



Pharmaceutical Industry Project Management Group

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RESPONDING TO CHANGE, MAXIMISING VALUE OF PRODUCTS IN DEVELOPMENT

Chaired by Ralph White (PPMLD) and Jayne LeCarpentier (Astra Zeneca)

Executive summary

The challenges of the of the 21st century mean that a successful product lifecycle, with good likelihood of approval, steep sales growth after launch, and an extended, high volume peak sales period, is extremely difficult to realise.

This workshop explored strategies in later stage development to maximise impact with constrained resources and explore many more avenues than the traditional 'new NCE'-dominated industry has done in past years. In particular:

- Early and thorough visioning and planning for a range of product line extensions – to expand products into franchises and expand therapeutic treatment algorithms
- Exploring specialist markets such as biodefence
- Therapeutic Switching – maximising value of existing assets, off-patent assets or undeveloped compounds, by finding new disease uses
- Exploiting the otherwise burdensome changes in regulation, such as paediatric requirements, to win back some exclusivity and product protection into the future and thrive in the face of increasingly sophisticated generics competition.

All of these issues have clear implications for continued, strong project management.

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Introduction

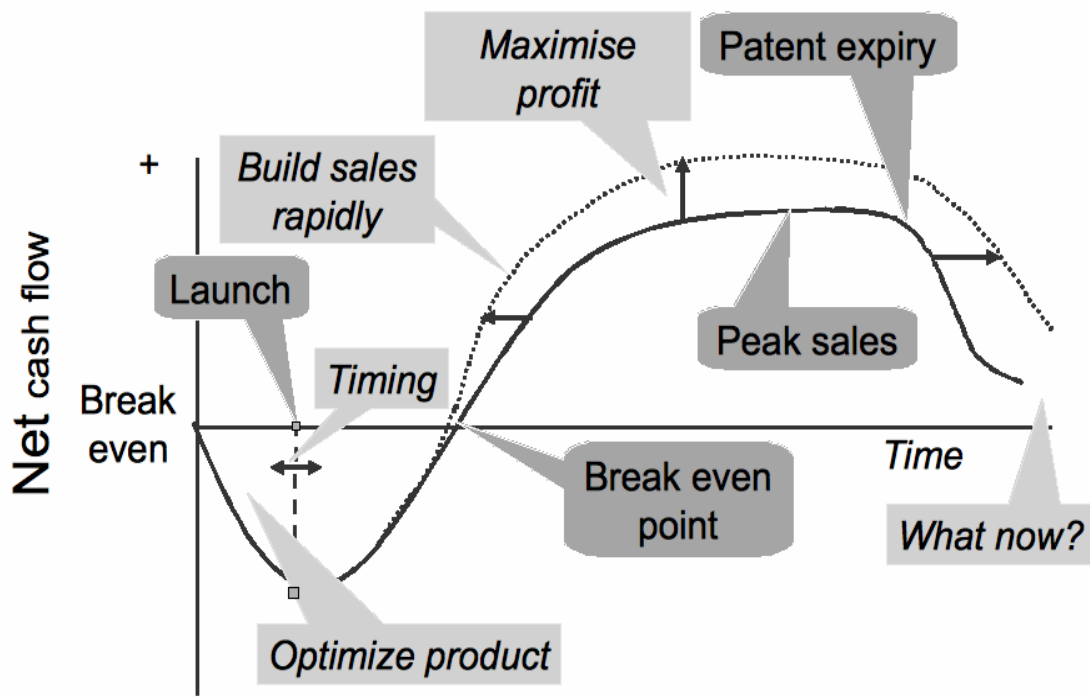
Jayne Le Carpentier and Ralph White

At the May meeting, we looked closely at the earlier phases of drug development, focusing on:

- Company strategy and environmental analysis
- Intelligent preclinical strategy
- Clinical
- Optimising regulatory strategy

In this workshop we focus on the later phases, in particular with a practical exercise concentrating on:

- Licensing products into this area
- Managing products already in this area



The diagram above was presented, and used as a backdrop for the day's work.

Optimising the life cycle from a portfolio management perspective

Tim Harris, GlaxoSmithKline

Typically, in early research, a vision is held of a steep curve of growth in the early commercial lifecycle, as well as continued success. But in reality, growth is often flatter, lasting success harder to maintain. This presentation outlined drivers for the lifecycle and options needing to be thought about at an early stage.

There are different business parameters in early and late stage development. Emphasis on science, desired profile at early stages, with many simultaneous projects, turns into a very few projects, with emphasis on what can be achieved in the Label, and heavy commercial involvement.

