Exploiting Innovation in Healthcare: gli strumenti

Le peculiarità della clinical innovation

10° Summer School Netval
Exploiting Innovation in Healthcare
Lecce, 11-14 settembre 2017

Medical Innovation – Innovazione clinica

Introduzione e/o sviluppo di ***innovazione tecnologica tangibile ed intangibile*** nel cuore del business ospedaliero:

- ✓ Innovazione **Biomedica / Biofarmacologica** (nuovi farmaci, nuovi composti biologici e/o chimici attivi)
- ✓ Innovazione **medica tangibile** (sistemi tecnici per uso diagnostico e terapeutico)
- ✓ Innovazione **medica intangibile** (protocolli, strategie assistenziali, diagnostiche o terapeutiche)

Impatto su ***qualità della cura, benessere, efficacia dei trattamenti, accessibilità, produttività, organizzazione del lavoro, natura del lavoro, spesa in sanità, crescita del territorio.***

Innovazione clinica: gli strumenti

✓***IPR - Brevetti*** – privative specifiche (es. ODD)

✓ ***Regolatorio*** (autorità competenti – FDA, EMA, AIFA)

✓***Sperimentazione clinica*** (etica, attrition rate, costi, tempi)

✓***Stakeholder analysis*** – il contesto in cui ci muoviamo

✓Rimborso (HTA, DRG - procurement)

✓Finanziamenti

✓Fattibilità tecnica

✓ Team Dynamics

✓Modelli di business

✓Competizione

✓Market Dynamics

✓…

✓…

I portatori d'interesse

Unmet Medical Need Stakeholders

- ✓ Pazienti
- ✓ Famiglie
- ✓ Associazioni di pazienti
- ✓ Dottori
- ✓ Società professionali
- ✓ Infermieri
- ✓ Facilities (ospedali, farmacie, laboratori)
- ✓ Amministratori ospedalieri
- ✓ Public payers (governi)
- ✓ Imprese
- ✓ Filantropia

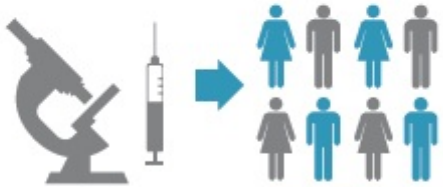
Sperimentazione Clinica

CLINICAL TRIALS EXPLAINED

CLINICAL TRIALS – A CRUCIAL LINK IN THE RESEARCH AND DEVELOPMENT (R&D) CHAIN

What is a Clinical Trial?

- Clinical trials are research studies of medicines in humans



- They assess whether a potential new medicine is safe for patients and effective in treating the target disease.
- A clinical trial study can be funded by academics, government or industry and are conducted by investigators.

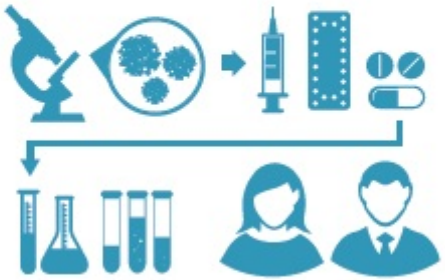
- The clinical trial participant eligibility criteria are specifically defined on a trial by trial basis. A research plan called a clinical trials protocol is designed to answer specific research questions and safeguard the health of the participants.

13 YEARS	2 YEARS	6 MONTHS – 2 YEARS	ONGOING

START ▸▸ ▸▸ END

Getting started

Scientists begin by analysing the disease and investigating a possible treatment. Pre clinical trials then establish initial safety and effectiveness before testing on humans. These tests are often done in the laboratory, using 'in vitro' (test tube) research.



CLINICAL TRIALS

CHECK FOR SAFETY

Phase I investigate the molecule's safety and research how it works and behaves in the human body
Population 20 - 80 healthy volunteers
Timeline between weeks and months

CHECK FOR EFFICACY; CONTINUE SAFETY EVALUATION

Phase II investigate efficacy; investigate side effects and risks
Population several hundred people who have the disease
Timeline between several months & several years

CONFIRM RESULTS

Phase III seeks to establish the benefit-risk, the right patients and the best way to manage the risks.
Population several thousand people who have the disease
Timeline between several months & several years

Regulatory approval

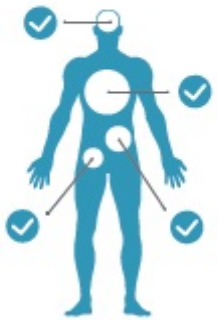
Regulators such as the European Medicines Agency (EMA) review safety, efficacy and quality and authorise a medicine for use.

Pricing and reimbursement processes

Decide on price and reimbursement of the product, including health technology assessment (HTA) of added value compared with current treatments.

