Outlines of Pharmaceutical Development Process

April, 7th 2016

Paolo Patri

Global Head of CMC – Zymenex Managing Director
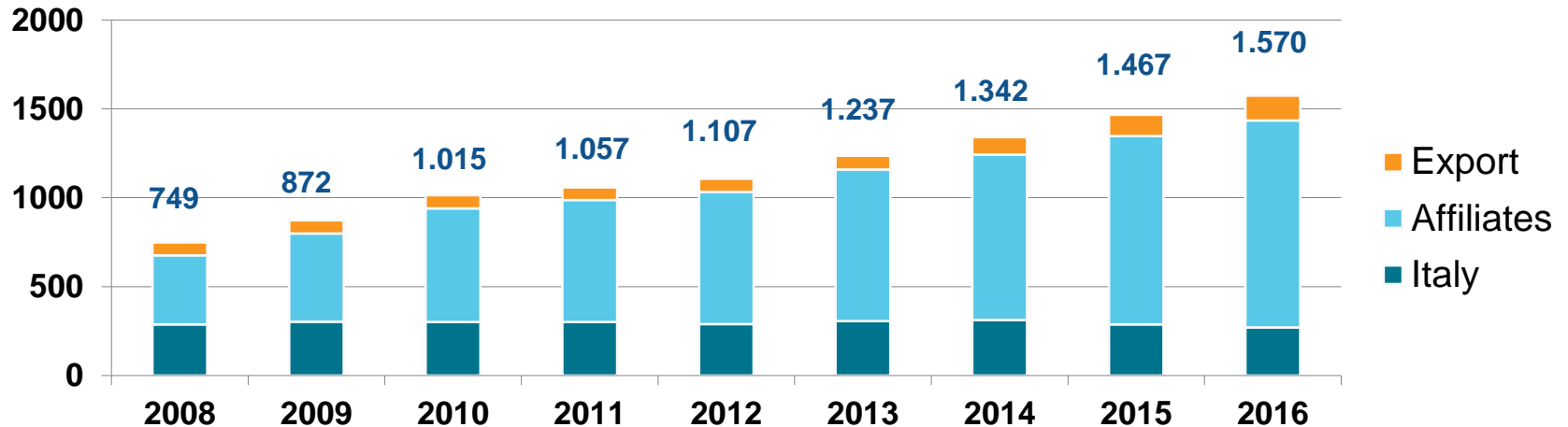
Chiesi Group. Facts & Figures 2016

Key Facts

- Founded in 1935/ Privately owned:
- Employees : 4.813; 1.758 in Italy
- Revenues : 1.570 M €
- R&D Investments: 340 M €
- Direct presence: 26 countries

Therapeutic focus

- Respiratory diseases
- Neonatology & Special Care Diseases
- Rare diseases

Consolidated Sales (millions €)

	2008	2009	2010	2011	2012	2013	2014	2015	2016
Sales	749	872	1.015	1.057	1.107	1.237	1.342	1.467	1.570
Headcount	3.243	3.534	3.737	3.814	3.830	3.885	4.077	4.500	4813

Legend: Export / Affiliates / Italy

Data refering to managerial second closing

The Strategic View

Research & Development with high level investments

Respiratory

Experience and expertise in the development of respiratory products are a core asset for the growth of the Group

Neonatology

Therapies developed by Chiesi offer concrete solutions for severe diseases that may arise in pre-term children

Rare diseases and special care

Unmet needs and the social impact of rare diseases are the focus of our commitment in this field.

