INTERNATIONAL CONFERENCE

European Clinical Trial day, the future of clinical research: is the 536/14 regulation enough?
Regulatory Authorities, Ethic Committees, Sponsors, Researchers, Sites and Patients

A Paradigm Shift in Clinical Trials

Prof. Claude Farrugia, President EIPG

13th October 2017
Milan, Palazzo Lombardia
### A look to the past..

<table>
<thead>
<tr>
<th>Phase</th>
<th>Subjects/Patients</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final selection compound</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early clinical development</strong></td>
<td><strong>Phase Ia</strong></td>
<td>40-60 healthy subjects</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td><strong>Phase Ib</strong></td>
<td>30-50 healthy subjects</td>
<td>6 months – 1 year</td>
</tr>
<tr>
<td></td>
<td><strong>Phase IIa</strong></td>
<td>50-200 patients</td>
<td>9 months – 2 years</td>
</tr>
<tr>
<td></td>
<td><strong>Phase IIb</strong></td>
<td>200-500 patients</td>
<td>2-3 years</td>
</tr>
<tr>
<td></td>
<td><strong>Phase III</strong></td>
<td>500-1000+ patients</td>
<td>2-5+ years</td>
</tr>
<tr>
<td></td>
<td><strong>Phase IV</strong></td>
<td>10000+ patients</td>
<td>2-4+ years</td>
</tr>
</tbody>
</table>

### Early clinical development (Exploratory)

### Full development (Confirmatory)

### Launch (Obligatory)
“The Committee’s decided to ban further research until it can be proven your ‘wheel’ poses no threat to the environment, society or public health”
The winds of change
More clinical trials registered

Number of Registered Studies Over Time
and Some Significant Events (as of October 10, 2017)

Source: https://ClinicalTrials.gov
The winds of change
Changes in NAS characteristics over time

Source: QuintilesIMS Institute, Sept 2016
Notes: Primary care and specialist-driven designations refer to the type of physician who initiates or treats using medicines in a given therapy class.
The winds of change
Changes in NAS characteristics over time

Source: QuintilesIMS Institute, Sept 2016
Notes: Primary care and specialist-driven designations refer to the type of physician who initiates or treats using medicines in a given therapy class.
The winds of change
Changes in NAS characteristics over time

Source: QuintilesIMS Institute, Sept 2016
Notes: Primary care and specialist-driven designations refer to the type of physician who initiates or treats using medicines in a given therapy class.
The winds of change
Changes in NAS characteristics over time

Source: QuintilesIMS Institute, Sept 2016
Notes: Primary care and specialist-driven designations refer to the type of physician who initiates or treats using medicines in a given therapy class.
The winds of change
Changes in NAS characteristics over time

Figure 1 NASDAQ biotech index over time. The data cover each year ending on December 31. *As of 5/26/2017.

The winds of change
Global medicines in late stage development in 2016

Source: IMS R&D Focus, Sept 2016; QuintilesIMS Institute, Oct 2016
Note: Drugs included are beyond Phase II development; Cardiovascular includes antihypertensives, anticoagulants, lipid regulators and other cardiovascular therapies; Gastro-urinary and Hormones includes women's and men's health, osteoporosis, urological and hormonal therapies. CNS is central nervous system.

Outlook for Global Medicines Through 2021: Balancing Cost and Value Report, QuintilesIMS Institute, Oct 2016
Some things don’t change
Clinical trials are still the main contributor to R&D cost

![Graph showing the distribution of costs across different phases of drug development.](Image)

Source: PhRMA, Annual Membership Survey 2016 (percentages calculated from 2014 data; total values may be affected by rounding)


Fig. 2. Pre-human phase, clinical phase, and total out-of-pocket and capitalized costs per approved new compound.
**Some things don’t change**

Clinical trials are still the main contributor to R&D cost

- 21.2% Pre-human/Pre-clinical
- 8.9% Phase I
- 10.7% Phase II
- 28.7% Phase III
- 5.1% Approval
- 16.6% Pharmacovigilance (Phase IV)
- 8.9% Uncategorized

