



## **Pharmaceutical Industry Project Management Group**

**Spring Meeting – 21 May 2008 – Hilton Metropole, London**

### **RESPONDING TO CHANGE, MAXIMISING VALUE OF PRODUCTS IN DEVELOPMENT**

Chaired by Janette Thomas (AccentBio) and Steve Harrison (Pharma Alliance International)

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#### **Introduction**

##### **Janette Thomas**

To ensure continued success, we must make sure that our programmes and projects are optimized.

There are many new drivers of change that must be considered: cost pressures, changed regulatory attitudes, new and more complex disease targets, IP challenges.

Many of our processes that we have been comfortable with are evolving:

- Clinical – adaptive trials, diaspora of study sites worldwide
- Emergence of Translational medicine
- Expansion in development of new indications and line extensions for existing drugs
- Imperative need for risk management

## Company Strategy and Environmental Uncertainty

### Maie Gall, Matems Consulting AG

The Pharma world is constantly changing. Significant pressures are affecting all areas of our work. Our success rate in bringing new medicines to market is reducing; there is intense competition in niches – good for the patient but not so for our profitability. Now more than ever there is a need for innovation.

Our **strategy must be competitive** and based on a wide set of questions:

- How well served is the market now?
- What needs are unmet?
- Do the authorities really want treatments in any one area?
- What are the expectations of prescribers and patients?

A medium quality strategy with **excellent execution** is better than vice versa! The spirit of a responsive organization must be behind it.

There are different options for us to be competitive:

- The best: win with superior knowledge and innovation
- Next best: provide products in a more attractive way
- Third best: market more effectively than others

Key **strategic imperatives**:

1. With an new indication entry by a large company:

Make it easy to differentiate; fit with disease management regimes

Go for a high unmet niche

2. Defending a strong position as a large company:

Careful time planning

Blocking competition by building relationships with stakeholders – listen to all types of customers, find competitor weakness/ further differentiate

3. New indication entry by a small company:

Ideally – have a unique mode of action

Take time building stakeholder relationships

Look for a large investor!

4. Defending a small company market position

Very difficult! Search for a large partner!

**Good leadership** is imperative – creating a situation of pressure for competitors / harnessing the creativity and commitment of employees  
Making decisions based on sound and thorough analysis – not ‘folk wisdom’ or rumour.

(See the output of the workshop sessions in appendix 1)

## Intelligent Preclinical design

**Elisabeth Mortimer, Fulcrum Pharma (Europe) Ltd**

### Selecting good molecules is crucial

There can be success in failing quickly – it also helps feedback to pipeline design

**Standard screens** could include: in-vitro cardiovascular, genetic, pharmacological, some ADME

Example: a CNS compound – where a company delayed early investigations into blood-brain barrier – compound failed later in Phase 2.

It's important to **understand exactly what the medics are planning** – both now and in the longer term – with respect to dosing, routes, populations etc.

Get the preclinical package **right first time** – seek advice – get multiple opinions.

Example: One company conducted preclinical studies using the wrong route – data collected was of little use, time/money was wasted and unnecessary animals sacrificed.

**Intelligent design** – very important with the first pivotal tox studies – where timing may be critical and finding tight.

Minimum packages such as '2 weeks for one human dose' can be a false economy.

Use a **recovery period** – rule of thumb is 2 weeks – helps to prove reversibility.

Spending now on radiolabelled ADME can save money later!

Seek **regulatory advice** for non standard development – phrase questions carefully and study responses carefully

**Seek suppliers carefully** – costs and time isn't everything. How much recent, relevant, experience do they have? Always then strive to build a collaborative approach with selected suppliers.

## Conducting Cost Effective Clinical Trials

**Mark Davison, SICPA**

Any clinical programme in the modern era costs >\$800m! Despite many years of experience, 78% of trials are delayed in starting.

Any one delay may not break the company, but it always reduces commercial potential. Consequences are much more serious however for biotechs – 30 – 40% have less than one year's cash left.

