The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Copyright: European Medicines Agency. Reproduction is permitted provided the source is acknowledged.

Conflict of interest: none

L. Fregonese
Outline

• Development of medicines for rare diseases: Where are the problems?
  - do we know enough?
  - why do we get “lost in translation”?
  - how do we know if trials REALLY fail?

• Regulatory pathway(s)

• Conclusions
What is RARE?

- working definition for public health/healthcare/regulatory
- Not more than 5 in 10,000 in the EU
- Not more than 200,000 in US
- includes diseases that could affect 1 or 250,000 people in the EU
- progeria: 25 patients
- cystic fibrosis: 40,000 (0.7 in 10,000)
How many medicines for rare diseases?

Orphan-drug designations, which come with perks for drug companies trying to find cures for rare diseases, are on the rise at both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

- 2003 Completion of the Human Genome Project spurs the identification of rare genetic disorders
- 2013 The FDA hands out a record 260 orphan designations

L. Fregonese
93 Orphan Medicines authorized in EU

A Alimentary tract and metabolism
B Haematology
C Cardiovascular
H Systemic hormonal;
J Anti-infective
I Immunology
L Antineoplastic;
N Nervous system
R Respiratory system
V Various

L. Fregonese
Rare Lung Diseases?

Tobramycin DPI, Ivacaftor, Mannitol, Aztreonam, Colistimethate sodium, Levofloxacin inh
More than 40 designated

L. Fregonese
### Alpha1 antitrypsin deficiency

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Disease / condition</th>
<th>Date of decision</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 proteinase inhibitor (for inhalation use)</td>
<td>Treatment of congenital alpha-1 antitrypsin deficiency</td>
<td>03/06/2008</td>
<td>Positive</td>
</tr>
<tr>
<td>Alpha-1 proteinase inhibitor</td>
<td>Treatment of emphysema secondary to congenital alpha-1 antitrypsin deficiency</td>
<td>15/02/2006</td>
<td>Positive</td>
</tr>
<tr>
<td>Recombinant adeno-associated viral vector containing human alpha-1 antitrypsin gene</td>
<td>Treatment of congenital alpha-1 antitrypsin deficiency</td>
<td>19/03/2007</td>
<td>Positive</td>
</tr>
</tbody>
</table>

- Four products designated at centralized level in the EU; none authorized
- No recent designations

L. Fregonese
Development is **slow** and **expensive**

- **Drug Discovery**
- **Pre Clinical Testing**

**Pre-Clinical Research**

- Closed & Open Innovation
- 5,000 Compounds
- 10,000 Compounds

**Clinical Trials**

- Phase 1
- Phase 2
- Phase 3

**Number of Patients**

- 20-100
- 100-500
- 1000-5000

**EMA Filing**

**EMA Approval for Sale**

**HTA Approval**

**Negotiation for Reimbursement**

**PhV Monitoring**

**Total Cost:**

$2 - $4 Billion USD

---

The problems?

Do we know enough?

Do we have good preclinical models?

Are we looking at the right disease?

Do we study the right patients?

L. Fregonese
Do we know enough?

Drug Action

Therapeutic Aims
What do we know of AATD?

The genetic defect... its protein correlates...

..how the deficiency acts in the body...

- Autophagy enhancing molecules (carbamazepine, fluphenazine)
- Prevention of polymerization (small peptides, molecular chaperones)
- Replacement therapy

...and its clinical manifestations

- Gene therapy
- Antisense oligonucleotides
- siRNAs, microRNAs
- Stem cells
- Alveolar regeneration

PANLOBULAR EMPHYSEMA - adult

L. Fregonese
Genotype-phenotype correlation: Ivacaftor and G551D Cystic fibrosis

In spite of good \textit{in vitro} data on different mutations, Ivacaftor alone works only on G551D (4\% of CF patients) and not on F508Del (more than 90\% of CF patients)

L. Fregonese
Why (When, and Where) do we get lost in translation?

"Failure of efficacy to translate from pre-clinical models to the clinical setting combined with the emergence of adverse events not predicted from the pre-clinical models remain at the core of late stage attrition” (IMI2 Strategic Research Agenda)
Which model?

Lung disease models

- **Cigarette smoking** expensive, cumbersome (months, high exposure), variability of damage, mild emphysema, comorbidities

- **Tissue-degrading approaches (PPE, human neutrophilic elastase, papain) and serine/cysteine proteases**: lower costs, higher homogeneity of the damage, dose-response, panacinar emphysema

- **“Natural models”**: e.g. tight skin, pallid mice. Defect and its consequences natural, no evidence of good translation

L. Fregonese
Poor translation of good results of an elastase challenge rat model

* 2 U/g Elastase +/- 0.5 mg/Kg retinoid

L. Fregonese

How do we know if those trials REALLY failed?

