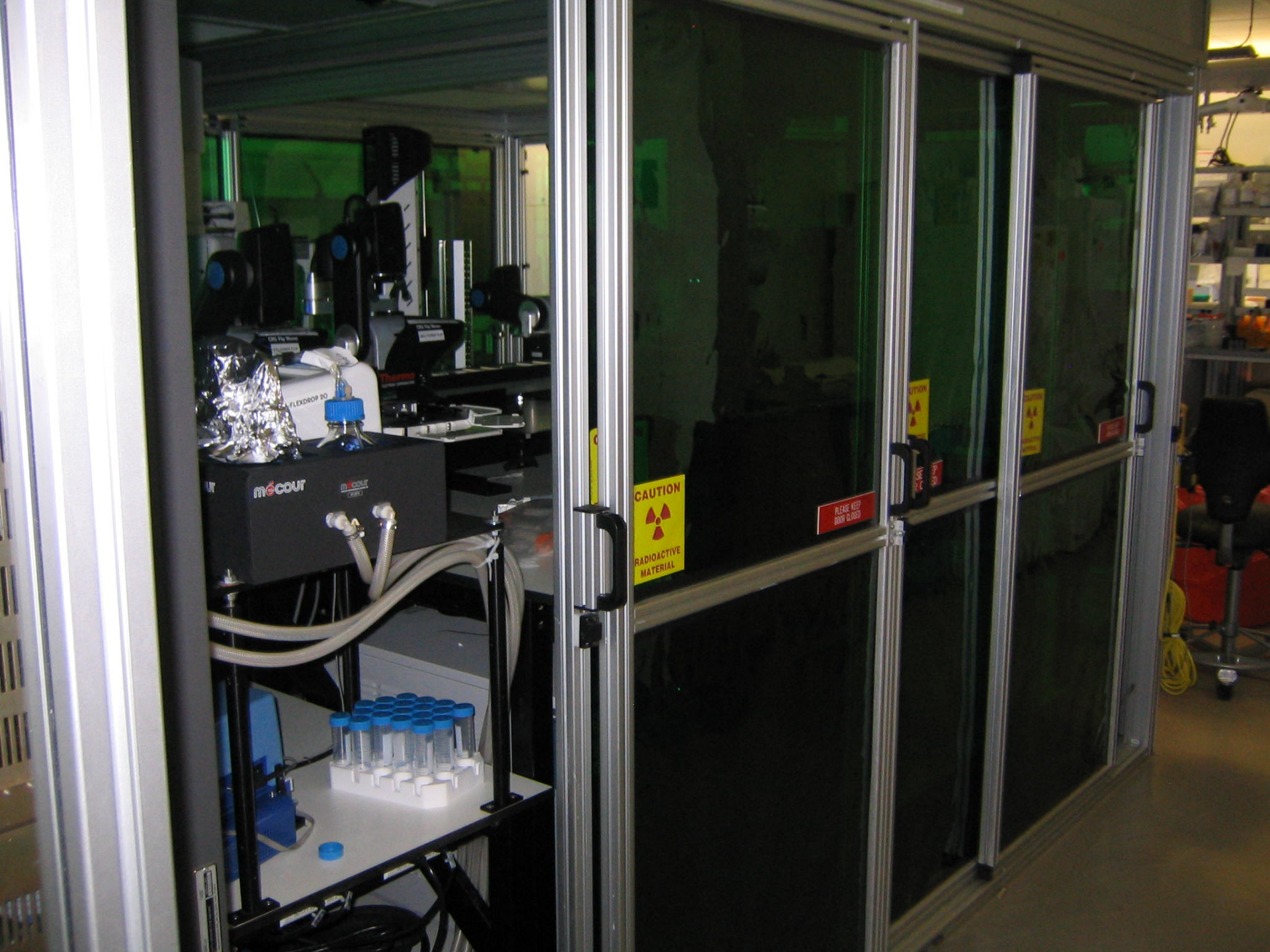












FLUXOROP 90

**mecour**

16 test tubes in a rack

**CAUTION**  
RADIOACTIVE MATERIAL

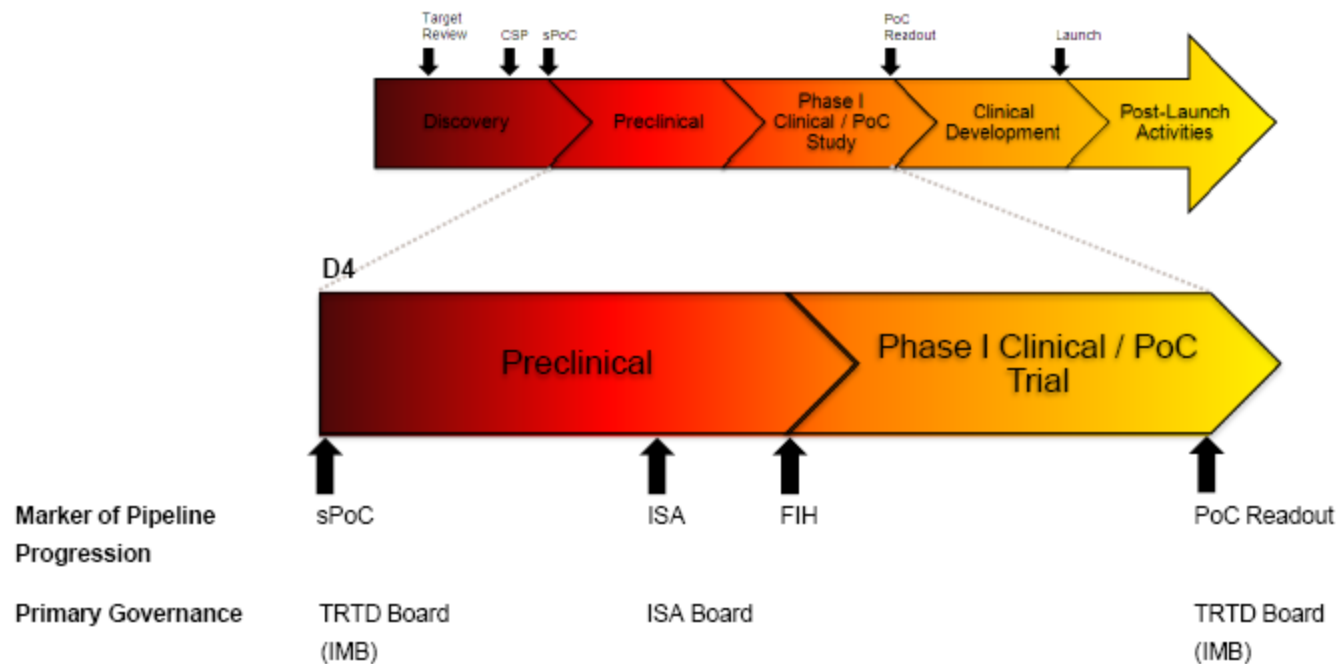
PLEASE KEEP BODY & CLOTHES AWAY

CAUTION

CAUTION

# Drug Discovery and Development at Novartis

## Pipeline Progression and Governance: Early Development

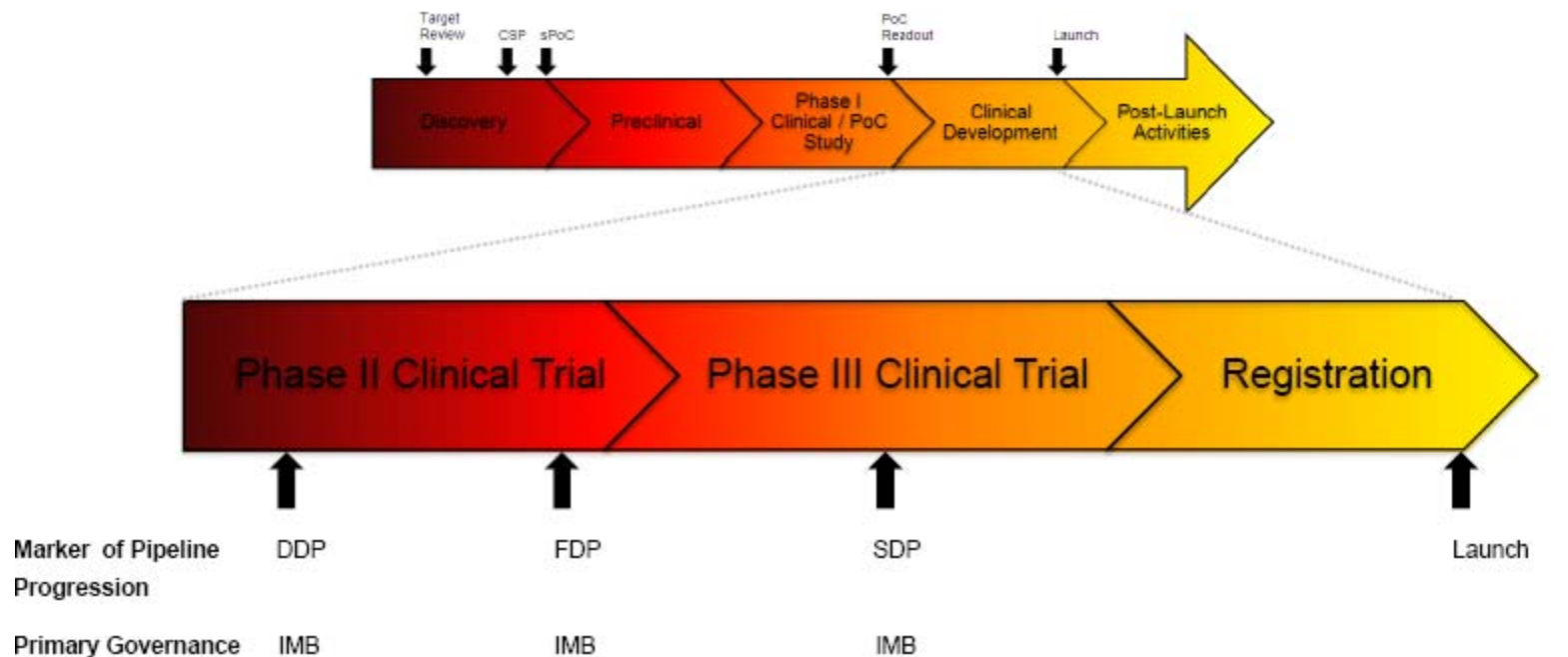


Note: DADB is responsible for project from inception to PoC