World-wide

Development of Chiesi proprietary respiratory technologies
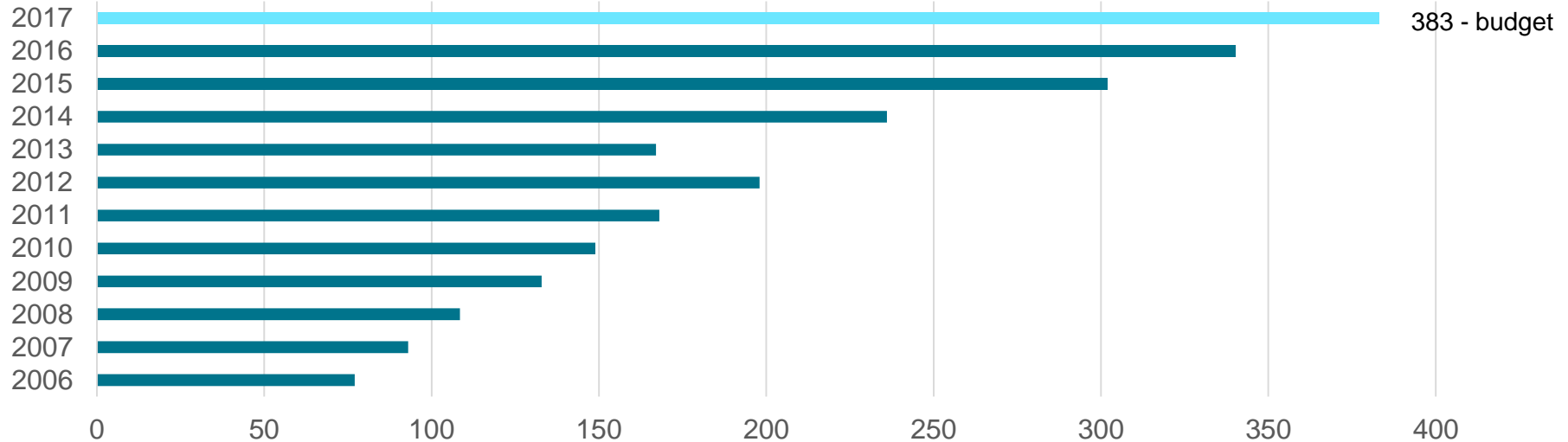
Research & Development – Facts & Figures
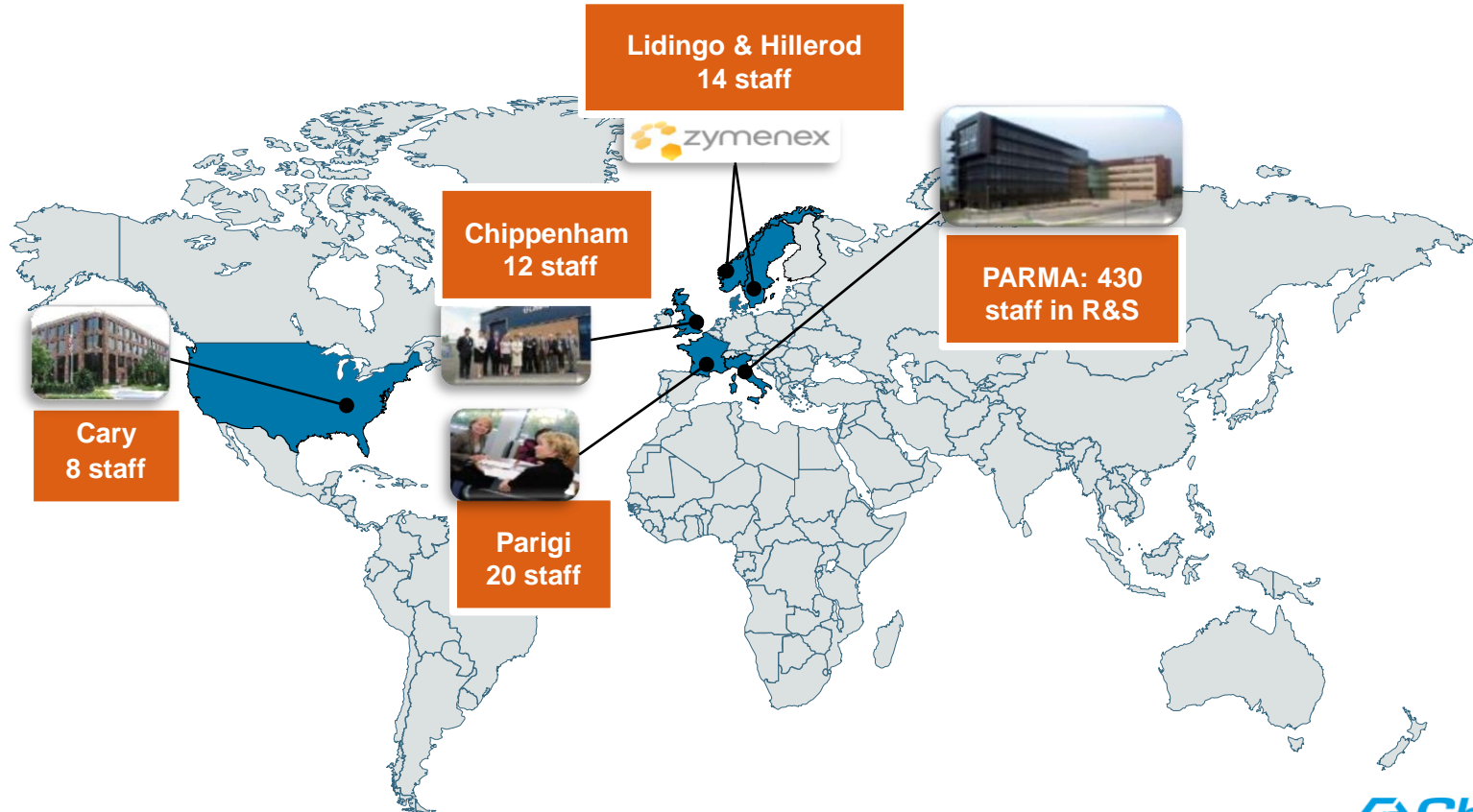
Headcount: 671 (including regulatory affairs)
Investments in 2015: 340 Million of Euro (21,6% on turnover)
51 projects active in R&D (at 12.31.2016)