L. Fregonese


<table>
<thead>
<tr>
<th><strong>Outcome</strong></th>
<th><strong>Endpoint</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>What the trial is measuring (e.g. lung function)</td>
<td>How it is measured (e.g. FEV1)</td>
</tr>
</tbody>
</table>

- “Ideally a trial would have an objective or 'hard' endpoint such as mortality, the complete disappearance of a tumor or no trace of infection in a sample”

- To detect a 40% reduction in mortality in 5 years, 684 α1-antitrypsin deficient individuals with FEV1 35%–49% predicted would need to be recruited over a 2-year period (Schluchter MD, Am J Respir Crit Care Med. 2000)

- Surrogate endpoints are those that measure e.g. function, QoL, etc.

- Important that the surrogate endpoints reflect the disease and its natural history

L. Fregonese
there are multiple ongoing global late-phase trials, this number is both unfeasible and financially ruinous even for the largest of pharmaceutical companies. In many disease areas, including cancer and cardiovascular disease, it can be reasonably assumed that death is an inevitable outcome of disease progression. In IPF it remains the case that lung transplantation is the one therapeutic intervention that has been shown to improve life expectancy [55]. Consequently transplantation is an option for patients with progressive disease and, although only available to a minority, it is more likely to be offered to the type of patient who is currently enrolled in a clinical trial, i.e. those of a younger age and with limited comorbidities. Therefore, the use of transplantation breaks the inevitable link between disease progression and death, thereby creating a statistical issue in how to handle the loss of patients to transplant in a mortality trial. Two main approaches have been taken in published studies. One is to censor individuals at the time of transplant; however, this introduces informative missingness. The second approach has been to use the date of transplant as the date of death. However, transplants are influenced by factors other than disease severity, including: donor availability and differing allocation protocols between countries and even individual hospital units, i.e. transplant centres, within countries. As an example of the size of the problem, in the INSPIRE study 16 subjects underwent a transplant [32].

### Table 1: Summary of late-phase idiopathic pulmonary fibrosis (IPF) Drug Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial acronym</th>
<th>Year</th>
<th>Study duration weeks</th>
<th>Subjects n</th>
<th>Primary end-point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-γ</td>
<td>2004</td>
<td>58</td>
<td>330</td>
<td></td>
<td>PFS</td>
<td>No effect [28]</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>2005</td>
<td>36</td>
<td>107</td>
<td></td>
<td>Change in lowest 6MWD, ( \text{SpO}_2 )</td>
<td>Reduced acute exacerbations [27]</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2005</td>
<td>57#</td>
<td>56</td>
<td></td>
<td>Survival time</td>
<td>Improved survival [30]</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in VC</td>
<td>Reduced progression [29]</td>
</tr>
<tr>
<td>Bosentan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in 6MWD</td>
<td>No effect [31]</td>
</tr>
<tr>
<td>Etanercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in FVC and ( D_{\text{LCO}} )</td>
<td>No effect [35]</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>2004</td>
<td>58</td>
<td>330</td>
<td></td>
<td>Survival time</td>
<td>No effect [32]</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>2005</td>
<td>36</td>
<td>107</td>
<td></td>
<td>Change in VC</td>
<td>Reduced progression [34]</td>
</tr>
<tr>
<td>Imatinib</td>
<td>2005</td>
<td>57#</td>
<td>56</td>
<td></td>
<td>Time to disease progression</td>
<td>No effect [33]</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>2006</td>
<td>52</td>
<td>182</td>
<td></td>
<td>Change in VC</td>
<td>No effect [46]</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2006</td>
<td>52</td>
<td>182</td>
<td></td>
<td>Change in % pred FVC</td>
<td>Reduced progression [36]</td>
</tr>
<tr>
<td>Nintedanib (BIBF1120)</td>
<td>2006</td>
<td>52</td>
<td>182</td>
<td></td>
<td>Rate of FVC decline</td>
<td>Trend to reduced progression [48]</td>
</tr>
<tr>
<td>Prednisolone+azathioprine</td>
<td>2006</td>
<td>52</td>
<td>182</td>
<td></td>
<td>Change in FVC</td>
<td>Increased mortality [49]</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>2007</td>
<td>52</td>
<td>182</td>
<td></td>
<td>PFS</td>
<td>Increased adverse events [50]</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>ARTEMIS</td>
<td>2013</td>
<td>35#</td>
<td>492</td>
<td>Cough questionnaire</td>
<td>Reduced cough [51]</td>
</tr>
<tr>
<td>Septrin</td>
<td>TUPAC</td>
<td>2013</td>
<td>52</td>
<td>118</td>
<td>Time to disease progression</td>
<td>No effect [52]</td>
</tr>
</tbody>
</table>

PFS: progression-free survival; 6MWD: 6-min walking distance; \( \text{SpO}_2 \): arterial oxygen saturation measured by pulse oximetry; VC: vital capacity; FVC: forced vital capacity; \( D_{\text{LCO}} \): diffusing capacity of the lung for carbon monoxide. \#: median follow-up.
Which endpoints for AATD?