**Practical advice to minimise delays:**

**Focus ruthlessly on 1 or 2 findings** that will hit PoC criteria

Trials need to be driven by **objectives and time**, not primarily by ethereal science – e.g. investigators need to be competent to achieve objectives, not necessarily KOLs.

Problems can be headed-off by **thinking like (and checking with) patients** – e.g. will they agree to it, perhaps if there are uncomfortable procedures; what visiting schedule is required?

A thorough **feasibility analysis** is 100 times cheaper than failure or delay. Plot algorithms for experts, consultants, sites, patient recruitment.

**Help investigators to succeed** – choose good recruiters, use well thought out tactics for recruiting. Don't set out an impossible protocol.

**CROs** are proven to save time and money – note that they respond best to a trusting relationship. Remember – delays and other problems can be advantageous to them – they charge more money.

**Supporting the sites** – demarcate nurse/investigator tasks – routine tasks given to high level investigators won't get done.

Take care to build relationships with patients. This will help with retention (as important as recruitment), and help with compliance.

(see the output of workshop session in Appendix 2)

## Optimising Product Development through Leveraging Regulatory Strategy

**Dr Gareth E Walters, Fulcrum Pharma (Europe) Ltd**

### **Incorporating Regulatory strategy into Product Strategy**

Regulatory input is crucial in defining product aims at an early stage – claims in the TPP, criteria for Proof of Concept, biomarker qualification. Also for advice on any specific guidelines for disease areas/ recent precedents.

### **EU trial approval in the EU**

CTAs are required to become more accurate and complete; QA/GCP auditing by Regulators is more likely. Cross functional hand-offs (eg drug supplies) are within remit of GCP.

### **First time in man studies**

EU guidance has broadened from 'high risk' to all studies, following TeGenero incident. The totality of preclinical evidence is looked at – not just safety. Has had a number of effects – lower doses, more cohorts, higher costs. UK in particular has been avoided for various reasons; US studies are often preferred – requirements are more like the 'old days' in the EU – but some bureaucratic issues with FDA.

### **Scientific advice**

There is a move to more formality – advance booking, more teleconferences with the FDA. In EU, advice requests need careful planning. Early requests are important, prior to implementing FDA advice. Advice should not be sought after starting trials.

### **Paediatric development**

A variety of incentives are now available for this, including patent extension, exclusivity extensions. A paediatric investigation plan should include measures to adapt the medicine, define timing in comparison to adults; the agreed PIP is binding.

### **Orphan drugs**

Benefits in EU are free meetings, exclusivity, fee reductions. Designed for high unmet need populations. Same standards are required at MAA – Ods have higher risk of failure.

### **SME Assistance**

Some fee reductions and exceptions are available for small organisations (micro - <10 staff, small - <50 staff, medium - <250 staff).

### **Document driven drug development**

Aligning messages using MIRS – Message (what do we want to say) Issues (what stands in the way) Response (How can we overcome this) Support (Where are the data?)

## Appendix 1

### Workshop sessions - Questions and team output – Company strategy and Environmental Uncertainty

#### 1. How to determine the ‘character’ of an organization and then take steps to making it successful

How much change is going on – are things stable or changing?

What are the values – are they in a state of flux? Are they consistent and visible? Are management seen as behaving in a way that is consistent with corporate values? Can things be driven from bottom up?

Success relates to the communication you provide

- the success of communicating mission/vision

Successful change also relates to the reward and recognition policies

#### 2. How best to correctly identify market changes coming in the future? And make plans to be ready for them?

Sources of information

- ignore vested interests
- acquire multiple sources – but note that this is expensive
- get primary data – and get it yourself

Replacement products – assess competitor information – how does your asset sit against?