Phase IV (post market launch)

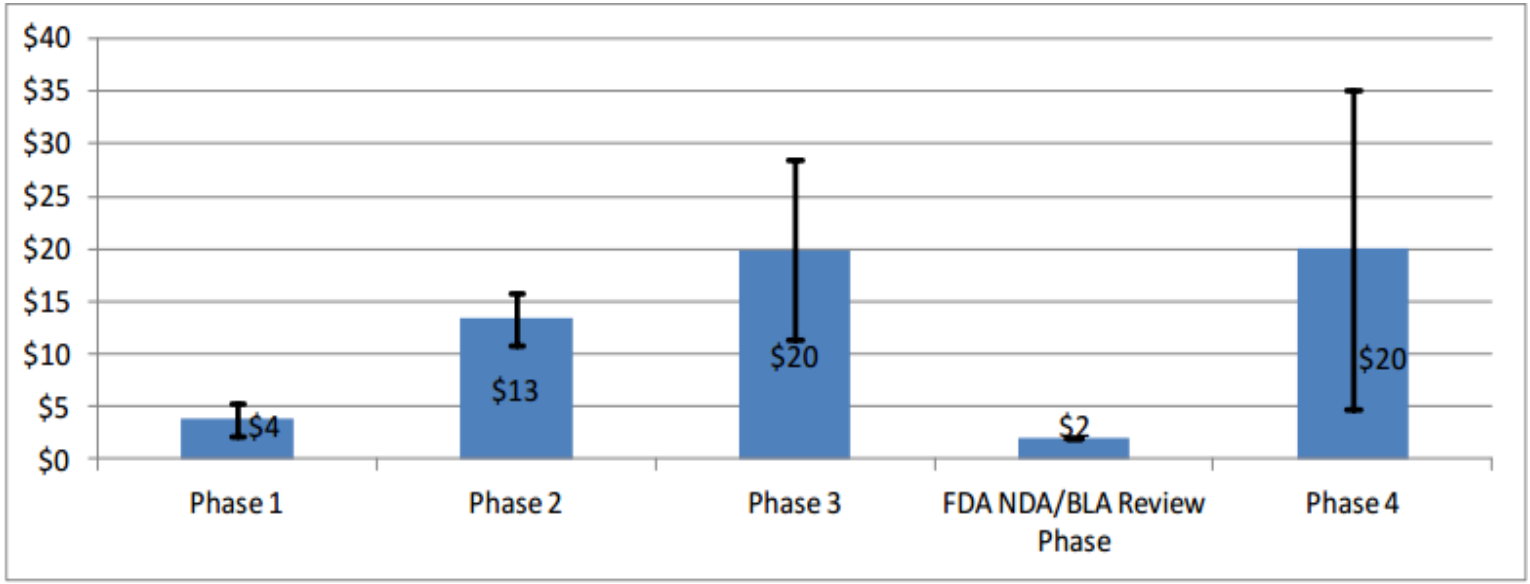
Continued safety surveillance through post market studies; identifying potential new uses for the medicine.



*timings used are averages and for illustrative purposes only

Costo della sperimentazione clinica

Average Per-Study Costs by Phase (in M$) Across Therapeutic Areas



U.S. Department of Health and Human Services, 2015

Sperimentazione clinica

- ✓ Innovatori ed imprenditori devono fornire **evidenza clinica del proprio prodotto** attraverso la Sperimentazione Clinica (clinical trials)
- ✓ La sperimentazione clinica è il più **complesso, lungo e costoso step di sviluppo** per tecnologie mediche
- ✓ Vi sono evidenti e ben normate **implicazioni etiche**, che vengono vagliate dai Comitati Etici; fondamentale il patto con i cittadini – pazienti – volontari: **consenso informato**!
- ✓ Vengono valutati gli schemi sperimentali e statistici più adeguati per fornire gli outcome attesi (primari e secondari)
- ✓ Necessità di impostare studi clinici in **Good Clinical Practice (GCP) - Contract Research Organization (CRO)!**

esempio d'implementazione di prassi

Immaginiamo che da un gruppo di ricerca X venga generata una nuova invenzione, o dei nuovi risultati che possono essere tutelati sottoforma di diritti di PI. In questo caso il ricercatore, o in senso generale, l'operatore del sistema contatta direttamente il Licensing manager seguendo una procedura che include i seguenti passaggi:

1. Compilazione "Invention disclosure Form" scaricabile dal sito
2. Invio "Invention disclosure Form"
3. Valutazione tipo di tutela/requisiti di brevettabilità
4. Executive firma decisione tutela
5. Registrazione/deposito brevetti
6. Strategia di valorizzazione
7. Campagna di mercato
8. Trasferimento

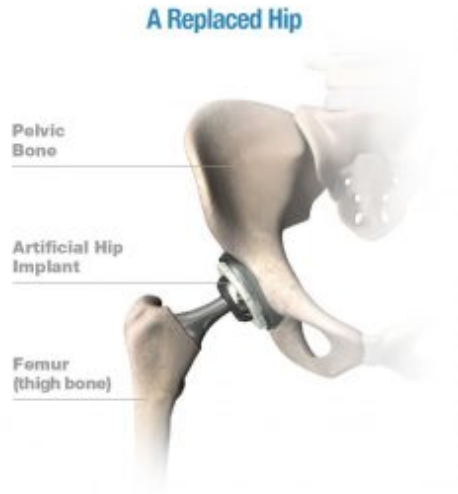
Esempi di attività TT per 3 aree sanitarie