Some things don’t change
Clinical trials are still the main contributor to R&D cost


Fig. 2. Pre-human phase, clinical phase, and total out of-pocket and capitalized costs per approved new compound.
Some things don’t change  
Success is rewarding but failure is costly

Most Valuable R&D Projects (Ranked by NPV) in August 2016  
Which Have Since Been Approved or Suffered Setbacks

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>Imfinzi</td>
<td>AstraZeneca</td>
<td>Phase III</td>
<td>Marketed</td>
<td>8,276</td>
<td>13,069</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>Kisqali</td>
<td>Novartis</td>
<td>Phase III</td>
<td>Marketed</td>
<td>6,370</td>
<td>6,921</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Amjevita</td>
<td>Amgen</td>
<td>Filed</td>
<td>Marketed</td>
<td>6,273</td>
<td>2,549</td>
<td>-59%</td>
</tr>
<tr>
<td></td>
<td>Ocrevus</td>
<td>Roche</td>
<td>Filed</td>
<td>Marketed</td>
<td>16,965</td>
<td>18,242</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Dupixent</td>
<td>Sanofi</td>
<td>Phase III</td>
<td>Marketed</td>
<td>12,884</td>
<td>18,775</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Sub-Total</strong></td>
<td><strong>50,768</strong></td>
<td><strong>17%</strong></td>
</tr>
<tr>
<td>Setback</td>
<td>Solanezumab</td>
<td>Eli Lilly</td>
<td>Phase III</td>
<td>Abandoned, Phase III</td>
<td>5,577</td>
<td>0</td>
<td>-100%</td>
</tr>
<tr>
<td></td>
<td>Fovista</td>
<td>Ophthotech</td>
<td>Phase III</td>
<td>Clinical trial setback</td>
<td>5,514</td>
<td>164</td>
<td>-97%</td>
</tr>
<tr>
<td></td>
<td>Verubecestat</td>
<td>Merck &amp; Co</td>
<td>Phase III</td>
<td>P/I/II trial discontinuation</td>
<td>5,219</td>
<td>1,748</td>
<td>-57%</td>
</tr>
<tr>
<td></td>
<td>JCAR017</td>
<td>Juno Therapeutics</td>
<td>Phase II</td>
<td>CAR-T class effect concerns</td>
<td>4,836</td>
<td>3,676</td>
<td>-24%</td>
</tr>
<tr>
<td></td>
<td>Vellparlb</td>
<td>AbbVie</td>
<td>Phase III</td>
<td>Missed PLL trial endpoints</td>
<td>7,502</td>
<td>1,321</td>
<td>-82%</td>
</tr>
<tr>
<td></td>
<td>Mongersen</td>
<td>Celgene</td>
<td>Phase III</td>
<td>Disappointing trial results</td>
<td>4,719</td>
<td>3,335</td>
<td>-29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Sub-Total</strong></td>
<td><strong>28,648</strong></td>
<td><strong>-76%</strong></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>79,416</strong></td>
<td><strong>66,465</strong></td>
<td><strong>-16%</strong></td>
</tr>
</tbody>
</table>

Source: Evaluate, May 2017
Some things don’t change
Success is rewarding but failure is costly

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>Imfinzi</td>
<td>AstraZeneca</td>
<td>Phase III</td>
<td>Marketed</td>
<td>8,276</td>
<td>13,069</td>
<td>58%</td>
</tr>
<tr>
<td>Kisqall</td>
<td></td>
<td>Novartis</td>
<td>Phase III</td>
<td>Marketed</td>
<td>6,370</td>
<td>6,921</td>
<td>9%</td>
</tr>
<tr>
<td>Amjevita</td>
<td></td>
<td>Amgen</td>
<td>Filed</td>
<td>Marketed</td>
<td>6,273</td>
<td>2,549</td>
<td>-59%</td>
</tr>
<tr>
<td>Ocrevus</td>
<td></td>
<td>Roche</td>
<td>Filed</td>
<td>Marketed</td>
<td>16,965</td>
<td>18,242</td>
<td>8%</td>
</tr>
<tr>
<td>Dupixent</td>
<td></td>
<td>Sanofi</td>
<td>Phase III</td>
<td>Marketed</td>
<td>12,884</td>
<td>18,775</td>
<td>46%</td>
</tr>
</tbody>
</table>
Some things don’t change
Success is rewarding but failure is costly