Investments in milion euro

Data refering to managerial second closing

Corporate Research Centers (R&D Staff)

Cary
8 staff

Chippenham
12 staff

Lidingo & Hillerod
14 staff

zymenex

PARMA: 430
staff in R&S

Parigi
20 staff

Chiesi

Investments in Research and development:

- 1st among Italian pharmaceutical companies*

- 4th among Italian manufacturing Companies*

- 17th among the European Pharmaceutical companies*

In 2016 **Chiesi** is the 1st Italian pharmaceutical company in Europe for patent deposits

- More than 2900 Worldwide patents in the portfolio Chiesi (12.31.2016)

*European Commission - 2016 EU Industrial R&D Investment Scoreboard

AGENDA

1. Brief Outlines of Pharmaceutical Development

2. R&D: Why a complicated business?

The drug

(greek: φάρμακον)

- A substance that, by interacting with a biological target, modifies a physiological or pathologic process to produce a therapeutic effect

bronchodilator: a substance that can expand bronchi by relaxing their smooth muscles, contracted during an asthma attack

Our task consists basically of…
«finding the right key for the right keyhole»

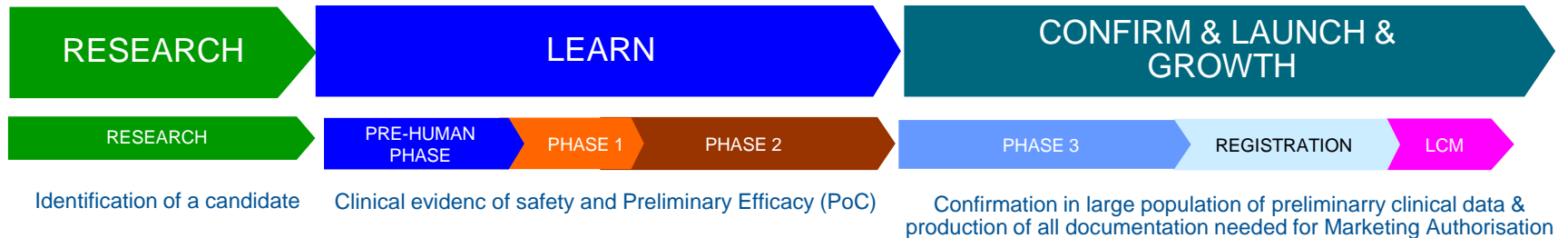# The Research & Development Process

1) **Research** :

- **<u>BASIC</u>**: study of the human biological functions at a molecular / cellular level, to identify new therapeutical targets [-> the keyhole]
- **<u>APPLIED</u>**: identification of new chemical entities with pharmacological activities on the established targets [-> the key]
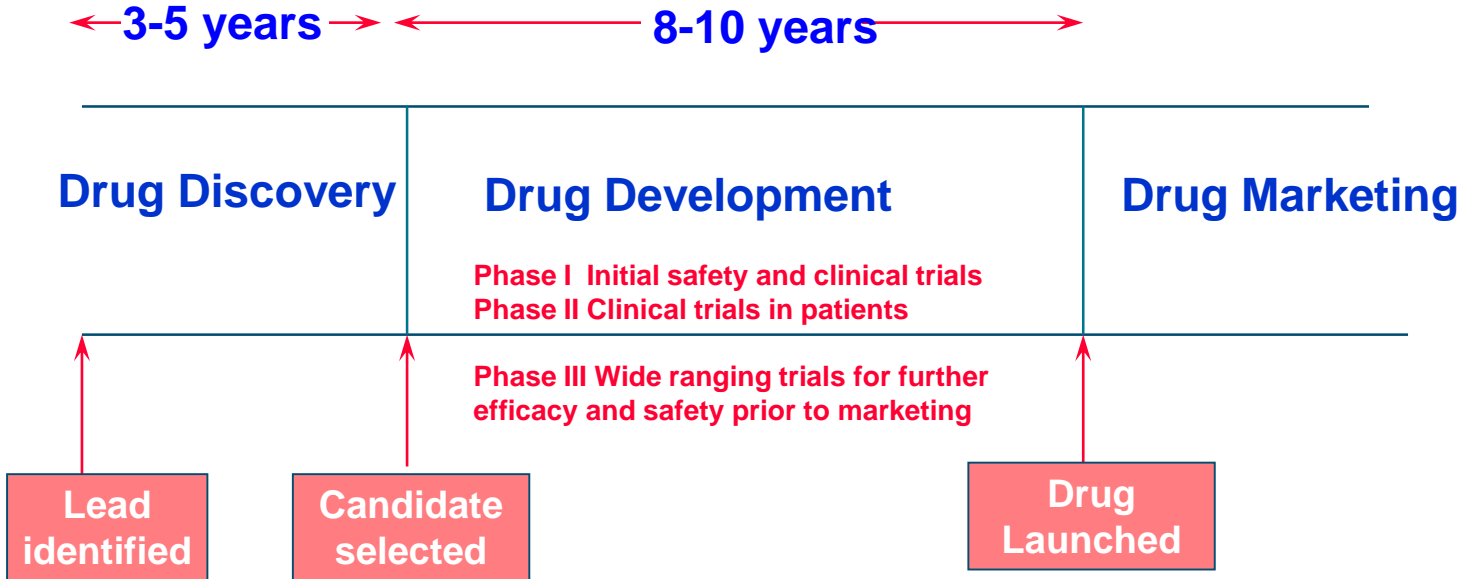
2) **Development** :