The most important drivers of success include thorough targeting of patient needs – talking to payers, physicians and patient groups and integrating all the information. Also, an acceptance of the balance between high return/high risk NCE projects, and thorough planning ahead for low risk (high probability of success)/ lower return line extensions (PLEs).

A portfolio-driven life cycle evolves a product over time into a franchise, and can transform a therapy area – expanding the patient base, improving compliance, adding claims – in some cases well beyond the NCE patent expiry. Examples were shown of how respiratory treatment has evolved, with both PLEs and new combination therapies, that become standard algorithms for treatment in healthcare worldwide.

Ultimately, many products can switch to OTC, where diagnosis is straightforward, there are minimal drug interactions and an established collection of safety data. It's important to build a vision for an OTC switch well in advance and incorporate necessary studies into development plans.

In summary – the development challenges of a range of PLEs need to be addressed before first filing of the product – any time after first clinical studies. The necessary mindset is the introduction of first PLE asap – seizing a narrow window of opportunity.

It requires experience to build and justify the vision – and strong project management to properly assess risk and manage the timing optimally. It must have long-term commitment from the organisation, building a strategic vision for the product and the therapy area.

Table exercise

This presentation was followed by a breakout session, where each table dealt with a key question related to aspects of the lifecycle. The feedback from these sessions is shown in the Appendix .

Case study – Biodefence vaccines: maintaining the stockpile meeting regulatory need

Howard S Tranter, Health Protection Agency (Porton Down)

There may be an increased threat from Bioterrorism in the world today, creating an ever present need for therapies to counteract the threat. This presentation outlined the opportunities for Pharma companies to market therapies to government agencies in various areas of the world.

'Category A' biological agents include those that cause smallpox, anthrax, plague, botulism, and others. Currently there are stockpiled countermeasures against some of these, but many opportunities for replacement and new therapies.

The major client is the Department of Homeland Security in the US, with the National Institute of Allergy and Infectious Diseases and Centres for Disease Control interested in early research up to proof of concept; Project Bioshield is a heavily funded agency interested in late stage development and manufacturing. The advantages to working in this market are minimised competition, available funding for R&D and large stockpiling contracts. The risks are the US-centric approach, always-likely change in legislation and changes in the regulatory environment.

Issues for project management: the US government wish list is for a treatment with fewer injections, hot-temperature stability and shelf life, small/compact and if possible, self administered. There are clear opportunities for continued PLEs: adjuvants, increased stability, combinations, needle-free formulations (oral, nasal, patches, jet injectors and so on)

In summary, the traditional vaccines that are stockpiled are facing challenges from new generation products. Yet vaccines must still be stockpiled while new products evolve and the challenges of new regulatory requirements are met. Older products do have a good outlook where potency can be improved, time to immunity, ease of delivery, increased shelf-life and so on.

The biodefence markets present opportunities for company growth – but companies do need to understand the markets properly to minimise risk.

Taking advantage of therapeutic switching: commercialisation in a world of generic substitution

Dr David Cavalla, Switch Pharma Group plc

(David Cavalla was indisposed and unable to present on the day – an abbreviated talk was given using his material by Tom Halliwell and Janette Thomas)

Despite ever increasing research spending and rapidly advancing new technology, the rate of new drug approvals is slowing (e.g. from 36 in 2004, to 20 in 2006). This provided the backdrop for this presentation, the opportunities to be realised from searching for new disease use for existing molecules – Therapeutic Switching.

Therapeutic Switch discovery is radically simpler than traditional work; much of the genetic, med chem and translational medicine exists – to do is preclinical biology, clinical development and regulatory work. Switch products make use of existing data packages, maintaining exclusivity for the molecule with new-use patients. Success rates are higher, development time is reduced.

There are opportunities for large Pharma: exploiting abandoned assets, increase value of marketed assets; for Biotech: accessing clinical stage candidate faster, with lower risk; for Generics: rapidity to market, lower risk.

The issues in Therapeutic Switching are: Prospecting, Progressing, Protecting.

Prospecting – there are different approaches:

- where a patented molecule is on the market (risk – new clinical findings damage primary market!)
- with an off-patent molecule (risk – generics competition)
- molecule not fully developed (tox risk, but low generics risk)
- stereoisomer of an existing molecule.

Ways to deal with these include:

- Genomics techniques to identify new uses
- Mass screening
- Clinical experimentation
- Leveraging existing knowledge

Progressing – we need to be clear about the portfolio of patents existing – do existing patents prevent development activities? What new data are required? Can a new use really be differentiated?

Protecting – can the new use obtain strong patent protection – in which territories? Are there other opportunities for patents?

In summary – Therapeutic switching can bring great productivity enhancements for companies. But procedures are fundamentally different from traditional NCE discovery.

