Requirements from regulatory agencies and post marketing surveillance
Assessment of Cardiovascular Drugs for the treatment of ischemic heart disease

• Acute coronary syndromes: STEMI - NSTEMI

• Chronic stable angina: 1. risk factors, 2. anti-anginals
Assessment of Drug Efficacy in ACS

- Mortality
- Cardiovascular Mortality
  - Discharge
    - 30 days
    - 3 months
    - 1 year
- Reinfarction
- Sudden death
Assessment of Cardiovascular Drugs for the treatment of chronic ischemic heart disease

- Chronic stable angina: 1. risk factors, 2. anti-anginals

  ✓ Risk factors: events, surrogate end points

  ✓ Anti-anginals: inducible ischemia parameters, GTN consumption
Cardiovascular Risk factors
Lipids

• Approval based on effect on lipid profile
  – Short term efficacy
  – Long term safety

• Approval based on MACE
Cardiovascular Risk factors
Blood pressure

- Approval based on effect on blood pressure reduction
  - Short term 12 weeks vs placebo
  - Short term 12 weeks vs comparator
  - Long term 52 weeks safety study
  - Adequate patient groups

- Approval based on MACE
Assessment of efficacy in CSA

• Drugs: secondary prevention – anti-ischemic
  • Mortality ?
  • Morbidity?
  • Degree of ischemia
Assessment of inducible myocardial ischemia

- Exercise ECG
- Holter monitoring
- Myocardial perfusion scintigraphy
- Stress echo
Assessment of efficacy for anti-anginals

- Exercise time during ETT
- Time to 1 mm ST segment depression
- HRQoL
- Number of episodes of angina
- No of GTN tablets used
- RRP to 1 mm ST
- RPP at peak exercise
Assessment of efficacy of antianginals

Study designs

• Rx vs Placebo
• Rx vs Beta blockers
• Rx+ beta-blockers vs other antianginals + beta-blockers
Assessment of anti-anginal drugs

Treatment of stable angina has not been subjected to the same scrutiny by large randomized trials as has, for example, that of myocardial infarction and unstable angina. Thus, although much has been achieved in comparing the symptomatic benefit of different modalities of treatment, there is relative paucity of information about their prognostic effects.

Antianginal drugs have classically been aimed to reduce myocardial oxygen demand and/or increase blood flow to ischaemic area. However, other therapeutic approaches with novel mechanisms of action are currently under investigation, which may reinforce the emphasis that should be placed on the need of reassuring pharmacodynamic and safety databases.

The clinical profile drugs for stable angina needs to be studied in an acute stress testing setting, i.e. with provocation of anginal attacks due to cardiac ischaemia, which is assumed to represent the conditions of normal practice. Valid data are only likely to be obtained if sufficient account is taken of such factors as the pronounced placebo effect in angina pectoris, the substantial variation in the nature and severity of symptoms, and the subjective character of 'chest pain'.
Assessment of anti-anginal drugs

Criteria of efficacy

As the assessment of the effect of antianginal drugs based on clinical measurements alone is as yet considered too unreliable because of the possible influence of uncontrolled variables, it has become accepted that measurements of exercise capacity using standardised exercise testing should be, in spite of an intrinsic amount of variability, the major criteria of efficacy. In addition to its more objective character, it is assumed that improved exercise capacity may accounts for the patient benefit in terms of reduction of symptoms. Moreover, exercise testing provides evidence that the relief of angina and increased exercise capacity are mediated by an anti-ischaemic effect. In addition, clinical evidence of symptomatic improvement in terms of anginal pain and HRQoL (Health-Related Quality of Life) should also be provided in the major therapeutic trials.
Example of a development plan of a drug approved for the treatment of chronic stable angina
Ivabradine and exercise-induced myocardial ischemia