All the activities needed to demonstrate the pharmacological and therapeutical efficacy of the new molecules.
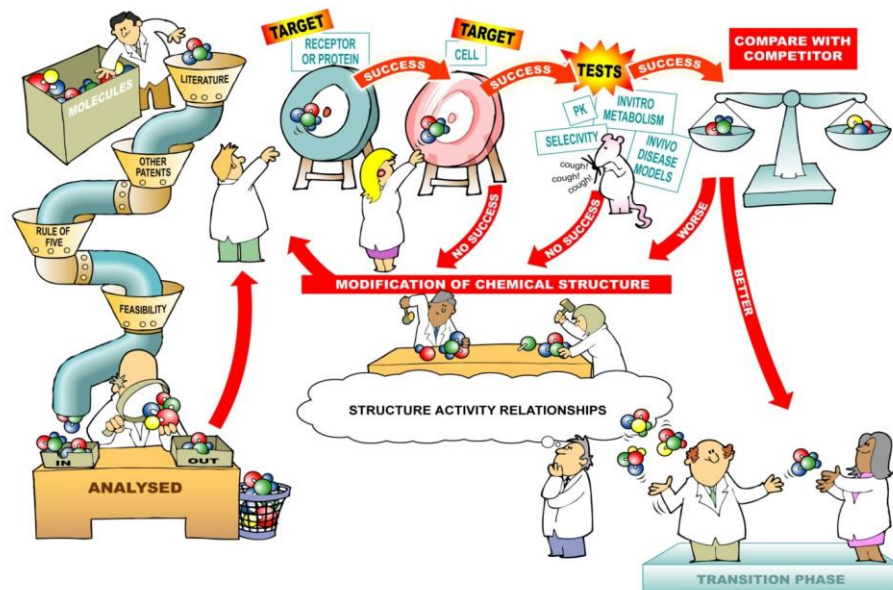
Study of the new molecole in animal models and in men

RESEARCH	LEARN	CONFIRM & LAUNCH & GROWTH

RESEARCH	PRE-HUMAN PHASE	PHASE 1	PHASE 2	PHASE 3	REGISTRATION	LCM

Identification of a candidate | Clinical evidenc of safety and Preliminary Efficacy (PoC) | Confirmation in large population of preliminarry clinical data & production of all documentation needed for Marketing Authorisation

From drug discovery to manufacture

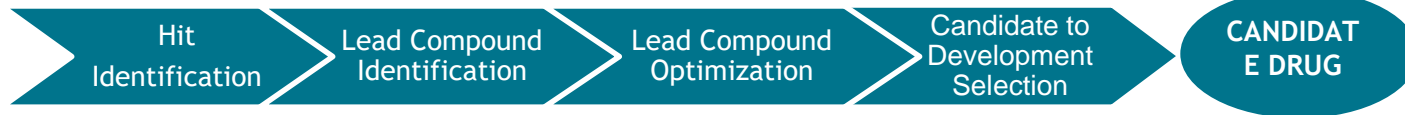Typical Timeframe for Pharmaceutical New Product Development Project

←3-5 years→ **←8-10 years→**

Drug Discovery **Drug Development** **Drug Marketing**

Phase I Initial safety and clinical trials
Phase II Clinical trials in patients

Phase III Wide ranging trials for further efficacy and safety prior to marketing

Lead identified

Candidate selected

Drug Launched

Chiesi

What are we doing during "Research"

The Research Phase is devoted to the development of a Lead Candidate (a pharmacological active substance with a demonstrated mechanism of action)

- We define the target we want to hit

- We synthetize/identify the molecules able to interact with the target

- We evaluate therapeutic efficacy and safety in in vitro and in vivo experimental models