FIH: First in Human
IMB: Innovation Management Board
ISA: Integrated Safety Assessment
NTRC: NIBR Target Review Committee
PoC: Proof-of-Concept
sPoC: Selected for Proof-of-Concept
TRTD: Translational Research and Translational Decision

# Drug Discovery and Development at Novartis

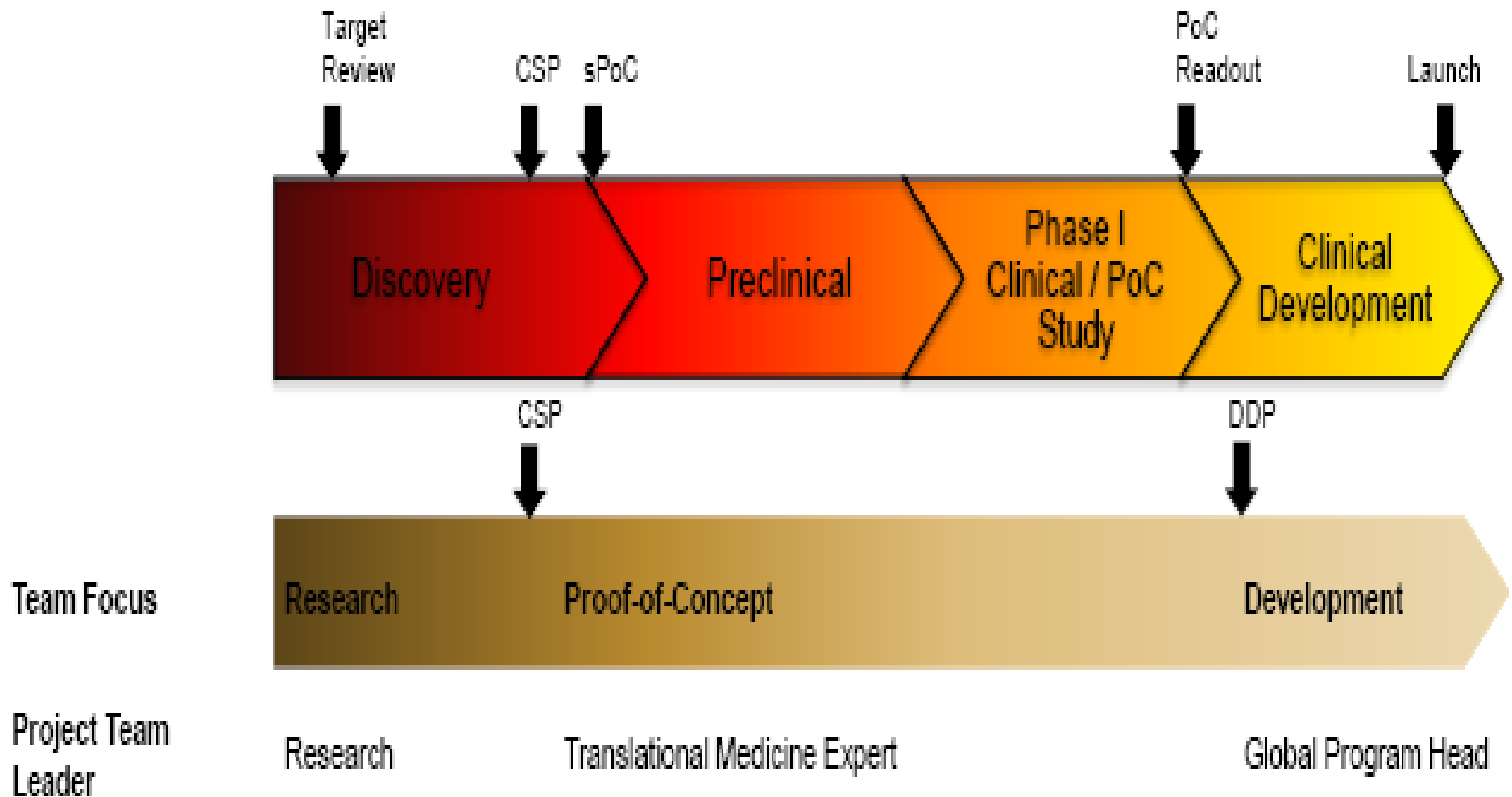
## *Pipeline Progression and Governance: Clinical Development*