Placebo bid

Ivabradine 10 mg bid

Ivabradine 5 mg bid

Ivabradine 2.5 mg bid

Placebo bid

Ivabradine 10 mg bid

Open label

Ivabradine 10 mg bid

Placebo bid

ETT: Exercise tolerance test

2 to 7 d

1 week

2 weeks

3 months

1 week

ETT

ETT

ETT

ETT

ETT

Ivabradine and exercise-induced myocardial ischemia

Increase in time to 1-mm ST-segment depression (s)

Dose ranging
All Patients received Ivabradine 10 mg twice / day

Time (days)

0 2 4 6 8 10 12

0 2 4 6 8

Placebo (n=28)

Ivabradine 10 mg (n=31)
Ivabradine 5 mg (n=31)
Ivabradine 2.5 mg (n=30)

Ivabradine and exercise-induced myocardial ischemia

<table>
<thead>
<tr>
<th>Washout 2-7 days</th>
<th>Run-in 7 days</th>
<th>1 month</th>
<th>3 months</th>
<th>Run-out 14 days</th>
</tr>
</thead>
</table>

ETT: Exercise tolerance test

Ivabradine and exercise-induced myocardial ischemia

*P<0.0001

P for non-inferiority

n=939

Review of Corlentor/Procoralan started

• No benefit in overall mortality/morbidity
• Increased mortality in patients with angina
Studies for approval of therapeutic agents for the treatment of heart failure
Selection of patients

- **AHF**
  Patients hospitalised because of HF should be randomised within a reasonable time in order to be able to adequately assess efficacy

- **CHF**
  - LVD alone will not suffice.
  - Patients should exhibit a wide range of severity of CHF.
  - Alternatively the information can be gathered by separate studies in different patient subsets
  - Patients should be in stable conditions, however a shorter period from the acute event and randomisation may be considered in patients with more severe forms of HF
  - It is advisable to exclude patients within 3 months from a MI and with a short (<3 months) duration of the disease
Selection of patients

• **AHF**
  Patients hospitalised because of HF should be randomised *within a reasonable time* in order to be able to adequately assess efficacy
  - Patients needing optimisation of background Rx
  - Patients already maximal Rx

• **HHF**
  Patients included at discharge after an unplanned hospitalisation for HF

• **CHF**
  - LVD alone will not suffice.
  - Patients should exhibit a wide range of severity of CHF. Alternatively the information can be gathered by separate studies in different patient subsets
  - It is advisable to exclude patients within 3 months from a MI and with a short (<3 months) duration of the disease
Criteria to assess efficacy

• AHF
  - In Hospital and 4 wks mortality
  - Depending on the indications claimed, long term mortality and duration of hospitalisation
  - Improvement in haemodynamic state and symptoms (categorical composite)
  - Relief of other manifestations of AHF including need of inotropic support and vasodilators

• CHF
  - Mortality, morbidity
  - Primary composite
Cardiovascular mortality

• Since no correlation exists between short term improvement in clinical symptoms and/or exercise capacity and mortality, many drugs are likely to require a trial which includes survival amongst its primary objectives before requesting an approval regardless of the claim being sought.

• If the investigational drug belongs to a new pharmacological class or when agents of the same class have been associated with detrimental effects, a prospective, RCT aimed at assessing survival is requested.

• Distinction should be made between a) sudden death b) death due to acute deterioration of clinical status c) death due to chronic progression of CHF.
Composite end points

May be appropriate but should include selected aspect of cardiovascular morbidity along with overall mortality. They all should be clinically relevant

- Hospitalisations for HF
- Causes of hospitalisation (co-morbidities, non adherence etc)
- Worsening Heart Failure without Hospitalization
- No. of hospitalisations/year
- Patient journeys
- Recurrent morbid events
Secondary end points

- **Exercise tolerance:** 6MWT seems to correlate better than Maximal exercise test (with or without gas exchange analysis) with the clinical effect of the drug
- **Haemodynamic data:** are insufficient to demonstrate benefit but may be useful to elucidate the mechanism of action
- **Neuroendocrine status:** data may be included but they can be only be accepted as supportive
- **Physical signs and renal function:** can be accepted as supportive only
- **Symptoms:** the effect on symptoms should always be coupled with data on mortality and morbidity
- **QOL:** supportive only
Safety aspects