<table>
<thead>
<tr>
<th>Setback</th>
<th>Solanezumab</th>
<th>Company</th>
<th>Status (Aug 2016)</th>
<th>Status Change Since Aug 2016</th>
<th>Aug 2016 NPV ($m)</th>
<th>Today’s NPV ($m)</th>
<th>Change vs. Aug 2016 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fovista</td>
<td>Eli Lilly</td>
<td>Ophthotech</td>
<td>Phase III</td>
<td>Abandoned, Phase III</td>
<td>5,577</td>
<td>0</td>
<td>-100%</td>
</tr>
<tr>
<td>Verubecestat</td>
<td>Merck &amp; Co</td>
<td>Phase III</td>
<td>Clinical trial setback</td>
<td>5,514</td>
<td>164</td>
<td>-97%</td>
<td></td>
</tr>
<tr>
<td>JCAR017</td>
<td>Eli Lilly</td>
<td>Phase II</td>
<td>CAR-T class effect concerns</td>
<td>4,836</td>
<td>3,676</td>
<td>-24%</td>
<td></td>
</tr>
<tr>
<td>Vellparlb</td>
<td>Eli Lilly</td>
<td>Phase III</td>
<td>Missed PII trial endpoints</td>
<td>7,502</td>
<td>1,321</td>
<td>-82%</td>
<td></td>
</tr>
<tr>
<td>Mongersen</td>
<td>Eli Lilly</td>
<td>Phase III</td>
<td>Disappointing trial results</td>
<td>4,719</td>
<td>3,335</td>
<td>-29%</td>
<td></td>
</tr>
</tbody>
</table>
Headwinds of change
Drug development is getting costlier

Fig. 3. Trends in capitalized pre-human, clinical and total cost per approved new drug.

Headwinds of change
Average time from launch to patent expiry for new active substances

Source: QuintilesIMS Institute; QuintilesIMS ARK Patent Intelligence, Sept 2016
Note: The complement of each product characteristic category is defined as the set of products not included in that category—e.g. non-orphans for the set of orphans. The complement index line sets the average time from patent to launch of the complement group to a value of 100 and calculates the average value for the product category accordingly.
**Headwinds of change**
**Trends in biotech financing**

Figure 3  Global biotech industry financing. PIPEs, private investment in public equity. Sources: BCIQ, BioCentury Online Intelligence. BioCentury updates its financing data on an ongoing basis.

Figure 4  Public biotech barometers. (a) Public biotech company revenue, R&D spending, net profits and loss. (b) Number of companies and employees by market cap. Large cap, ≥$5 billion; mid-cap, $1 billion < $5 billion; small cap, $250 million to < $1 billion; micro-cap, <$250 million.

Headwinds of change
Trends in biotech financing

Figure 3  Global biotech industry financing. PIPEs, private investment in public equity. Sources: BCIQ, BioCentury Online Intelligence. BioCentury updates its financing data on an ongoing basis.

Headwinds of change
Trends in biotech financing

Figure 3  Global biotech financings from PIPEs, private investments into private and public companies. Sources: BCIQ Biotechnology & Life Sciences Research Database and BioCentury update. Data reported as of December 31, ongoing basis.