Hit Identification → Lead Compound Identification → Lead Compound Optimization → Candidate to Development Selection → **CANDIDATE DRUG**

Fonte: «Project Team Handbook»

What are we doing during "Learn" Phase
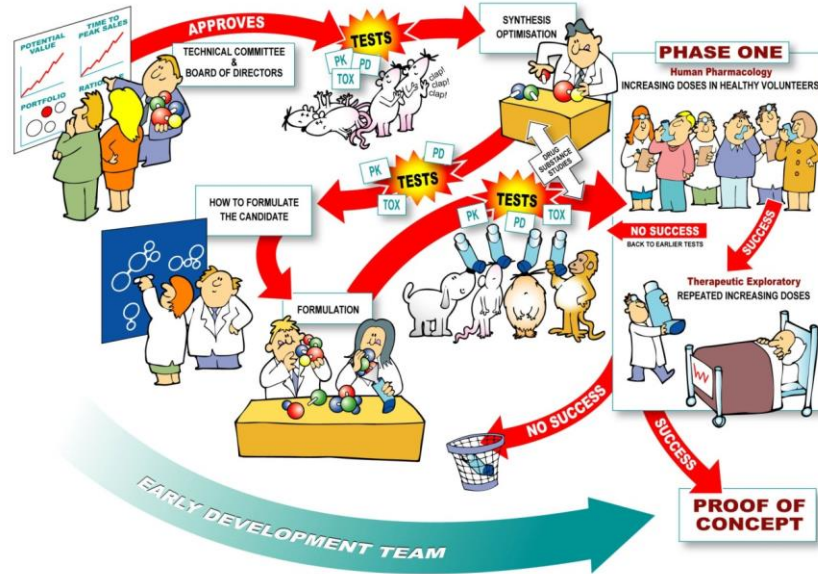
The Learn Phase is devoted to establish the so-called "proof of concept" (POC = Evidence of Clinical Safety and Efficacy).

- We identify an appropriate formulation
- We conduct GLP tox studies in various animal species
- We study the drug metabolism in the human body
- We establish safety and active doses
- We identify a maximum of two effective doses in the desired indication to progress into full development
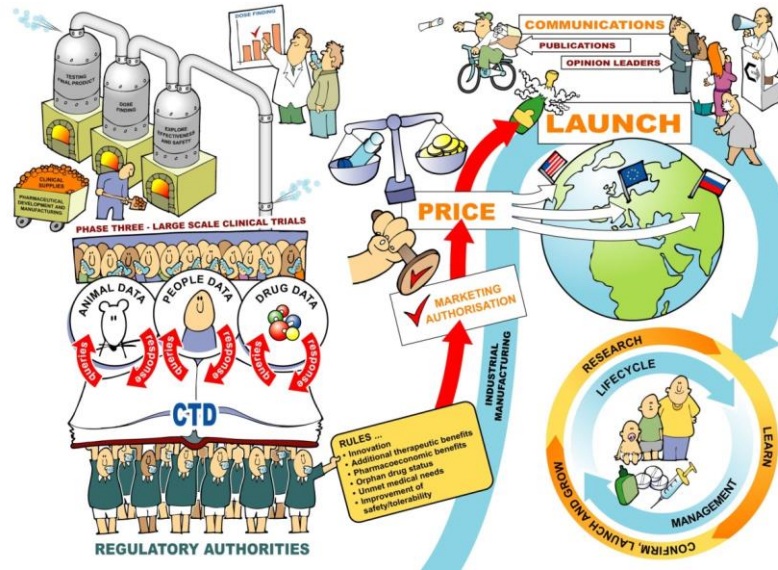
Create and analyse Pharmaceutical Form > Pharmacological and ADME Profile > Animal Toxicology (GLP regulated) > Clinical Safety in Healthy Volunteers > Therapeutic Efficacy in Patients

Chiesi

What are we doing during "Confirm, Launch and Grow " Phase

The Confirm, Launch and Grow Phase is devoted to produce a regulatory dossier necessary to achieve marketing authorization and peak sales in all geographic regions in all indications and patient population of interest

- We demonstrate efficacy and safety in patients with a rigorous comparison with "standard of care" in a large number of patients