- ✓ *Chirurgia e Riabilitazione*
- ✓ *Specialità Mediche*
- ✓ *Medicina di Laboratorio*

Device chirurgico per riabilitazione

- ✓Key Opinion Leader
- ✓Company – KOL
- ✓R&D

Regolamenti e procedure



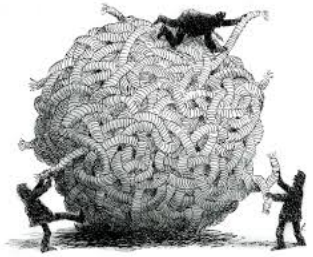
- ✓Gestione IPR e strategia combinata di valorizzazione (contratto di co-sviluppo)

- ✓ Sperimentazione clinica: quale inquadramento? (supporto del Clinical Trial Office)

Comitato etico

- ✓Custom device, REG.EU 2017/745, CE certification
- ✓ Public procurement per soluzioni innovative vs. Royalties inventore!

Conflitto di interessi

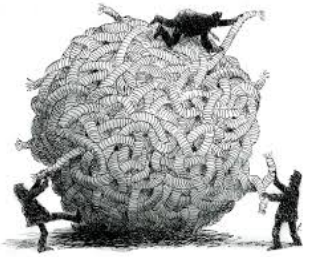


- ✓ Farmacia Ospedaliera vs. Centrale d'acquisto regionale

Sviluppo Farmaceutico

- ✓ Clinico rianimazione pediatrica
- ✓ Sperimentazione clinica no-profit ROP / <u>no patent</u>
  (dati clinici, pazienti, collirio)

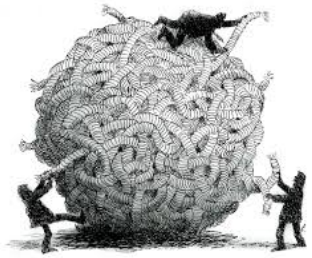
Regolamento e procedure



- ✓ Interesse Imprese – KOL
  (brevetto device dispensatore – collirio)
- ✓ Sperimentazione Clinica e GCP - Dati ROP???

Supporto GCP necessario!

- ✓ Accordo quadro: royalty su prodotto, IRR + finanziamento ricerca

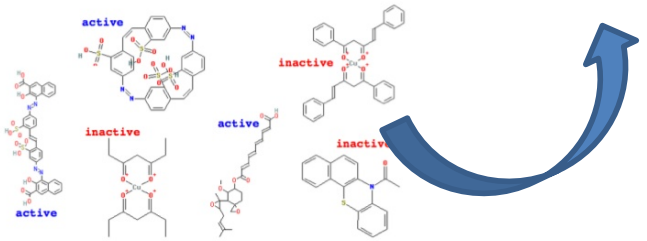


- ✓ R&D su nuove molecole

Pubblicare vs. Sviluppo

Trasparenza atto

Da una nuova molecola al farmaco sviluppo pre-clinico autorizzativo



Pharmaceutical development

- ✓Method set up for molecule synthesis
- ✓Development of analytical methods and related substances API
- ✓Chemical characterization of API

Non-GMP API

- ✓API for in vitro activities
- ✓API for animal PK
- ✓API for no clinical studies

Non-Clinical Development

- ✓In vitro selectivity and confirmation of activity
- ✓In vitro inhibition of cytochromes
- ✓In vitro metabolic profile
- ✓Intrinsic clearance in hepatocytes
- ✓Genotoxicity in vitro, cardiac safety and citotoxicity
- ✓Validation of the analytical method and formulation procedure
- ✓ Validation of the analytical method and toxicokinetic analysis
- ✓Bacterial mutation assay
- ✓PK study in rats
- ✓Tox study in rats and dogs
- ✓Irwin test in rat
- ✓Effects on the cardiovascular function on the conscious dogs