Figure 4  Public biotech barometers. (a) Public biotech company revenue, R&D spending, net profits and loss. (b) Number of companies and employees by market cap. Large cap, $\geq$5 billion; mid-cap, $1 billion < $5 billion; small cap, $250 million to < $1 billion; micro-cap, < $250 million.
Pharma 3.0
From drugs to healthy outcomes

Drivers of change
- R&D productivity
- Patent cliff
- Globalization
- Demographics
- Pricing & reimbursement
- Health care reform
- Health IT
- Consumerism
- Value mining

Business Models
Pharma 1.0
Blockbuster drugs
Pharma 2.0
Diversified drug portfolios
Pharma 3.0
Healthy outcomes

Customer
- Physician
- Payor
- Patient
A paradigm shift
Patients as partners

Patient involvement in medicines R&D

Settling Research Priorities
- gap analysis
- horizon scanning
- defining patient-relevant added value and outcomes

High expertise in disease area required

Protocol Synopsis
- design
- target population

Design of Protocol
- relevant endpoints
- benefit/risk balance
- inclusion/exclusion criteria
- diagnostic procedures
- quality of life and patient reported outcomes
- ethical issues
- data protection
- mobility issues/logistics
- adherence measures

Research Priorities

Trial steering committee
- protocol follow-up
- improving access
- adherence

Data & Safety Monitoring Committee
- benefit/risk
- drop-out issues
- amendments

Regulatory Affairs
- MAA evaluation
- EPAR summaries
- layout summary of results
- package leaflets
- updated safety communication

Investigators Meeting
- trial design
- recruitment
- challenges
- opportunities can trigger amendments

Information to trial participants
- protocol amendments
- new safety information

Research Design and Planning
- content
- visual design
- readability
- language
- dissemination
- patient information
- practical considerations

Research Conduct and Operations
- summary of interim results
- dissemination in patient community
- study reporting

Dissemination, Communication, Post-approval
- assessment of value
- patient reported outcomes
- patient priorities

Health Technology Assessment
- contribution to publications
- dissemination of research results to patient community / professionals
- post-study communication

Fundraising for research

Ethical Review
- content
- visual design
- readability
- language
- informed consent

Medium expertise in disease area required

EUPATI
European Patients’ Academy on Therapeutic Innovation
www.eupati.eu

Geissler, Ryli, Leta, Uhlenhopp
EPALCO/EUPATI (2015, unpublished)
A paradigm shift
From clinical trials to the real world

Improving R&D's ROI

New data sources/tools

- More rapid/cheaper sequencing
- Robotics/automation
- E-enrollment/e-consent/virtual trials
- Accelerated approval/MAPPS/adaptive licensing
- Real World Evidence (RWE)

Discovery
- Early biomarker ID
Development
- Targeted patient population, smaller trials faster to statistical significance
Approval
- Early approval based on smaller trials
Post-launch
- Outcomes data

Personalization of medicine

Savings
# A paradigm shift

*From clinical trials to the real world*

<table>
<thead>
<tr>
<th></th>
<th>Efficacy (Clinical Trial Data)</th>
<th>Effectiveness (Real-World Data)</th>
<th>Post-Marketing Surveillance (PMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Works under ideal circumstances</td>
<td>Works under usual circumstances</td>
<td>Works under customary condition of the drug use</td>
</tr>
<tr>
<td><strong>Setting/Design</strong></td>
<td>Controlled clinical trial</td>
<td>Real-world clinical practice</td>
<td>Controlled/spontaneous/cohort/case control studies</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>Regulatory approval (FDA)</td>
<td>Drug performance in real world</td>
<td>Monitoring the safety of the drug</td>
</tr>
<tr>
<td><strong>Intervention or Treatment</strong></td>
<td>Fixed regimen</td>
<td>Flexible regimen</td>
<td>Flexible regimen</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Active comparator/usual care</td>
<td>Active</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Homogenous/highly selective (stringent inclusion/exclusion criteria)</td>
<td>Heterogeneous/any subjects</td>
<td>Heterogeneous/any subjects</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>High</td>
<td>Low to high</td>
<td>Low to high</td>
</tr>
</tbody>
</table>
What do we need?

Technology tectonics

Quality transparency

Collaboration and continuity
What do we need?

Technology tectonics
What do we need?

Quality transparency
What do we need?

Collaboration and continuity
What do we need?

Collaboration and continuity
Thank you for your attention