Listen to payers, patient organisations – and the project team – make sure you can do what’s really being asked

Unmet needs/ Opening markets – look for any opportunities, get marketing involved early, keep options open in your portfolio

Risk analyze your portfolio

Walk away from opportunities that don’t look attractive

### **3. How to implement structures and process to ensure a higher quality of plan implementation**

Start with big picture – clarity of goals – essential to engage people

Important to get buy-in from stakeholders

Clear operating models – make sure people know how to communicate

- set up charters
- ensure people know where they fit

Less is more with processes – challenge current processes, but:

- does it really need revision
- is it too rigid?
- does it add value?

Line vs. Matrix – ensure goals of each is clear

- is there a battle – both should be aligned
- does this matter in small companies – yes, but there the full structures and divides may not be so defined

How do we measure delivery?

- we need to assess whether a team is delivering against plan
- may be use a variance analysis
- don't use an irrelevant metric

Have the courage to drop a plan when it's not working

### **4. Is our organization ready for change? If not, what does it have to do to get there?**

Is the organisation ready for change?

- People are resistant if there has been much change in the recent past
- Hopefully there is a continuous improvement culture – and regular change is accepted

What do you need to do?

- It's all about communication
- Generating an understanding of why, what is needed, when etc
- It must come strongly from the top

**5. Are we getting the right information at the right time from the right sources? If not how to install valuable filters and source checks to guarantee quality?**

Must have multiple sources

- our networks
- leveraging tacit knowledge
- listening to customers
- scrutiny of editorial and publications
- market research

Filters

- sense checking – avoid groupthink
- pay for a non-executive advisor to question and challenge
- revisiting what the original plan was and comparing knowledge acquired with it

**6. Is it better to focus on company or portfolio strategy? How to recognize the difference and what actions do we need to take to focus on the right one for us?**

If the two are contradictory it's a pre-programmed disaster

Key example – where a new opportunity arises that is outside the company strategy

What does the company's survival depend on?

Company strategy must be broad – not too detailed or prescriptive – an enabler of innovation and flexibility

## **7. When does loyalty start hindering effectiveness? How to maintain motivation over long periods of time?**

It's two way – loyalty of employees to company and vice versa

If there is an ineffective or misguided leader it's dangerous for people to blindly follow

If a company is growing rapidly, there may be great loyalty and a reluctance to focus on the outside world

Loyalty to processes can be very dangerous – a business case-driven way of chopping projects is vital

Maintaining motivation

- an open culture where challenge is expected
- transparency over goals and priorities
- good leaders
- recognition of experience
- ways to utilise and retain very effective people

## Appendix 2

### Workshop sessions – Questions and Team Output - Conducting Cost Effective Clinical Trials

#### 1. Factors that influence the choice of study sites for Phase 0/1 and the effects they have on planning and timelines

Reputation of the principal investigator

- But not necessarily with volunteer studies
- there can be conflicts when there are interesting biomarkers

Facilities of the unit and infrastructure

- emergency facilities?

National considerations

- expense in different territories
- language barriers
- timing (e.g. holiday times / seasonal allergy likelihood)
- governmental views about various procedures and biologics
- some regulatory differences (e.g. in Russia no CMC info is reqd.)
- Local and regional Ethics timings
- Can you do things in parallel viz. various approvals

Import and Export rules

Patient populations – we may need treatment naïve patients

- sometimes genetic variations mean that certain findings are surprising
- high placebo effect with questionnaires and treatments in poorer countries
- only the US may have 2<sup>nd</sup>/3<sup>d</sup> line treatment patients

How important we're perceived to be if we are a small company

Insurance – sudden changes to a study may add a big premium addition

**2. Factors that affect the lead up to initiation of early stage clinical trials?** Discuss some of the key tasks (and timelines) that need to be captured in the lead up to a clinical study.

Early agreement of the protocol

What do we really expect?