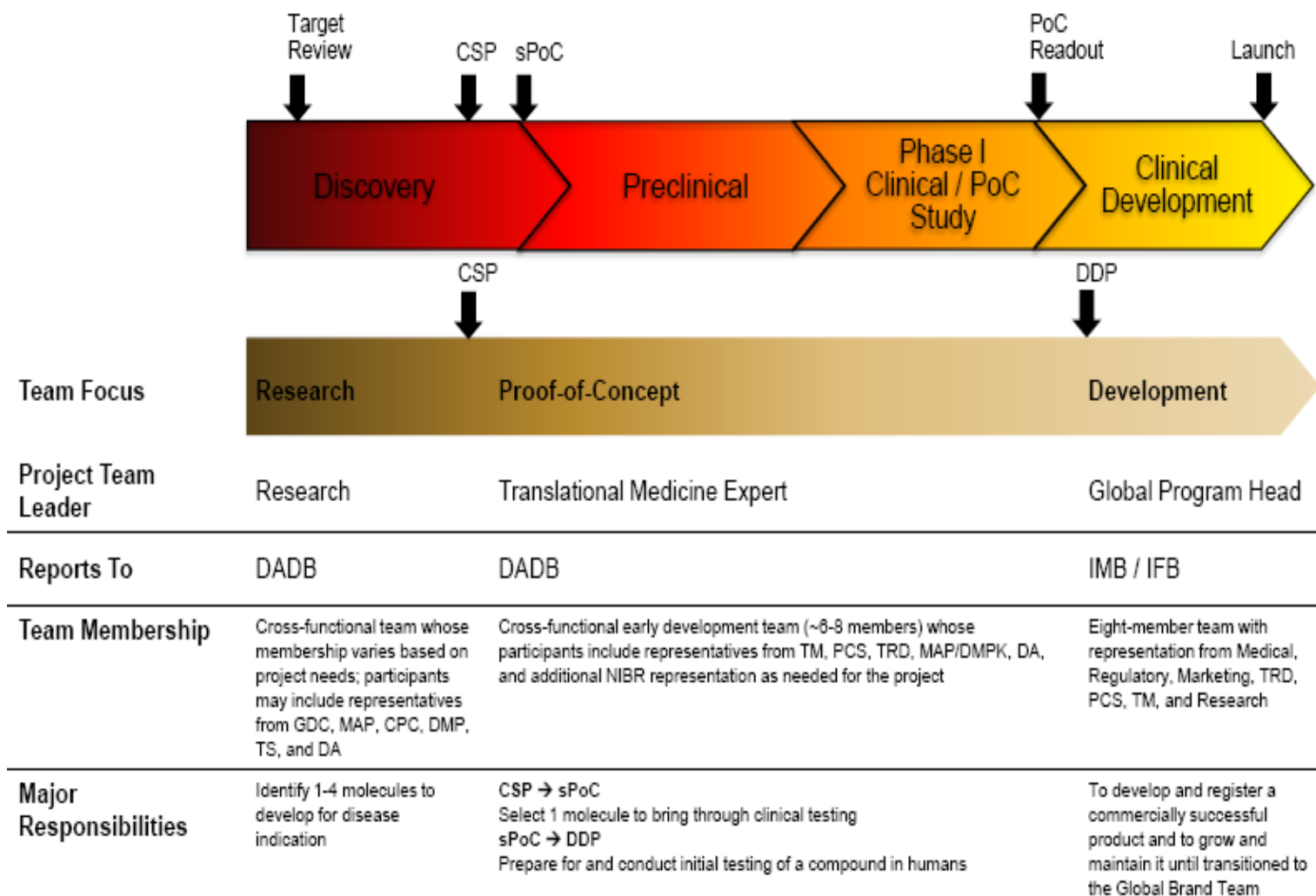
DDP: Development Decision Point  
 FDP: Full Development Decision Point  
 IMB: Innovation Management Board  
 SDP: Submission Decision Point

# Project Teams

A Project has a single team whose leadership and membership changes as the Project's needs change



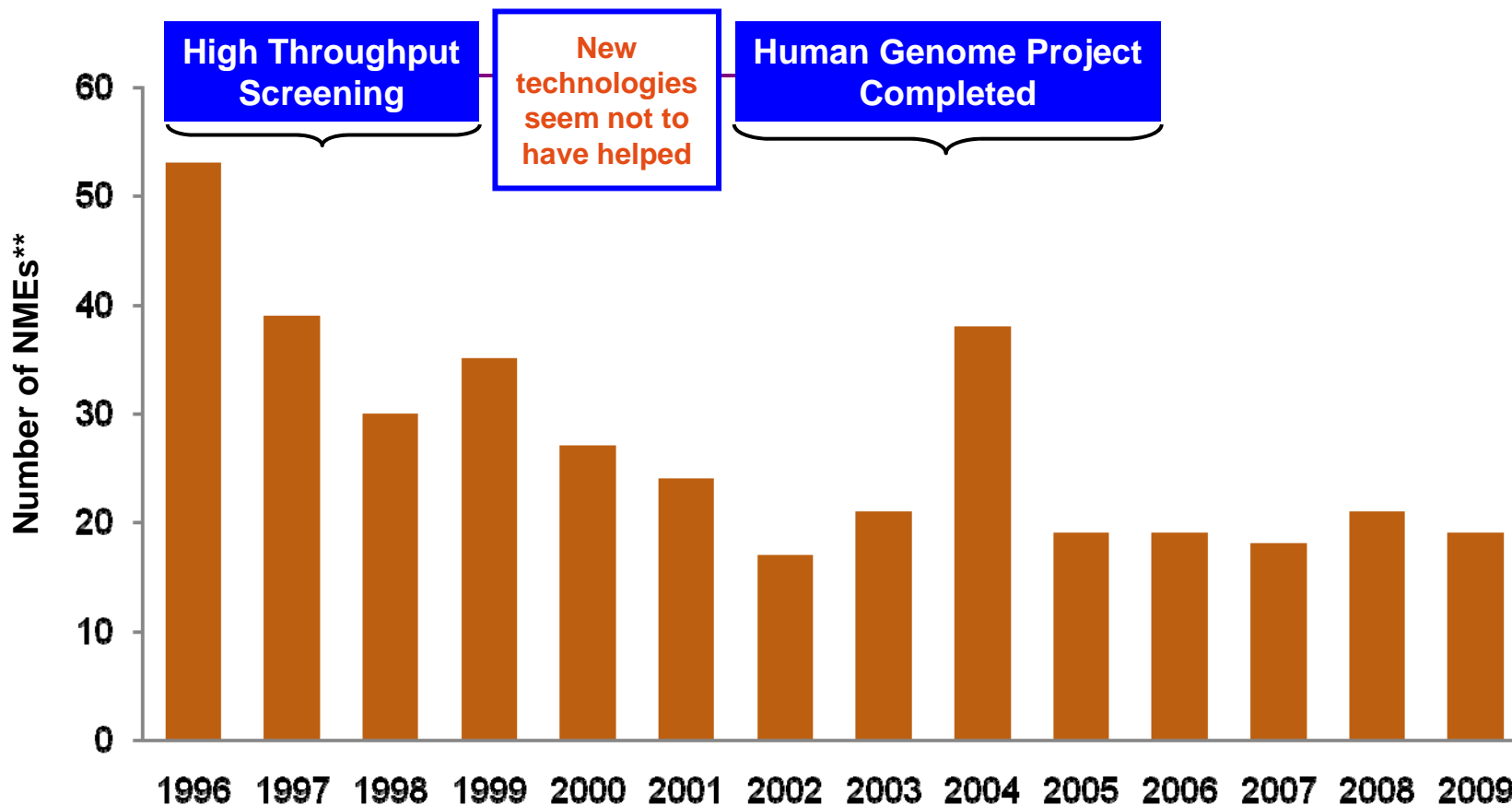
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# Current Status of Drug Discovery:

*Few new drugs are approved each year from all Pharma*

## FDA-approved Drugs\*



\* Drugs defined as 'New Molecular Entities' (NMEs) - a term which is applied by the Food and Drug Administration to both new pharmaceutical and immunological agents

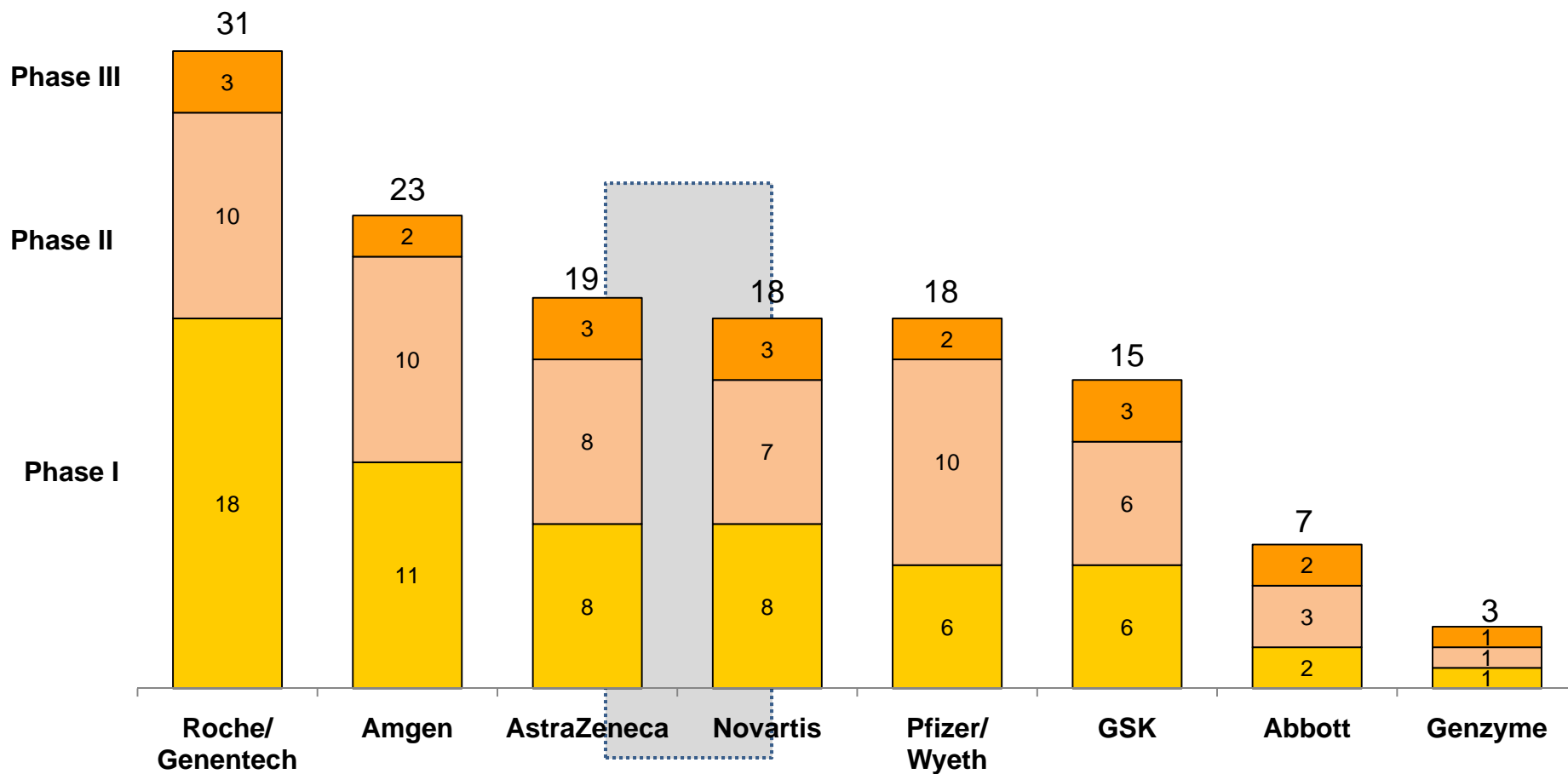
\*\*Does not include Biologics

Source For NMEs: Nature Reviews Drug Discovery 7, 107-109 (February 2008)