- Hypotension
- End organ consequences (Heart, CNS, kidney)
- Effect on cardiac rhythm
- Pro-ischaemic events
Regulatory requirements in clinical trials

What constitutes meaningful change
Meaningful change

• Any change in a primary end point that correlates with an improvement in mortality/morbidity

• A change in a primary end points that significantly improves QOL in end stage disease patients
Dyspnoea in AHF
Significant Improvement of VAS AUC Endpoint
Effect evident early and maintained

19.4% increase in AUC with serelaxin from baseline through day 5 (Mean difference of 447.7 mm-hr)

AUC with placebo, 2308 ± 3082
AUC with serelaxin, 2756 ± 2588
*P=0.0075

* P-value is based on a two-sided two sample t-test for serelaxin versus placebo comparing area under the curve (AUC, mm-hours) of change from baseline of dyspnea visual analog scale (VAS) from baseline to Day 5.
Absolute value of changes in VAS scale

4 mm
Exercise capacity
Riociguat in pulmonary arterial hypertension

Macitentan on exercise capacity and on Mortality-Morbidity end points

6-MWT
+ 7.4 m macitentan
- 9.4 m in Placebo
-(treatment effect 16.8 m; 97.5% CI, −2.7 to 36.4; P=0.01)
Macitentan on exercise capacity and on Mortality-Morbidity end points

6-MWT
+ 7.4 m macitentan
- 9.4 m in Placebo
-(treatment effect 16.8 m; 97.5% CI, −2.7 to 36.4; P=0.01)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=250)</th>
<th>Macitentan (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of M/M Events</td>
<td>116</td>
<td>76</td>
</tr>
<tr>
<td>Hazard ratio (HR)</td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>97.5% CI of HR</td>
<td></td>
<td>0.392, 0.762</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Pirfenidone in pulmonary fibrosis

Change in FVC

Mean Change (ml)

Week

Pirfenidone (N=278)

Placebo (N=277)
Pirfenidone in pulmonary fibrosis

Progression-free Survival

Hazard ratio, 0.57 (95% CI, 0.43–0.77)
P<0.001
How to define a meaningful change

- Change in a parameter that correlates with mortality and/or morbidity or that has a clinical relevance
- No fixed value
- Has to be related to baseline function
- Attenuation of the decline in function
- Must be significantly related to the disease
- Must have a biological plausibility
Scientific background: The clinical trial programme in the pre-authorisation phase

• Focused on efficacy

• Safety is a secondary endpoint, generally underpowered and not pre-specified
Clinical trial limitations:
small sample size

<table>
<thead>
<tr>
<th>Drug name</th>
<th>No. Exposed to product in USA during testing</th>
<th>Approximate exposure prior to withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terfenadine</td>
<td>5.000</td>
<td>7.500.000</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>340</td>
<td>6.900.000</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>1.200</td>
<td>2.300.000</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>3.400</td>
<td>600.000</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>2.400</td>
<td>2.500.000</td>
</tr>
</tbody>
</table>

Friedman MA et al., JAMA 1999; 281:1728-1734
Challenge Faced by Regulatory Authorities at Marketing Approval:

How to ensure that life-saving therapies are available in a timely fashion

while

Still guarantee that medicines are safe
What we do not know at time of approval

Full safety profile including adverse drug reactions which are:

- Rare.
- Delayed (long latency).
- From chronic exposure.
- Due to cumulative effects.
- Medication error/off-label use.
- Associated with abuse/misuse.
- Associated with populations not studied in trials
  (e.g. children, elderly, pregnancy, co-morbidities).
Tools for monitoring and assessing risk-benefit profile

Data Sharing

FDA → EMA
( transparency )

Publicly available PhV Database (FAERS)
Risk Evaluation and Mitigation Strategies (REMS)
Drug Safety Initiatives:
- Critical Path Initiatives
- Sentinel (Mini-Sentinel)
Drug Safety Consortia:
- iSAEC
- CSRC
- HESI