Circa 1 milione di euro ed un anno d'indagine

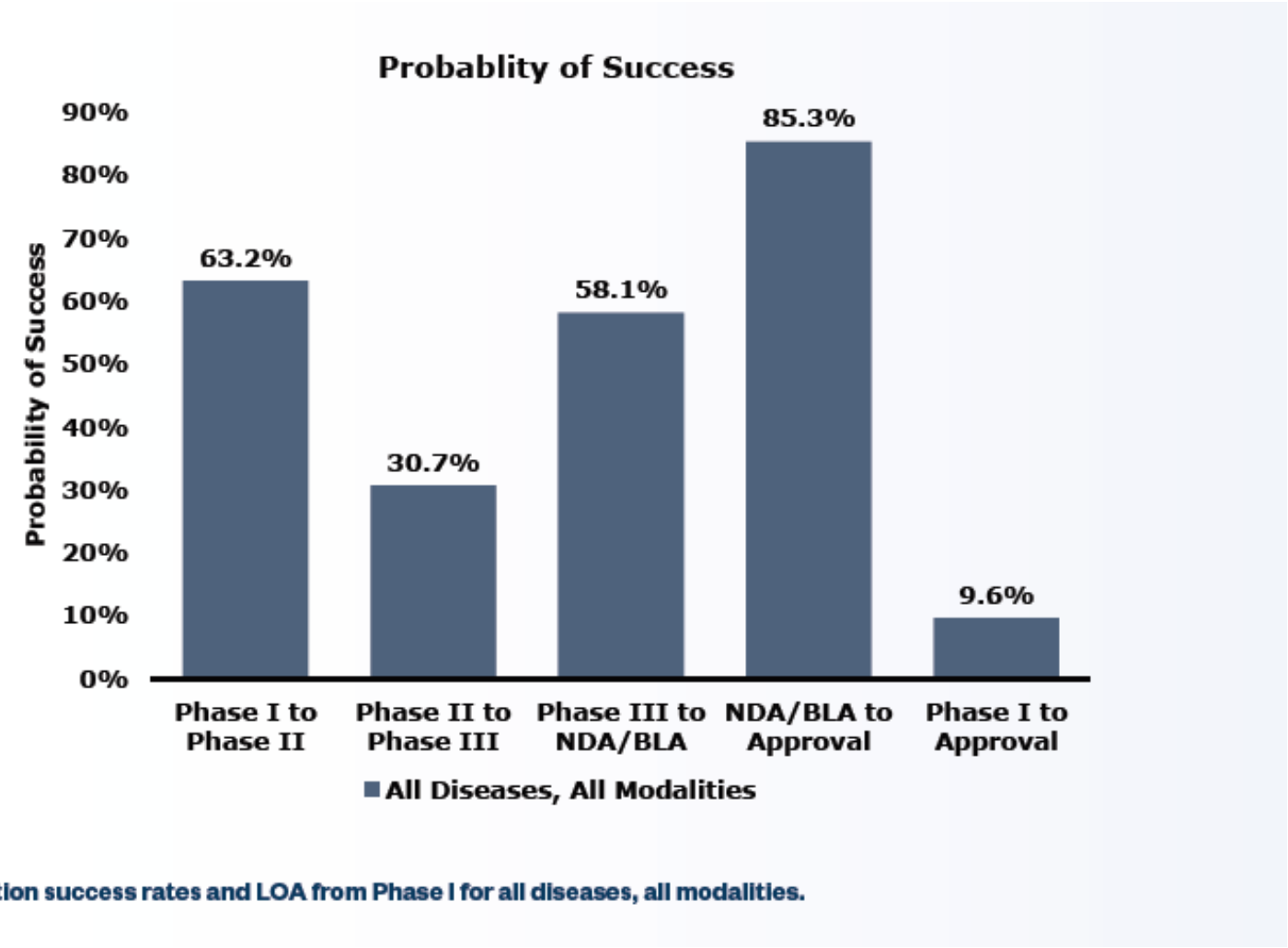