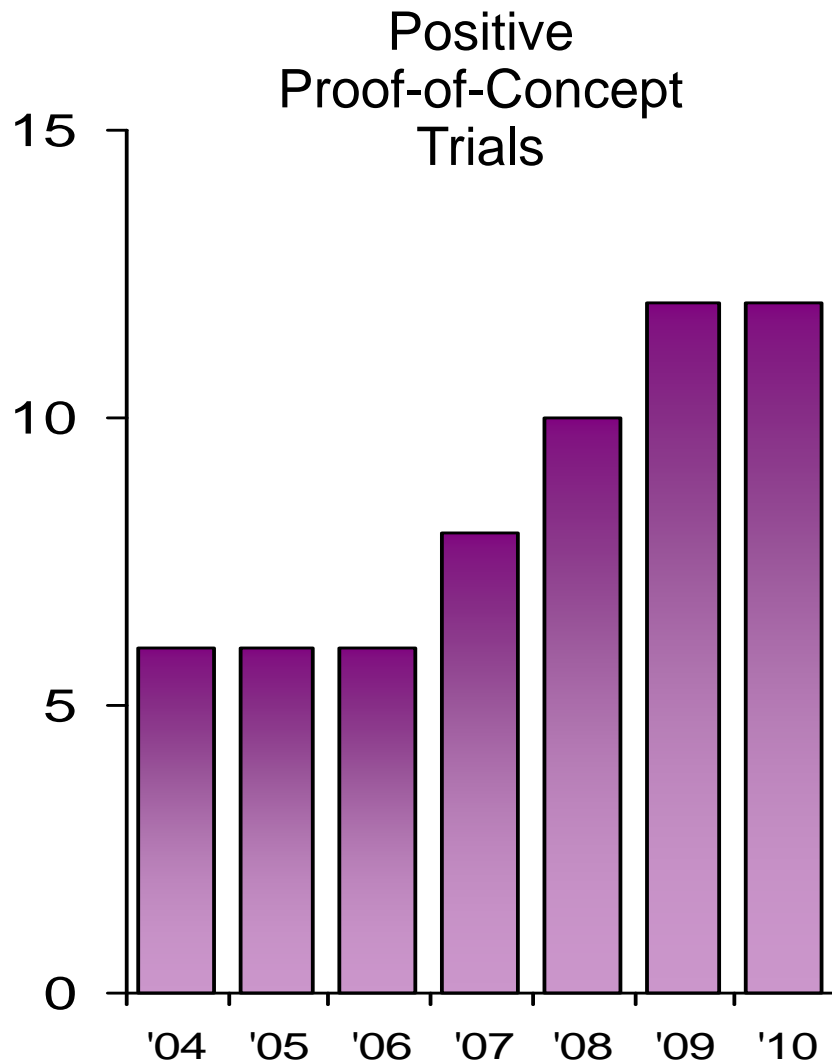
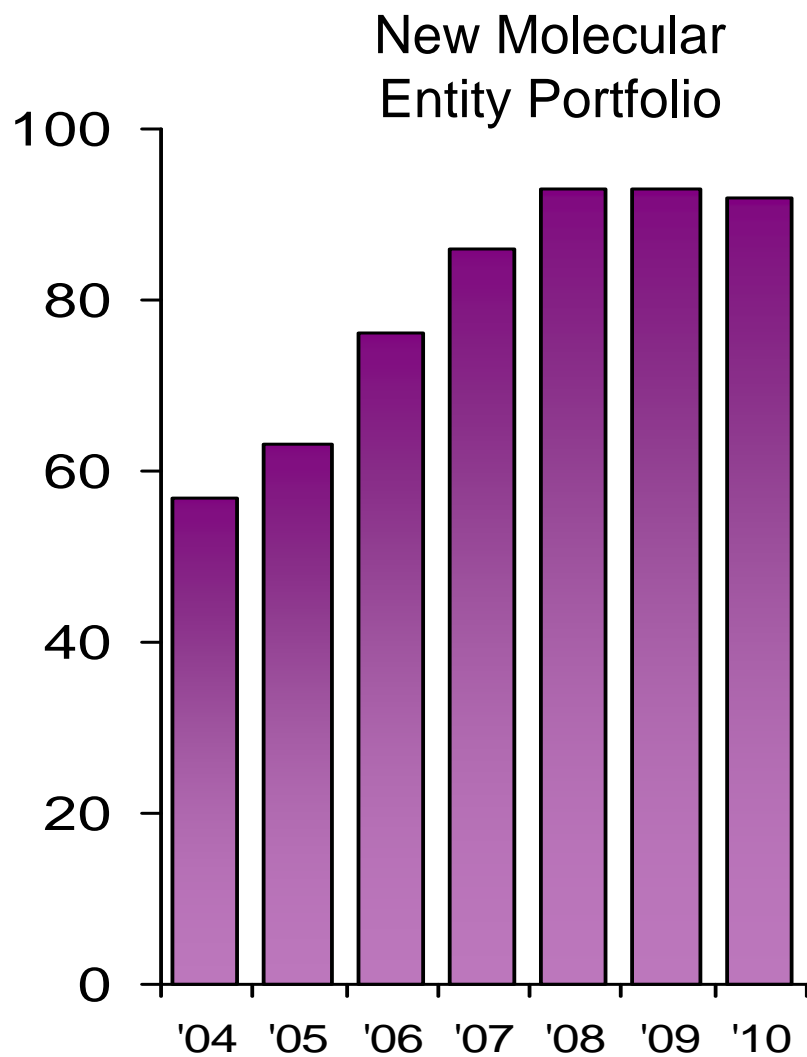
# Building a Robust Biological Therapeutic Pipeline

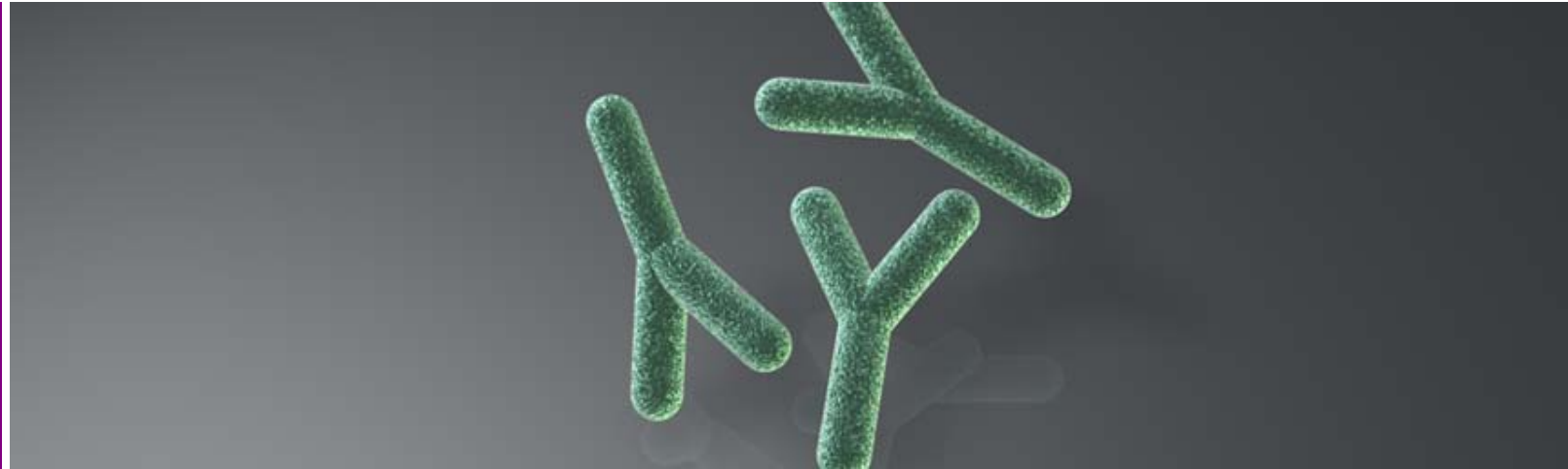
## *Number of novel molecules in clinical trials*



\* As of October 2010. For molecules with multiple indications, phase of lead indication was counted  
 Source: EvaluatePharma; TPP; Novartis pipeline data