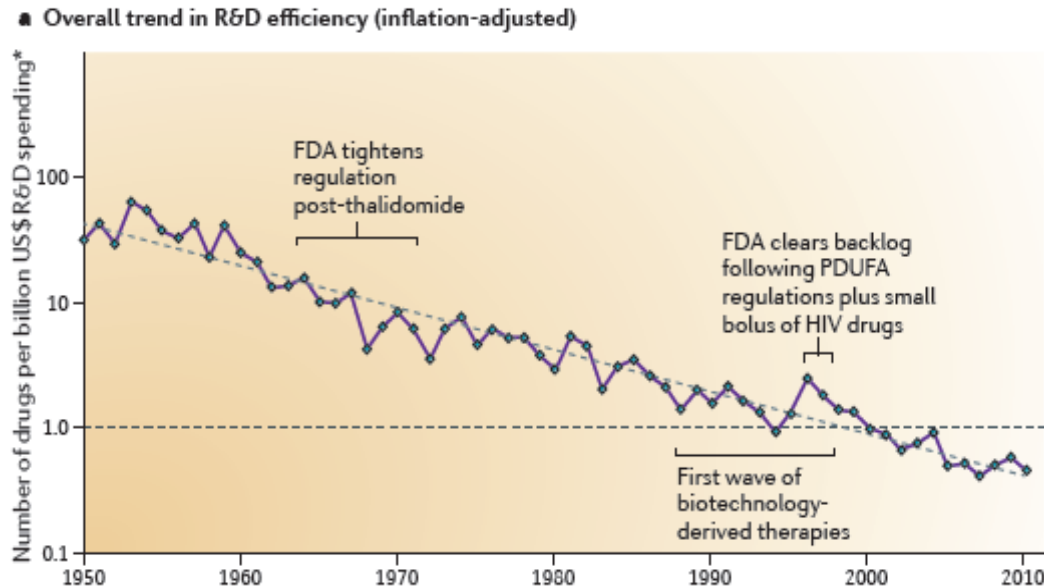- We expand the use with studies in all indications and patient populations of interest

Definitive Confirmation of Efficacy and Safety → Regulatory Dossier → FILING → LAUNCH → Line Extensions
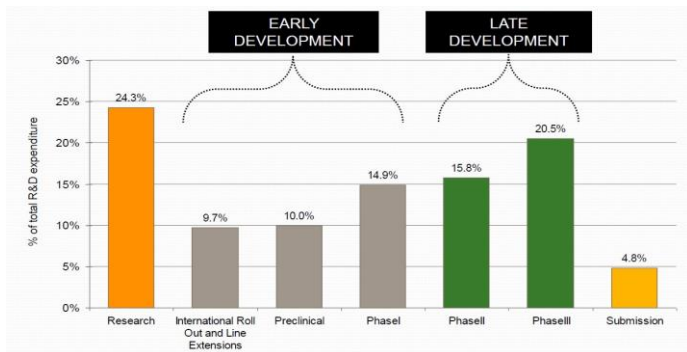
R&D: a complicated business

"Here's how it works. First we discover the drug and identify the market, then we invent the disease."

R&D Productivity Paradox

- The number of new Drugs Approved by FDA per Billions of USD spent in R&D (inflation adjusted) has been reduced by half every 9yrs…

Overall trend in R&D efficiency (inflation-adjusted)

Scannell, Jack W. et al. Nature Reviews Drug Discovery Vol 10, 191-200 (March 2012)

The cost of Pharmaceutical R&D

"Deloitte and [Thomson Reuters](#) examined all drugs recently marketed by the 12 Pharmaceutical companies with biggest R&D budgets. Develop&Launch a new Drug is estimated in the range of 1.3 Billions USD.
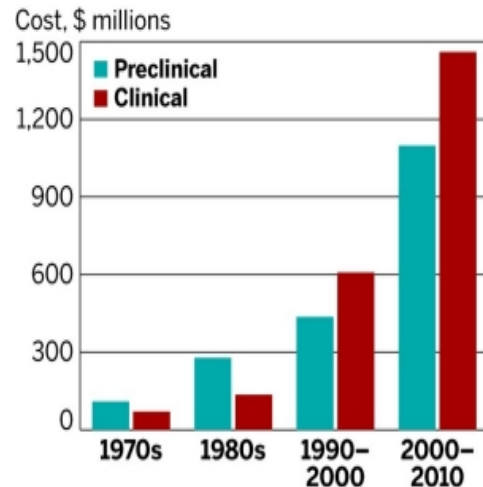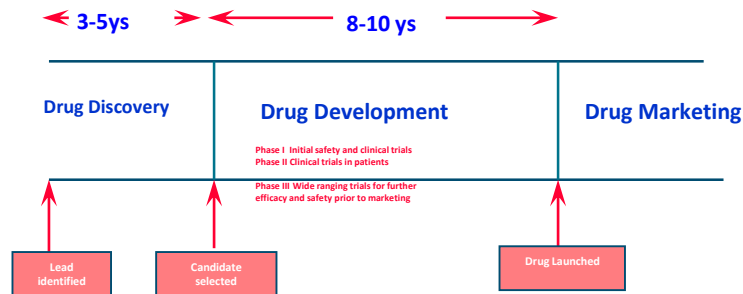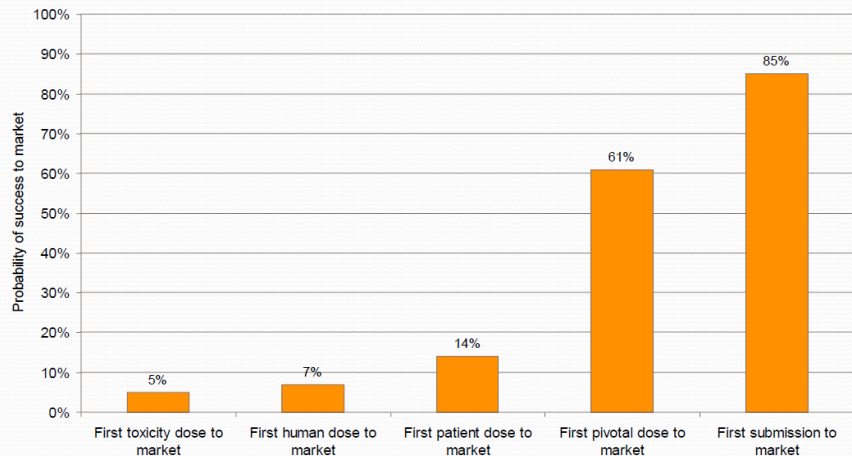