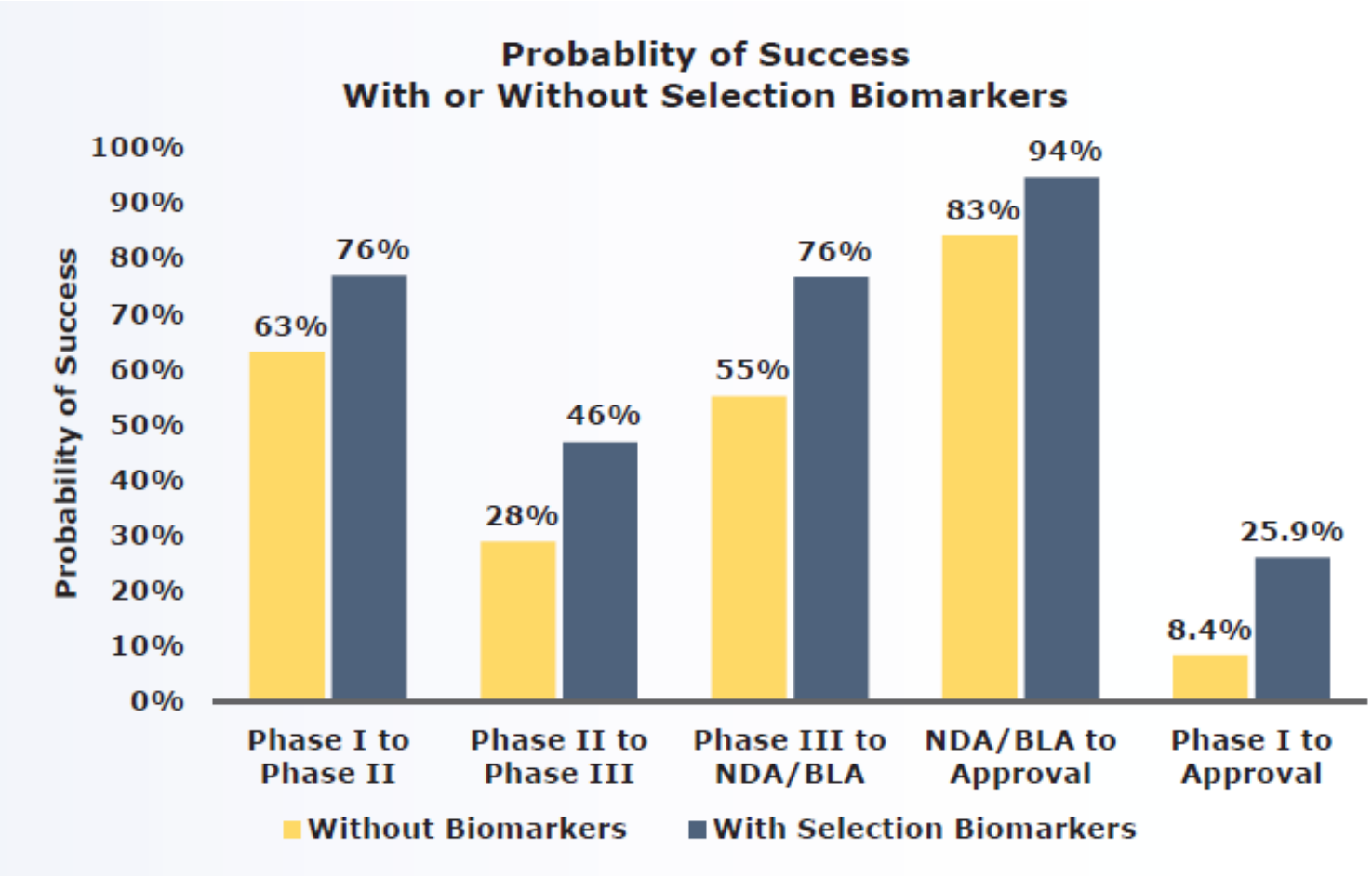
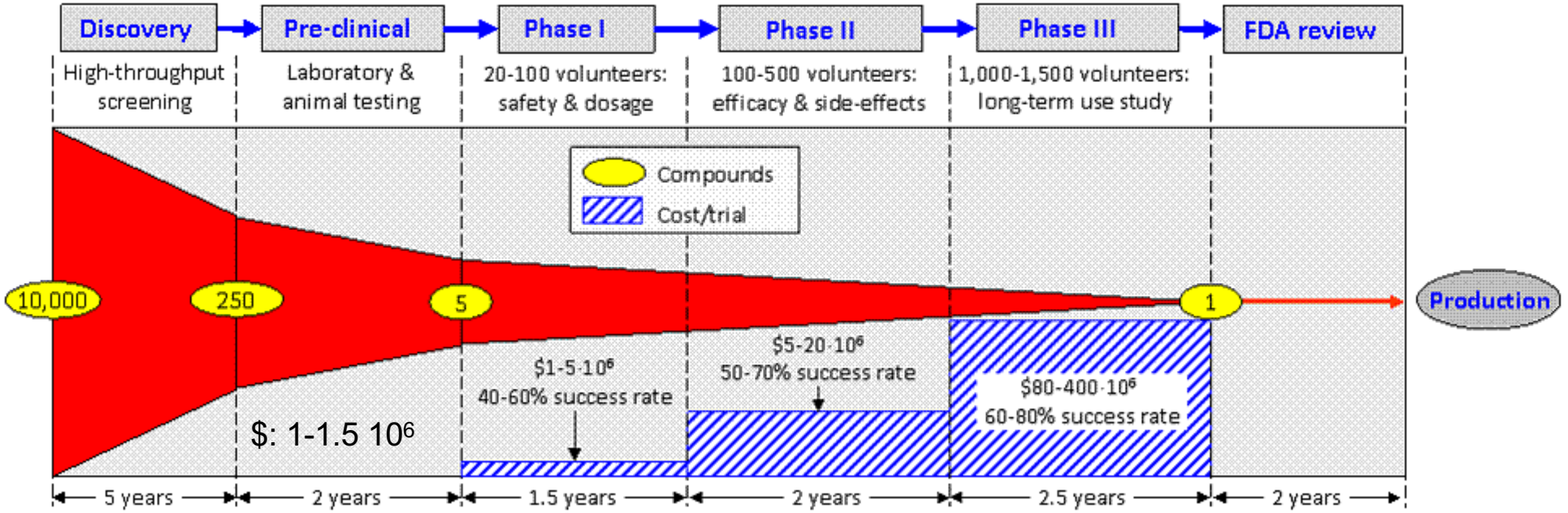