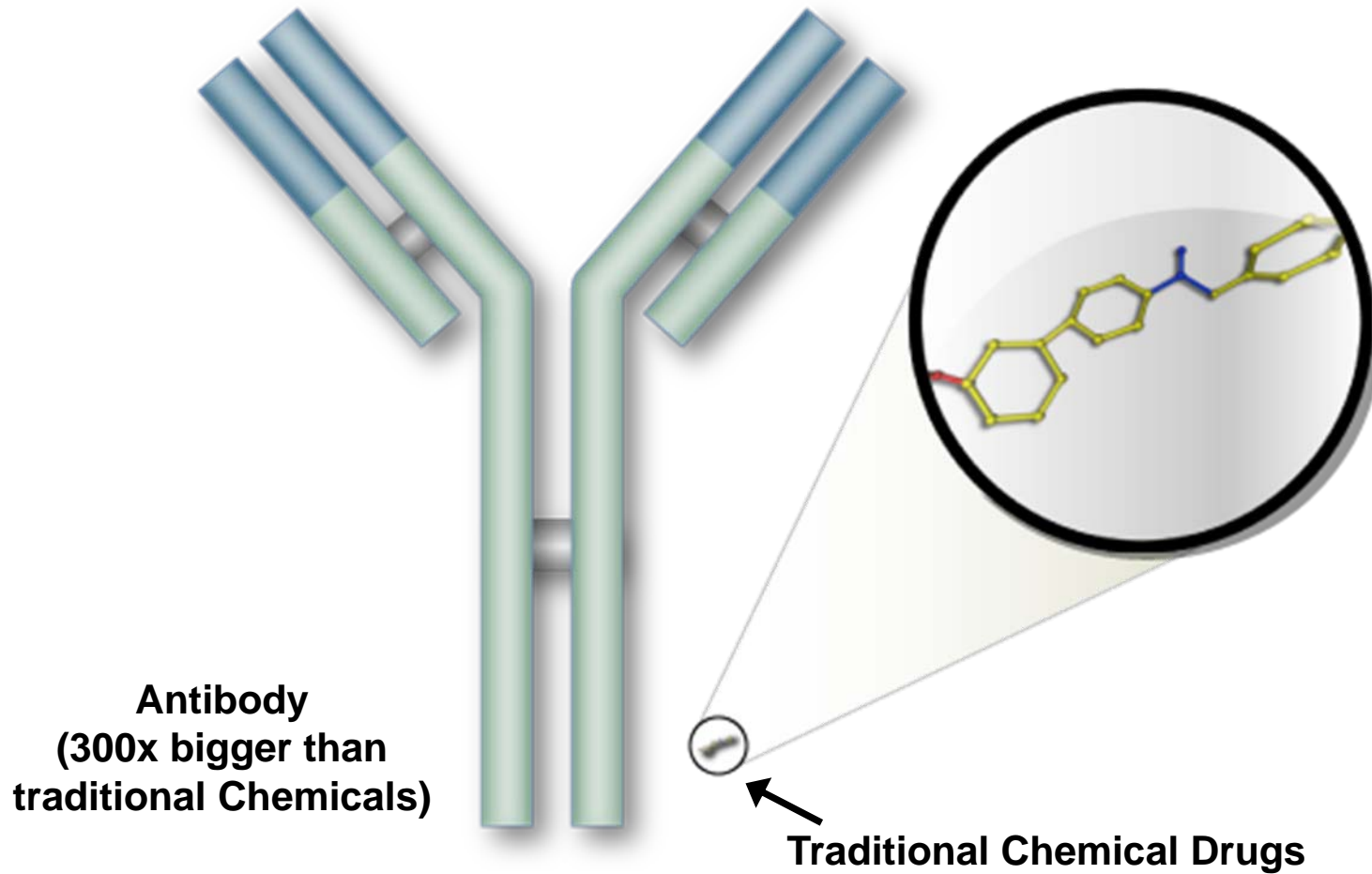
# 2010 Pipeline Progress





# Small (Chemical Actives) vs Large (Biologics) Entities

# Biologics and Chemicals Are Different



# Key Differences between Antibodies and Low Molecular Weight Chemical Drugs

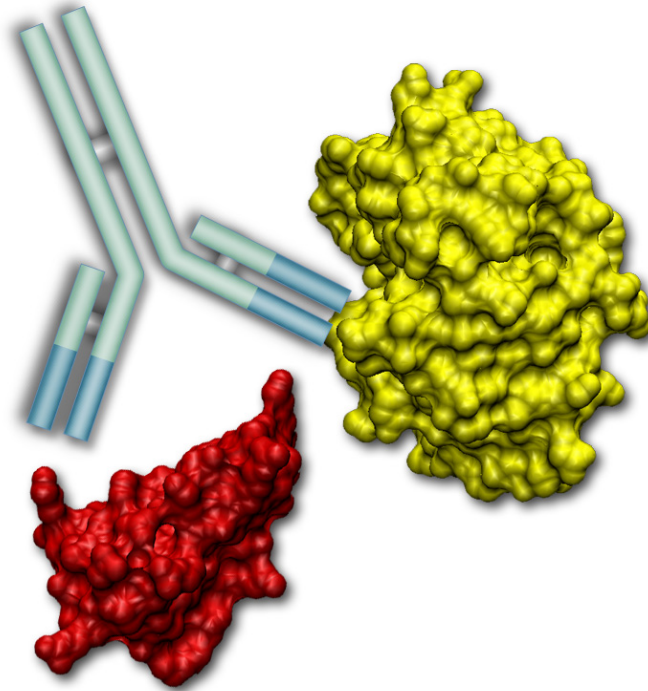
Descriptor	Antibody	LMW drug
<b>Drug Characteristics</b>	<ul style="list-style-type: none"> <li>• Parenteral administration</li> <li>• Dosed weekly-monthly</li> <li>• Physician administered</li> </ul>	<ul style="list-style-type: none"> <li>• Often orally administered</li> <li>• Dosed hourly to daily</li> <li>• Self administered</li> </ul>
<b>Target</b>	<ul style="list-style-type: none"> <li>• Extracellular mechanisms</li> <li>• Good at protein interactions</li> </ul>	<ul style="list-style-type: none"> <li>• Any druggable target</li> <li>• Enzymes/receptors/channels</li> </ul>
<b>Side effects</b>	<ul style="list-style-type: none"> <li>• Specific action</li> <li>• Low off target toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Less specific</li> <li>• Can inhibit multiple mechanisms</li> </ul>

# Antibodies Offer Specific Advantages Over Traditional Chemical Drugs

	<b>Small Molecules</b>	<b>Antibodies</b>
Clinical success rate	5%	24%
Specificity for target	Varies	Very High (100 x> sm. Mol.)
Threat from generics	High	Low
Delivery	Oral	Injectable
Dosing frequency	Usually daily	Weekly or less frequent
Size of molecule	Very small (500Da)	Large (150kDa)
Cost to produce	Low	High
Molecular targets of FDA approved drugs	248	18
Risk of side effects	Varies	Usually well tolerated
Accessible targets	Intra- and extra-cellular	Extra-cellular and secreted proteins

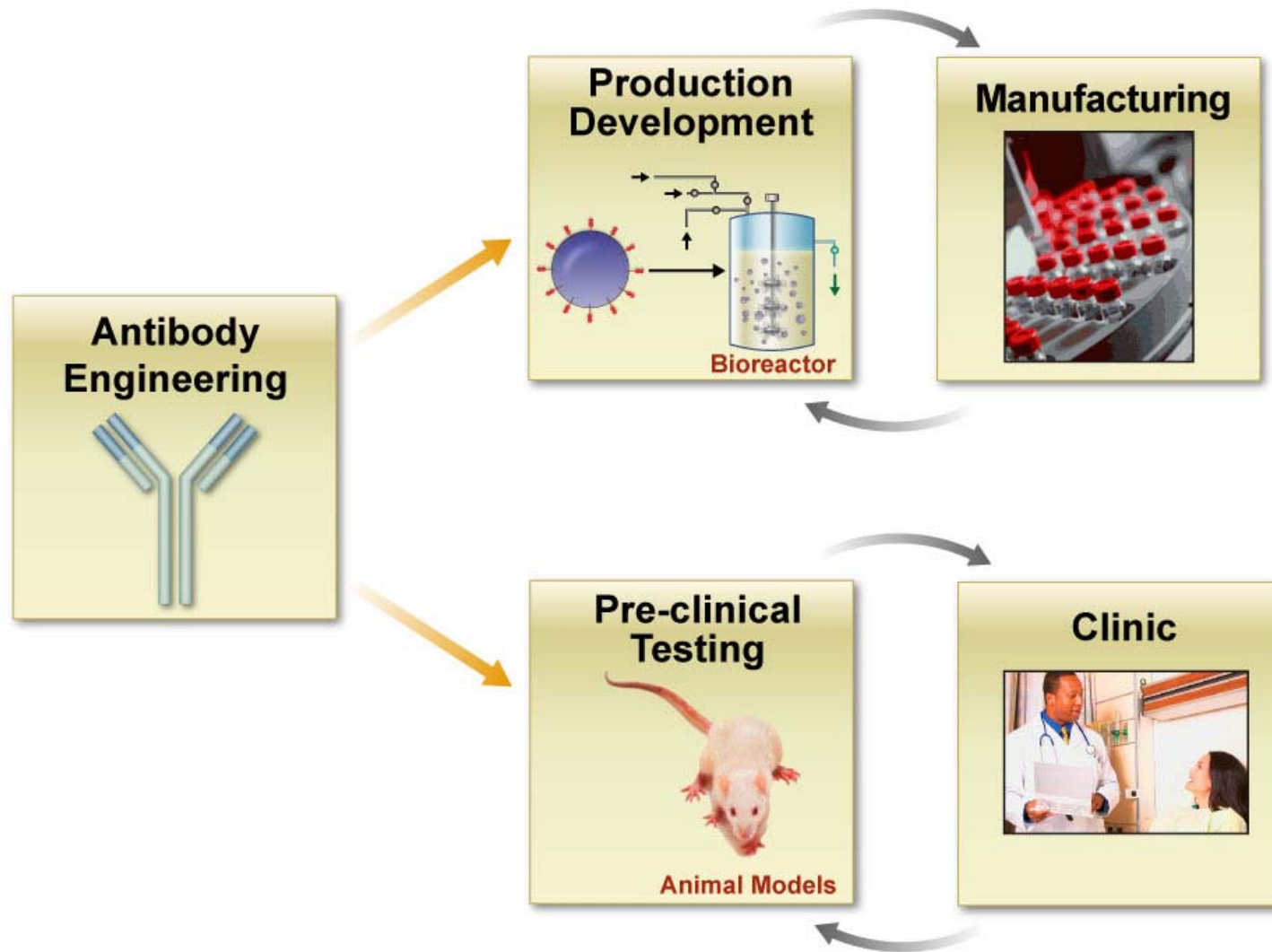
# When Are Antibodies Better Than Chemical Therapeutics?