- FEV1
- CT scan density
- 6MWT
- SGRQ
- Exacerbations?
- Other PROs?
- Mortality?
- AAT levels (e.g. gene therapy)

The overall results of the combined analysis of 2 separate trials of comparable design, and the only 2 controlled clinical trials completed to date, has confirmed that IV AAT augmentation therapy significantly reduces the decline in lung density (Stockley RA et al, 2010).

Cochrane review from 2010 conclude on no certainty on efficacy.
Trial designs

- Replacement therapy IV 60 mg/kg/week based on “protective” threshold of 80 mg/dL (patients with heterozygous phenotypes whose levels of α1-antitrypsin exceed this level do not usually develop lung disease.
  
  How do we know if this is really the protective dose?

- Slow decliners/worsening vs. fast decliners/ worsening:
  
  do we know which ones we are studying?

- Lack of significant changes at CT scan in most studies
  
  Observation period: how long is long enough?

- Which endpoint and design for which therapeutic indication/product? (e.g. gene therapy, regeneration/stem cells)
The regulatory pathway in the EU

“The areas of science used in the assessment of quality, safety and efficacy of human and veterinary medicines throughout their life-span”

“..basic and applied biomedical sciences (genetics, pharmacology, biostatistics, ...), social sciences such as decision sciences, risk assessment and communication sciences...”

L. Fregonese
With the final aim that patients may have an early access to effective, safe and affordable drugs.
Drug development in the centralized EU regulatory system

- Discovery/Manufacture
- Non-clinical
- Clinical
  - Human Pharmacology
  - Therapeutic Exploratory
  - Therapeutic Confirmatory
  - Therapeutic Use
    - ("Phase I")
    - ("Phase II")
    - ("Phase III")
    - ("RMP/PAES/Phase IV")
  - Scientific Advice
  - Paediatric Investigation Plan
  - Orphan Drug Designation
  - Pharmacovigilance Risk Management
  - Scientific Advice
  - Marketing Authorisation Application
  - Extension Application
  - Maintenance Procedures

L. Fregonese
The Committee for Orphan Medicinal products (COMP)

- 1 member per each of 28 Member States
- 3 members representing patients' organisations
- 3 members nominated by the European Commission
- 1 member nominated by Iceland and one by Norway.

- Decides on orphan status at early development stage and on its confirmation when a medicine reaches marketing authorization
- Patients inputs in e.g. deciding on advantages of new formulations and administration routes, among others
Orphan Status

Early development phases
• Proof of concept
• Prevalence criterion
• Serious (life-threatening and or chronically debilitating)
• Significant benefit (EMA only)

Gives access to incentives
• 10 years market exclusivity
• EU and national funding
• Data protection
Can be granted to companies or private citizens

L. Fregonese
EMA Committees (Human products)

<table>
<thead>
<tr>
<th>Orphan designation &amp; PIPs</th>
<th>Scientific Advice &amp; Protocol assist.</th>
<th>MAA Pre-submission</th>
<th>MAA Evaluation</th>
<th>Changes MA + PhV</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMP</td>
<td>SAWP /CHMP</td>
<td>CHMP</td>
<td>CHMP</td>
<td>CHMP</td>
</tr>
<tr>
<td>PDCO</td>
<td>CAT</td>
<td>PDCO</td>
<td>CAT</td>
<td>PRAC</td>
</tr>
<tr>
<td></td>
<td>HMPC</td>
<td></td>
<td>PDCO</td>
<td>CAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PRAC</td>
<td>COMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PDCO</td>
</tr>
</tbody>
</table>

Pre-submission phase

- Submission
- Evaluation
- Post authorisation

Evaluation

Launch
PCWP

Since 2006, the Agency has had a permanent Patients' and Consumers' Working Party (PCWP) in place, to provide advice to the Agency and its scientific committees on matters of direct and indirect interest to patients in relation to medicines.

Three main areas:

- transparency and communication;
- safety of medicines;
- involvement with EMA and its scientific committees regarding medicines evaluation.