Figure 1. Phase transition success rates and LOA from Phase I for all diseases, all modalities.

dati BIO Association 2006 -2015

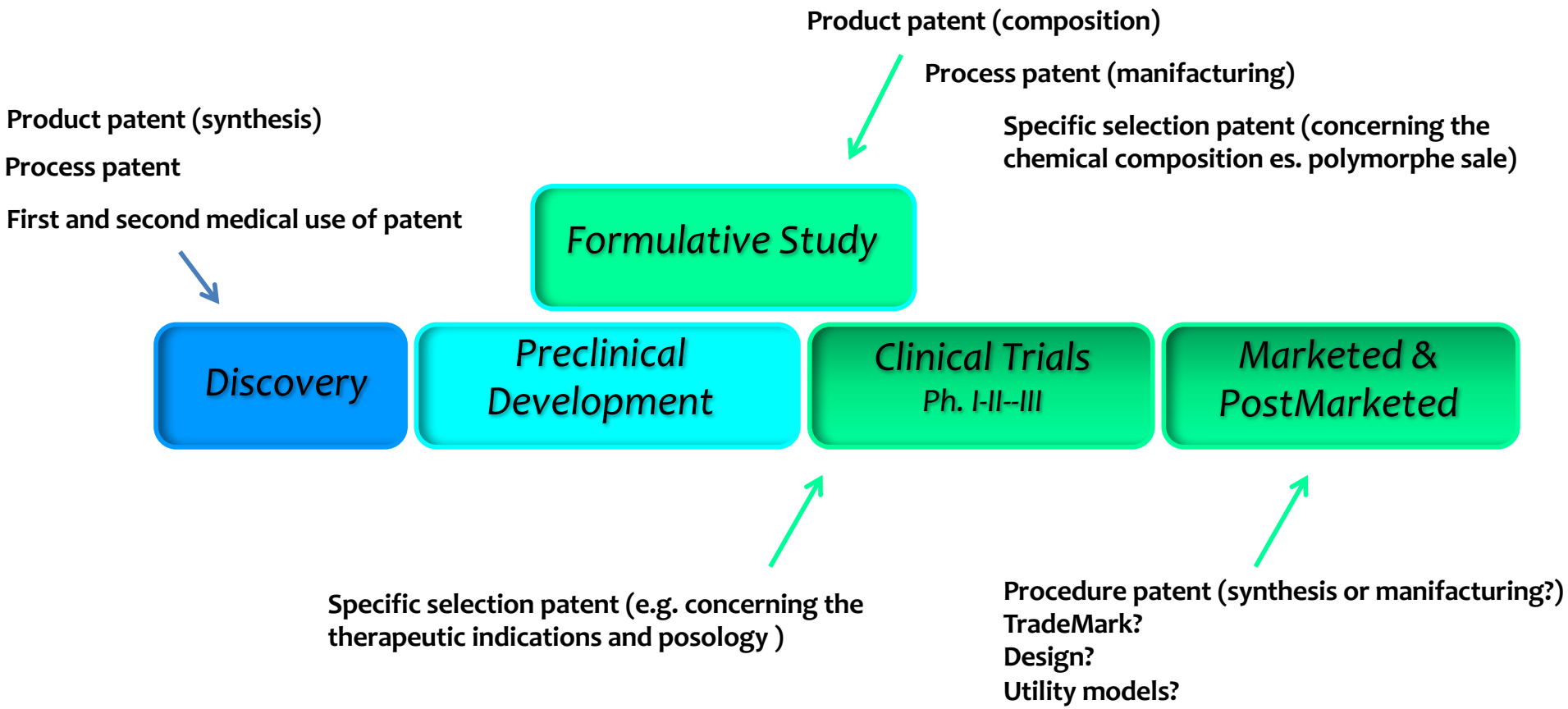

Probablity of Success
With or Without Selection Biomarkers
Probability of Success
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
63%
76%
28%
46%
55%
76%
83%
94%
8.4%
25.9%
Phase I to Phase II
Phase II to Phase III
Phase III to NDA/BLA
NDA/BLA to Approval
Phase I to Approval
Without Biomarkers
With Selection Biomarkers