1. Getting to inaccessible targets



2. Great specificity, without the significant, unpredictable, off-target toxicities of LMW drugs

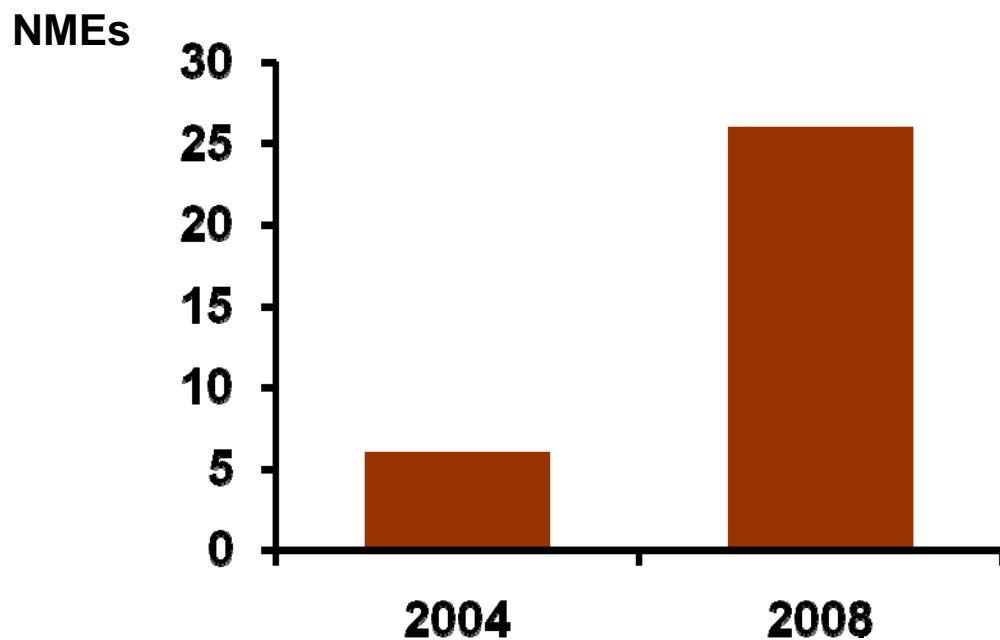
# Steps to Developing an Antibody Therapeutic



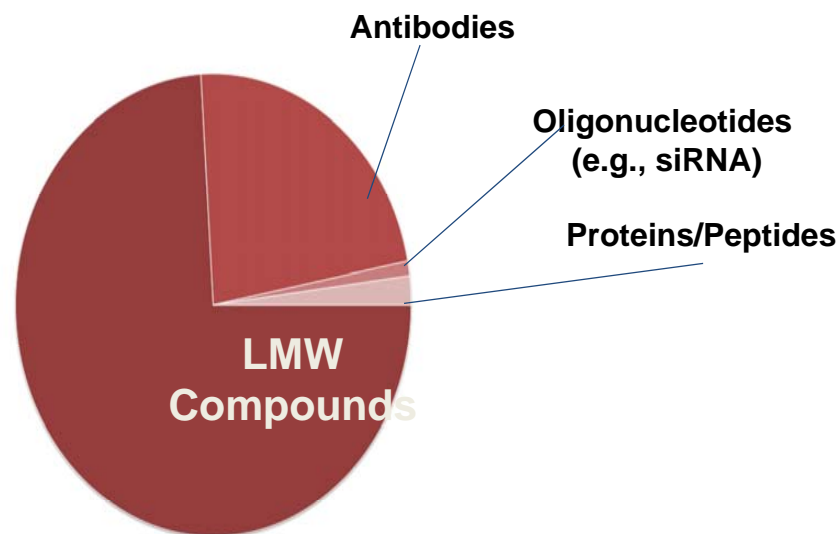


# Building A Robust Biological Therapeutic Program

Steady Growth of Biologic New Molecular Entities



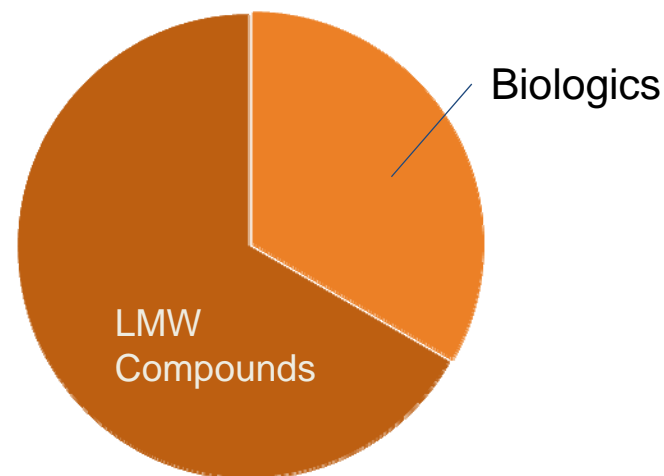
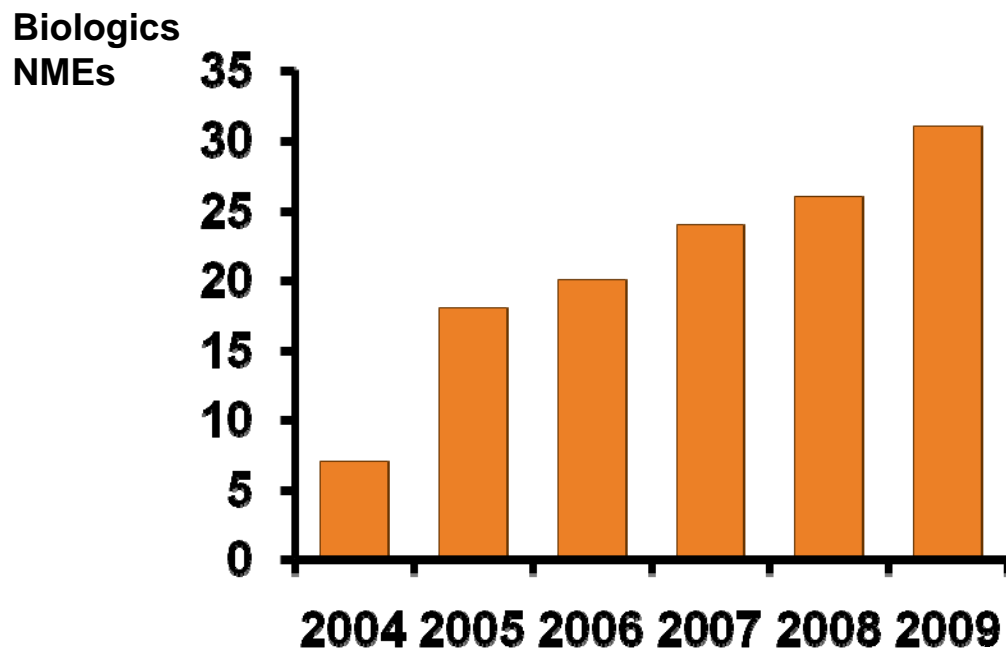
Biologics Constitute >25% of NME Drug Candidates