Publicly available PhV Database (EudraV)
Risk Management Plans (RMP):
- PASS/PAES (New PhV Legislation)
Drug Safety Initiatives:
- Encepp
- IMI (Innovative Medicines Initiatives)
Drug Safety Consortia:
- SOS
- EU-ADR
- ARITMO
- Safeguard
PASS
Post-authorization safety study: definition

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures.
Post-authorization safety study: objectives

- to quantify potential or identified risks
- to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (i.e. pregnant women, specific age groups, patients with renal or hepatic impairment)
- to provide evidence about the absence of a risk
- to assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (i.e. indications, dosage, co-medication, medication errors)
- to measure the effectiveness of a risk minimisation activity.
PASS: triggering factors

- PASS initiated, managed or financed by a MAH
  - Pursuant to an obligation imposed by a competent authority
    - as a condition to the granting of the marketing authorisation, or after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product (category 1)
    - as part of a marketing authorization granted under exceptional circumstances (category 2)
  - Voluntarily/required
    - studies required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimisation activities (category 3)
    - any other PASS (category 4)
Post-authorisation efficacy studies

Delegated Regulation to determine situations for a PAES:

In order to determine the situations in which post-authorisation efficacy studies may be required [...] the Commission may adopt [...] delegated acts" (Article 22a of Directive 2001/83/EC and 10b of Regulation (EC) No 726/2004)
PAES – Practical aspects

- Exceptional tool for 'standard' marketing authorisations
- Context: efficacy evaluation
- Identified concern - burden of proof with regulators
- Justified on a case-by-case basis
- Goal: address well-reasoned scientific concerns with direct impact on the maintenance of the marketing authorisation
- Design: appropriate to answer the scientific question – focal point: supplementing efficacy data
The Sibutramine experience

✓ 1997 sibutramine approved for weight loss by FDA labelled warning re BP and heart rate increases

✓ 2002 EMA requires CV outcomes trial (SCOUT)

✓ 10,744 overweight/obese with CV disease and/or diabetes over 3.4 years
sibutramine

SCOUT (Sibutramine Cardiovascular Outcome Trial) requested by CHMP at the time of MAA to define risk-benefit profile in overweight high-risk cardiovascular patients

age ≥55, standard WHO BMI criteria + CVE or T2DM & add CVRF

1EP composite of MI, stroke, resuscitated cardiac arrest, CV death

N=9000
interim analysis found 16% increased risk of CV events such as MI and stroke compared with placebo-treated patients (HR 1.161 [95% CI 1.029–1.311]; p=0.016)
The Sibutramine experience

1997 sibutramine approved for weight loss by FDA labelled warning re BP and heart rate increases

2002 EMA requires CV outcomes trial (SCOUT)

10,744 overweight/obese with CV disease and/or diabetes over 3.4 years

<table>
<thead>
<tr>
<th></th>
<th>sibutramine</th>
<th>placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-fatal MI</td>
<td>4.1%</td>
<td>3.2%</td>
<td>.02</td>
</tr>
<tr>
<td>non-fatal stroke</td>
<td>2.6%</td>
<td>1.9%</td>
<td>.03</td>
</tr>
<tr>
<td>CV death</td>
<td>4.5%</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>primary composite</td>
<td>11.4%</td>
<td>10.6%</td>
<td>.02</td>
</tr>
</tbody>
</table>

hazard ratio 1.16 (95% CI 1.03 to 1.31)

published NEJM Sept 2, 2010
drug withdrawn by FDA, EMA etc. soon after
CONCLUSIONS

Often, the Benefit/Risk balance of a medicinal product cannot be fully identified until after a drug is on the market and has been used by a large, diverse group of patients over time.

Clinical trials conducted before approval may be too small, too short, based on surrogate endpoints..... to detect all possible risks(…and efficacy).

Studies based on post marketing surveillance need to be defined at the time of MAA (case by case basis)