New Chemical Entity development



Costs, Time and Attrition Rate

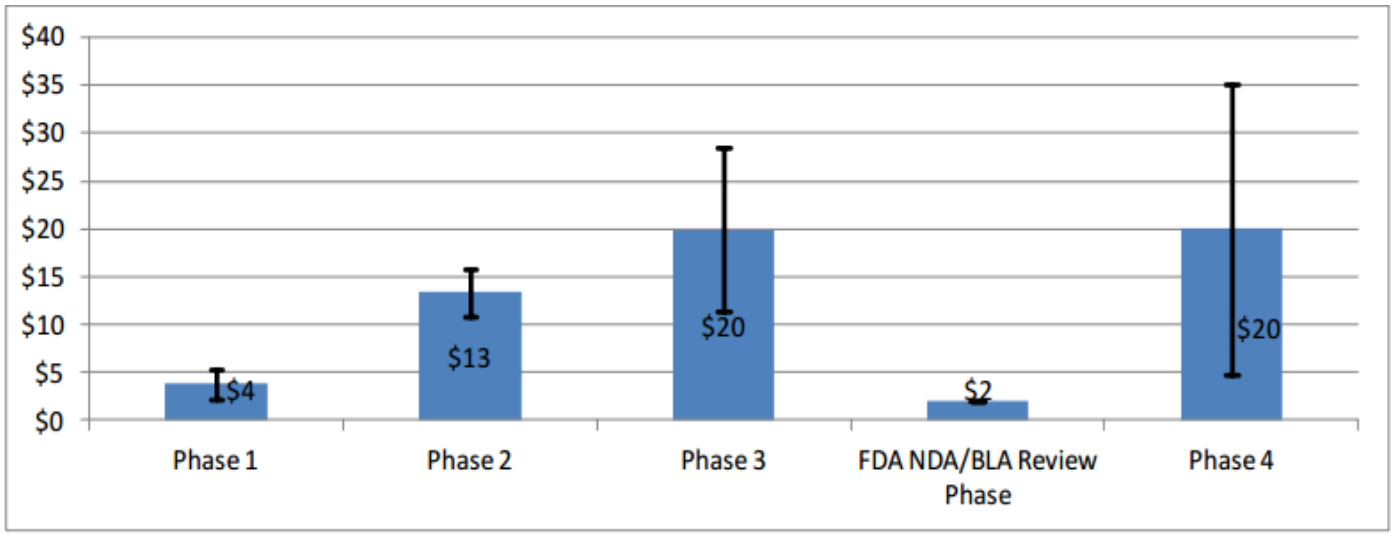
Streategia brevettuale / IPR complessa



Costi di sviluppo esorbitanti

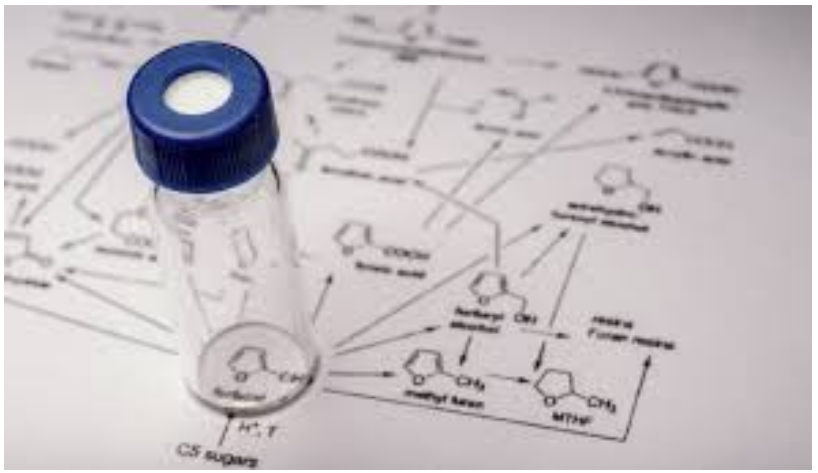
✓GMP manufacturing e GLP

✓EU Pharma Reg, Orphan Drug e PRIME: procedure accelerate per patologie rare/orfane



Device for In Vitro Diagnosis: Laboratory Medicine

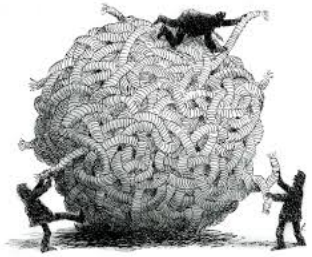
- ✓ Newborn screening (dried-blood-spot)
- ✓ Brevetto storico (2009…) – first champion!
- ✓ Novità: miscela di estrazione – analisi GC/MS
- ✓ Detection di metaboliti per ADA – SCID
- ✓ Kit commerciali per analiti multipli
- ✓«UserFriendly» vs. «Homebrewers»



✓ Brevetto depositato 2010 (metodo di estrazione – analiti – ADA/SCID)

✓ US / EP
- EP rilascio metodo e KIT
- US rilascio metodo / divisionale KIT

Evoluzione brevetto

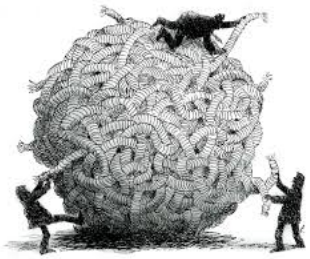


✓ KIT vs Method: Different inventions?