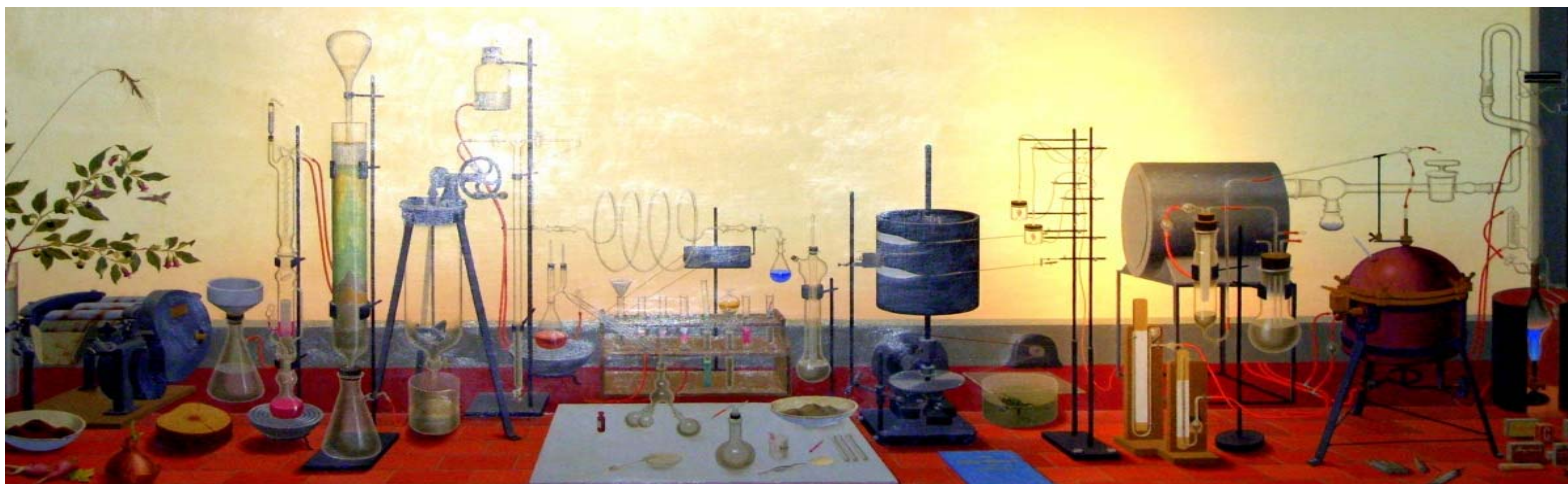


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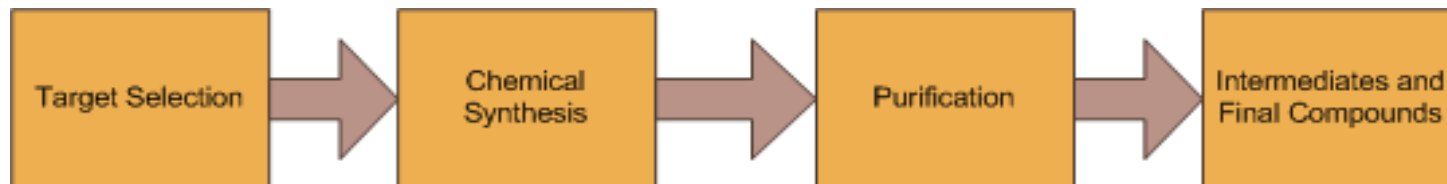




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# TUR Opportunities in Drug Discovery

# TUR Considerations in Drug discovery



## Synthesis and purification steps.

### Choice of solvents, reagents and purification techniques

- Solvent selection could be the simplest way to green a Med Chem process
- Use a less toxic solvent with less environmental impact...and use less of it.

# Solvent Selection Guide

## Pfizer Solvent Selection Guide for Medicinal Chemistry

### Preferred

Water  
Acetone  
Ethanol  
2-Propanol  
1-Propanol  
Ethyl acetate  
Isopropyl acetate  
Methanol  
Methyl ethyl ketone  
1-Butanol  
*t*-Butanol

### Useable

Cyclohexane  
Heptane  
Toluene  
Methylcyclohexane  
Methyl *t*-butyl ether  
Isooctane  
Acetonitrile  
2-MethylTHF  
Tetrahydrofuran  
Xylenes  
Dimethyl sulfoxide  
Acetic acid  
Ethylene glycol

### Undesirable

Pentane  
Hexane(s)  
Di-isopropyl ether  
Diethyl ether  
Dichloromethane  
Dichloroethane  
Chloroform  
Dimethyl formamide  
N-Methylpyrrolidinone  
Pyridine  
Dimethyl acetate  
Dioxane  
Dimethoxyethane  
Benzene  
Carbon tetrachloride

A 'use this instead', rather than 'don't use' philosophy.

Reference: "Green chemistry tools to influence a medicinal chemistry and research chemistry based organization", Dunn and Perry, et. al., Green Chem., 2008, 10, 31-36

# Solvent Selection

- Safer for the scientist: less toxic, carcinogenic, mutagenic etc.
- Safer for the process: less flammable, lower emissions, less chance of peroxide formation. etc.
- Less harmful to the environment: lower potential to deplete ozone, less ecotoxic, derived from renewable resources.

# Principles of Green Chemistry.

- ∅ Prevention
- ∅ Less Hazardous Chemical Syntheses
- ∅ Designing Safer Chemicals
- ∅ Safer Solvents
- ∅ Design for Energy Efficiency
- ∅ Use Renewable Feedstocks
- ∅ Reduce Derivatives
- ∅ Catalysis
- ∅ Design for Degradation
- ∅ Real Time Analysis for Pollution Prevention
- ∅ Inherently Safer Chemistry for Accident Prevention
- ∅ Atom Economy