The crisis highlighted by Tufts Center for the Study of Drug Development Novembre 2014 Developing a new Drug costs $2,6Billions: Double the size compared to 2003"

Chiesi

Probability of Success PTS

Reason for Failure:

- Toxicology   45%
- Pharmacokinetic: 10%
- Clinical Profile: 25%
- Commercial Reasons: 20%

Chiesi R&D Strategic Vision

To meet business goals including revenue targets

- Ensure productivity
- Increase focus on Special Care
- Ensure global coverage
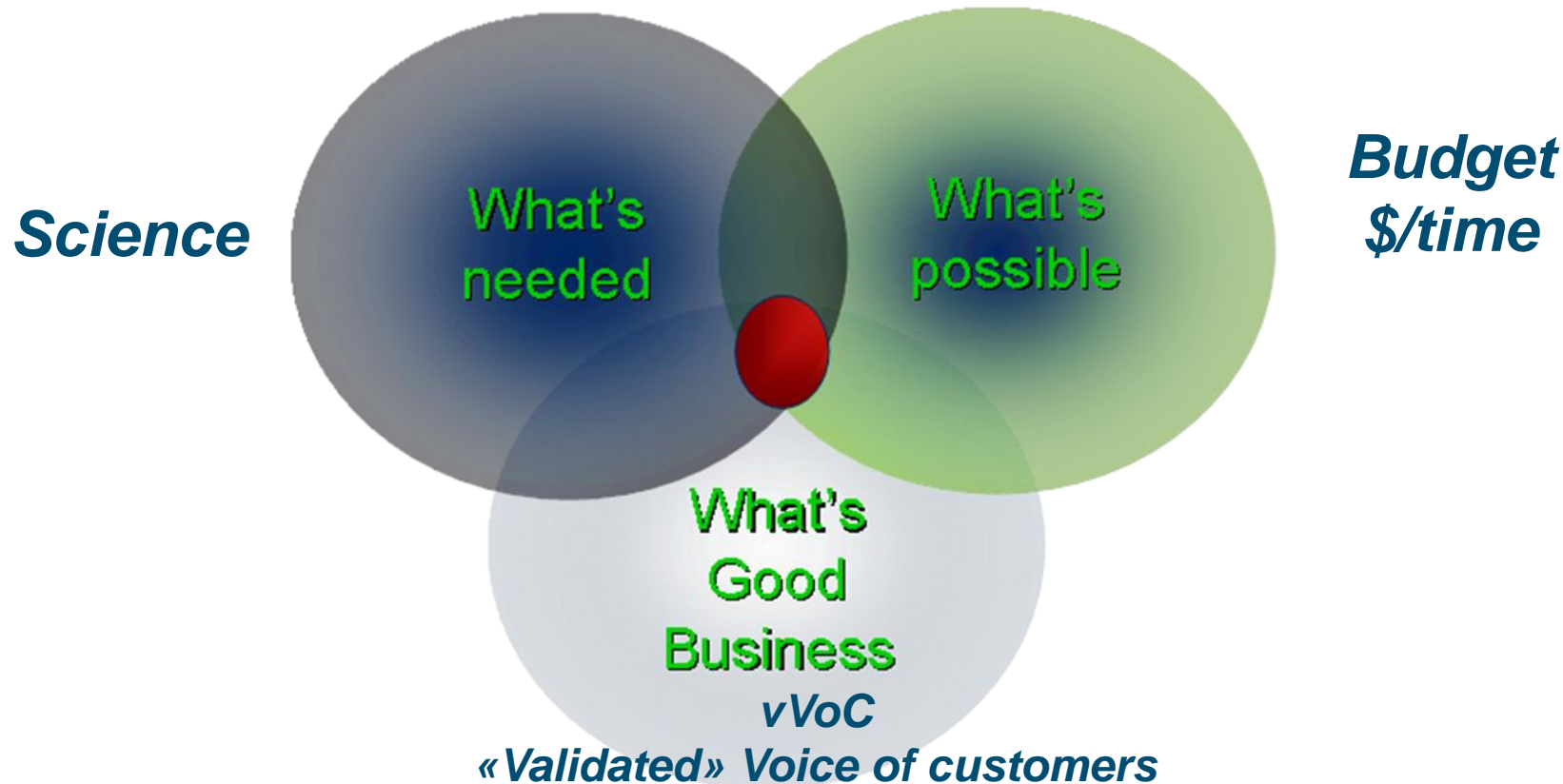- Embrace partnerships
- Deliver competitive innovation