✓ One step (low performance - competitor) vs. Two steps (high performance)

✓ analisi leggi per screening neonatale – in evoluzione - … 2016!
- ADA /SCID nei pannelli ?... EP vs. US
- monitoraggio CDC – EC/EMA – Ministero

Quadro normativo



✓ Other emerging technologies:
✓ GCMS vs. TREC and NGS - Technology Turnover

✓ Licenza non esclusiva EU (a competitor) – stand-by US (esito divisionale)
✓ Licenza non esclusiva EU (newco) – valutazione licenza US esclusiva per enforcement
- trade off pagato con royalty in paesi non coperti

Biobanking , Omics and Big Data: The basis of precision medicine

A *biomarker* is a **molecular, biological or physical attribute that characterizes, with others, a specific (patho)physiological state.**

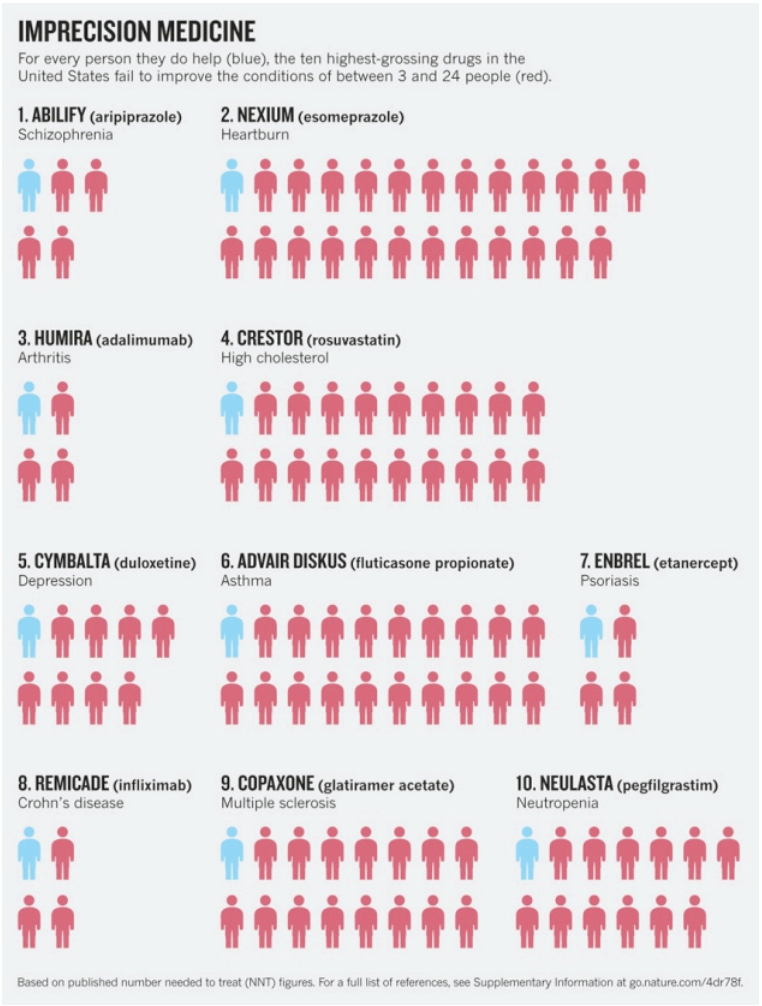
- ✓ **preventive** (risk of developing the pathology),
- ✓ **diagnostic** (presence of a pathology),
- ✓ **prognostic** (stratification of the risk of progression of the pathology),
- ✓ **therapeutic** (measure of response to the therapy)

Some people propose subdividing the vision of the future of precision medicine in:

"***explicit***" (algorithms based on scientifically identified and understood relationships)

"***implicit***" ("*black box medicine*" – when these relationships are not defined, and are directly based on opaque algorithms).

Precision vs. “imprecision” medicine



Attempts to **fractionate or stratify** the larger population into smaller groups likely and not likely to benefit from specific treatments.

Quality of the data and organization

Given the complexity of the data that can potentially be aggregated, in order to develop individualized research there is a need for the **creation of a precision research ecosystem that binds clinicians, researchers, companies and the systems charged with the aggregation of clinical information.**

Standardizing the way in which the enormous amounts of personal data of patients is evaluated in diagnostic and prognostic terms is fundamental.

The robustness of clinical and research databases is a key point to guarantee the efficacy and quality of the interpretation of the data.

For this reason the organization of the information within dedicated databases is the resolving step for the foundation of an individualized research.

Basis for a new valorization

The primary benefit of individualized research, which lies in a greater penetration of the drug due to an improved stratification of patients, will reduce the reference market (a vision in which **every disease will be "rare"**).

There is an evident positive impact of precision medicine on the theme of **"appropriateness"!**

Innovation and commercialization depend on **regulatory frameworks and intellectual property rights**, which must certainly be reviewed on the basis of the above.

Bear in mind

1. Alto time-to-market, attrition rate, investimenti
2. Regolamenti e procedure *ad hoc* per settore sanitario
3. Forte **regolamentazione ricerca** – compliance AIFA, EMA, FDA, … (**certificazione**, **GxP**, **SOP**, test accreditati…)
4. Componente **etica** della ricerca imprescindibile
5. **Dualismo Assistenza/Ricerca**
6. Rapporto con medici e clinici: entry point il **key opinion leader**
7. Inquadramento sperimentazione Profit – No profit (no-profit pubblico per definizione…)
8. Sviluppatore coincide con il procurer PUBBLICI (PCP – PPI risolverebbero parzialmente): potenziali conflitti d'interesse