L. Fregonese
How do we assess medicines?

- Clinical Evaluation
- Non-clinical Evaluation
- Quality Evaluation

Decision on benefit-risk balance

- Evaluator’s recommendation
- Peer review
- Expert opinions/Consultations
- Medical/Scientific Advisory
- Dialogues with applicants

- Regulatory Decision – Market approval and post-market commitments

QSE
Quality Safety Efficacy

Benefit-risk assessment

Is everything equal?

Or are some more important?

EVOLVING EXPECTATIONS…

- Benefit-risk balance
- Moving away from separate contribution of efficacy evidence and risk data
- The balance will change along the life cycle of the product

Is everything equal?
Or are some more important?
Areas of failure

Phase 2 Failures: 2008 – 2010
(N = 87 compounds)

- Efficacy: 51%
- Safety: 19%
- Pharmacokinetics/bioavailability: 1%
- Strategic: 29%

Phase 3 Failures: 2007 – 2010
(N = 83 compounds)

- Financial and/or commercial: 21%
- Safety (including risk-benefit): 7%
- Not disclosed: 6%

Efficacy is the major problem

Arrowsmith J. Nat Rev Drug Discov 2011;10:82 and 328
The patient’s voice on benefit/risk

Maximum Acceptable PML Risk
Crohn’s Disease

Progressive Multifocal Leukoencephalopathy

<table>
<thead>
<tr>
<th>Therapeutic Benefits</th>
<th>Maximum Acceptable 10-Year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Remission</td>
<td>0.00%</td>
</tr>
<tr>
<td>Moderate to Remission</td>
<td>0.16%</td>
</tr>
<tr>
<td>Severe to Remission</td>
<td>0.98%</td>
</tr>
</tbody>
</table>

3rd year risk
1st year risk
What comes out of the assessment

• Medicine licensed for a specific **therapeutic indication** within the patient population
  - Depends on the trial (e.g. vs. placebo, add-on, resistance to existing treatments)
  - Positive Risk/benefit ration cannot necessarily be extrapolated to different populations with the same disease (e.g. different age)

• Warnings and description of side effects
• Risk management measures

---

**The Problem of comparative effectiveness**

Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care

L. Fregonese
Decision makers on the road to market access

Drug candidates

Regulatory Agency

Payer / HTA body

Prescriber

Patient as payer

Market and patient access

Does the drug do more good than harm in a defined group of patients?

What are the health and cost consequences associated with this drug relative to other interventions in this patient?

How does the drug perform relative to other interventions in this patient?

Am I willing and able to pay for this treatment out-of-pocket?

One decision valid in 28 EU + 3 EEA countries

- 30+ different HTA methodologies and interpretations
- 40+ independent decisions about whether the medicine should be paid for
EMA initiatives helping innovative products

- Reinforce relationships and support to Academia and SME
- New EU clinical trial regulation
- Guidelines (for biologics, biosimilars, clinical trials, etc)
- Scientific advice
- Medicines Adaptive Pathways to the Patients
  - Accelerated MA for innovative orphan drugs
  - Early HTA
  - Adaptive licensing
- Open data, access to documents
Adaptive Licensing (pilot, EU)

Current scenario:
Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation.

Adaptive Licensing:
After initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information.
Where to?
Rare Catch 22

Disease poorly known

Few patients

Uncertainty on endpoints and biomarkers

Challenges in trial design

Limited drug development/attrition

No treatments available

Limited drug development/attrition

Disease poorly known

Few patients

Uncertainty on endpoints and biomarkers

Challenges in trial design

L. Fregonese
Some actions

• Stimulate companies to early dialogue with regulators on innovative products (gene therapy, oligonucleotides, etc)

• Help and promote the study of phenotypes/different forms of the disease (registries)

• Participate in discussion and creation of endpoints (e.g. patient reported outcomes, discussions on CT scan)

• Stimulate scientific community to consistency in trial design

• Stimulate real-life studies for comparative effectiveness!!

• Participate in development of treatments for COPD in general

L. Fregonese
The right medicines for the right disease

- Good knowledge of a disease together with coherent work on preclinical and clinical data can improve medicines development

- Negative studies, translatability relative to potential therapeutic use, identification of phenotypes, standardization of endpoints, etc.

L. Fregonese
Clinical research and real-life effectiveness

- **Identification of responder’s phenotypes**---risk to reduce even more population size for establishing efficacy/effectiveness

The role of Precision Medicine

Precision medicine is becoming an integral part of the R&D process making it possible to more effectively prevent, diagnose and treat diseases. Precision medicine could help to control costs by reducing unnecessary treatment and side effects.

**“Real life” effectiveness studies** --- also allowing impact of non-drug interventions (e.g. lung disease)

L. Fregonese
Thank you
for your attention

Laura.Fregonese@ema.europa.eu