" It is clear to me that delivering innovation is going to be a substantial way to sustain our growth in the future"
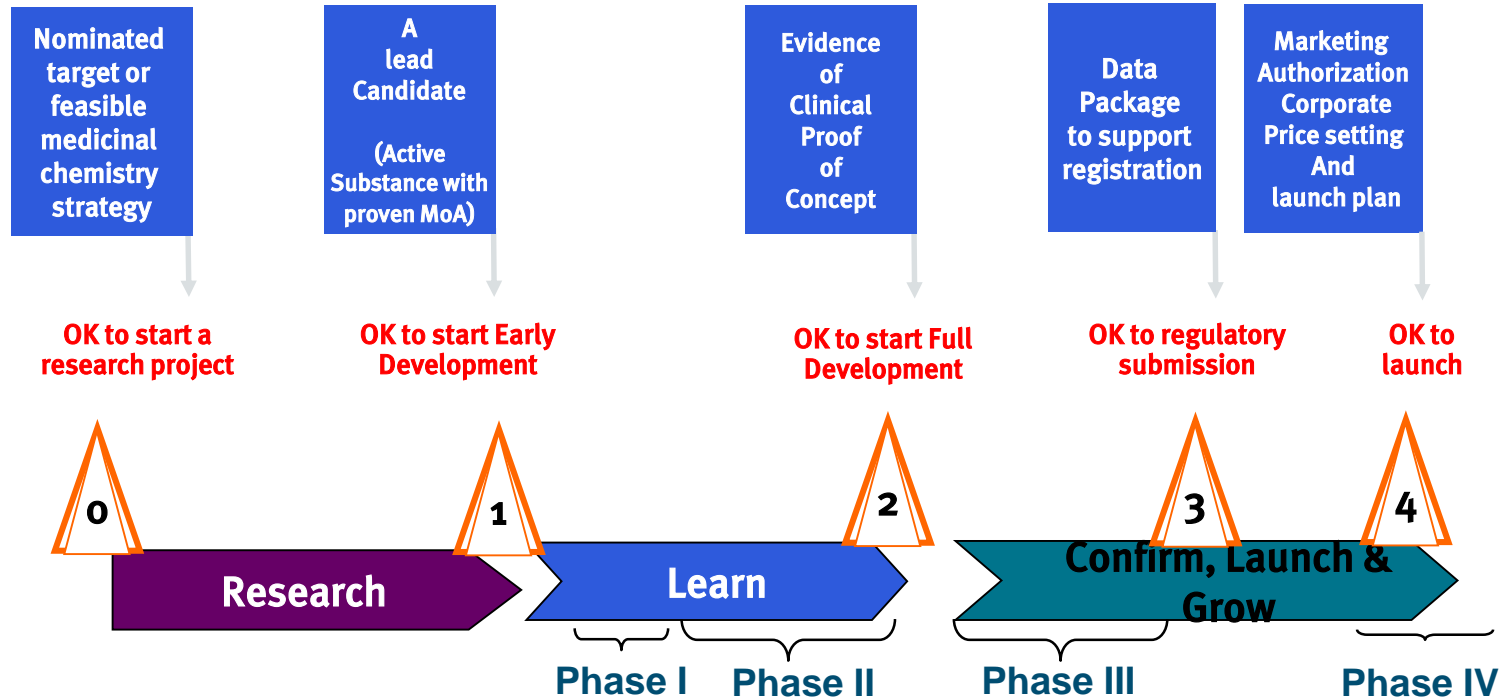
Dr. Alberto Chiesi

The value of an R&D project

What triggers the progression: Gates as Decision Making Points

Stage Gate Processes typically provide a framework by which project teams move ideas through development to the market

Welcome in CHIESI!