Backwards planning to signal when we need to start various things

PreClin data – awaiting results for regulatory submissions etc

Availability of drug substance – dosage, stability, expiry date

Assay availability

- ensuring that the assay is validated
- coping with changes in delivery

Insurance – finding a company willing to cover; different countries with different requirements

Regulatory approval – ensuring the package is complete

Timelines

- ensuring everyone delivers their work packages
- planning for holidays

**3. Discuss the different regulatory considerations when planning for Phase 0/1 clinical trials in EU, USA, ROW**

Regulatory team member is vital – advising on the TPP and involved right through

- Helping identify where value might lie
- Helping identify processes and interfaces

Regulatory will be responsible for:

- Components of CTA/IND etc
- Organising and interfacing with scientific advisory committees
- Scheduled attendance at pre-IND meetings
- Supplying common templates – preferred if possible but sometimes difficult to use in early stages

Territory differences – depends on indication and timelines

Amendments in the EU can be time consuming

Countries have varying views on minor safety concerns – from ‘accepting’ to ‘anti’

Certain countries have objections to placebo controlled trials

**4. Factors that affect choice of country(ies) for Phase II/III.** Discuss some of the practical issues that arise in different countries when performing clinical trials.

Clinical practices vary from country to country

Do we need naïve patients?

Would we accept patients on concomitant meds?

Are we capable of continuing drug supply?

Distribution – shelf life sufficient for shipping etc

Equipment - do territories have scanners etc?

Ethical submissions

Varying cost

Genetic variation

Access to countries – is it easy to get the drug around? What do the CROs do?

Is it easy to get things to central labs?

How confident are we of recruitment/retention stats?

Are there competitors doing similar studies?

Can we use incentives (e.g. a bus pass for patients)?

CROs

- use them as a source of experience
- be aware of seasonal variation – eg Rhinitis

KOLs – not always the best recruiters

- they could recommend other investigators who are

**5. Contracting vs in house? What are the common problems and advantages with outsourcing (in relation to planning clinical trials)?**

PROs of using CROs	Cons
<ul style="list-style-type: none"> <li>- They have wide experience of many trials</li> <li>- They can give a company flexibility</li> <li>- Overall they are cheaper than managing in house (Pfizer have proved this) (perceived costs of trials are not the same as actual costs)</li> <li>- Location – CRO can work in the local language</li> </ul>	<ul style="list-style-type: none"> <li>- Someone may have to manage several CROs</li> <li>- Can be hard to ensure CRO is giving sufficient effort to your study (especially if they are the preferred provider for someone else)</li> <li>- Management of handoffs, samples</li> <li>- Managing relationships is tough – blame game can be difficult</li> </ul>

Structure of contract is important – fixed prices or time/materials – eye on the ball is vital

Enablers

A good kickoff with everyone present

Establish a single point of contact on either side

**6. Factors that affect the lead up to initiation of pivotal clinical trials?**

Discuss some of the key tasks (and timelines) that need to be captured in the lead up to a clinical study.

Confirm Objectives – primary and secondary end points

- Don't try to do too much
- Include health outcomes

Look at internal vs CRO management options

- perform feasibility studies – location / no's of sites required
- Look at the competition for sites

Regulatory approvals

- start ethics approvals
- Look at the pharmacovigilance plan
- Set up a data safety board
- Plan for paediatric/elderly studies

Check CMC – plan labelling, distribution chain, pre-PQ batches

Site performance

- look at incentivising clinicians, providing study nurse etc
- think about advertising

Timelines

- regulators will operate to fixed timelines

- build n company review times
- look at contingency for problems
- using EDC?
- Brainstorm potential difficulties in various locations
- Insurances

## **7. Discuss the different regulatory considerations when planning for pivotal clinical trials in EU, USA, ROW**

Looking across the globe

Get going early; make a synopsis of trials available very early on

Depends where you want to market

Which territories allow placebo-controlled studies

Gold standard is different is various territories

Prior experience –

- you may have experience of import/export issues
- availability of patients
- territories may be used to translation (e.g. Thailand has 5 languages!)

Clarifying regional requirements

- will therapy be considered 'lifestyle or serious'
- is it necessary to continue treatment after the trial?

Holding EOPII meetings with the FDA/EMA