The challenges and opportunities afforded by the EU Paediatric Legislation

Georg Mathis, Appletree

The status quo with regard to paediatric medicine is very much changing. Currently, half of the medicines used to treat children have not been tested in children. Off label use provide data, often much later than ideal – new, innovative products are denied to children.

A key issue is that children are not 'little adults'. Does extrapolation is impossible. There are differences in metabolism, excretion, water/fat ratios etc. There can be either insufficient effects or toxic effects, without proper investigation.

The EU has proposed categories for new, mandatory investigations: preterm, newborn, infant, children and adolescent. New regulations have come into place in the EU since Jan 2007, designed to further paediatric medicines development and ensure high quality, relevant research. Key features of legislation are:

- Paediatric Investigation Plans required, waived only for medicines unsuitable for children
- Establishment of Paediatric Regulatory committee
- EU inventory of therapeutic needs of children
- Establishment of network of investigators and centres
- Database of paediatric studies
- New EU paediatric logo to be used as addendum to brands

As a reward for the added cost of paediatric development, companies will receive an extended SPC/patent. This applies regardless of whether the paediatric use is finally approved. There is in addition 'PUMA', a new type of marketing authorisation for off-patent medicines, giving data and marketing protection of 8/10 years. The EMEA paediatric working party (PEG) has established a list of high-need indications, existing drugs for study and off-patent priorities.

There are consequences for the industry – it will impact project management and lifecycle management, with no reward if development fails. But it will enhance positive image and open potential new business models.

Appendix: Feedback from Table Exercise

Questions answered by groups of participants from organisations with products intended for licensing out

When you are developing a new product for licensing out, what do you think potential investors will be looking for?

Table 1

- Patent protection/patent strategy
- Patent family extensions
- ROI potential / sales growth
- Market share / future size
- Competitor environmental
- Scope for PLEs (within existing TA)
- PoC? Data package to support it?
- New therapeutic indications
- Good company 'fit'
- Initial indication: how strong is the data package – preclinical data / CMC process, efficiency
- Potential to globalise the product
- Can it be moved to OTC ultimately?
- Combination strategy
- oral vs injectable
- One a day vs. 3x etc
- Fixed dose combos – proprietary/generic
- Improve ease of use / compliance
- Potential for 2nd generation product
 - other interested parties?
 - Sole exclusivity?
- Safety profile – likelihood of emerging safety signals
- How 'clean' would the licensing deal be?

(Extra notes from Table 2)

- De-risked asset
- Clear, sorted (background/foreground) IP
- Good quality data about the assets
- Fit with acquiring company strategy
- does it have potential usp/differentiation?
- Good data integrity / proven due process
- Early deals
- Confidence in our team(s)
- Thoroughly established CMC etc

Some 'worst-practice' examples!

Taking an asset into a different/new market – after the decision, it was found that the data wasn't right – many more studies were required.

Communications/trust problems at top level between small and large pharma companies:

- project team level people on both sides could not get going / collaborate
- with major deadlines approaching, the project teams on either side were not empowered to resolve day to day problems

(Extra notes from Table 3)

- Early work on in-vivo pharmacology for potential indications

What has been worked through to maximise profits?

Table 2

- 'The product' – Where are we going?
- A label that best fits market environment
- TPP that fits the market environment

- 'The Plan' – development plan
- Time to best license
- Time to marketplace
- Costs to get to marketplace
- Timing the sequence of additional indications
- IP – patent life at launch
- CMC – CoGs are clear

- 'The potential market'
- What are we/what will be competing against
- Payers/physicians/PAGs needs and attitudes
- ideal partner strengths

(Extra notes from Table 3)

- Do it properly – makes it much more convincing package – less re-work to do.

What patent considerations have been made?

Table 3

- Small company has:
 - Greater risk
 - less choice
 - More focus
 - less resource

- Biologicals – Abs-epitopes / Formulation / Indication
- NCE – molecule / formulation

- Process vs use
- Glycosylation to increase life
- Review of competition – 18 months until apparent – freedom to operate unclear until then
- What is the attraction for the buyer?
- Breadth of patent cover
- Duration (remaining)
- Competition – others working in the same area
- Blocking strategy
- Patent busting strategy – large legal costs
- New strategies?
- Lack of consideration by the project team – may be considered an executive decision
- Territories – global strategy
 - marketability – small company, single territory
 - Formulations
 - Genetic predispositions
- Relative timings of patents in same family

- Early and broad is best
- Consider market needs – IP strategy should fit business model
- Ensure you have the best external advice

(Extra notes from Table 2)

- Does the patent cover the right areas?
- Is the data robust enough to patent?
- Strength of the patents?
- Freedom to operate?
- Timing, viz. Target launch time
- Comprehensive breadth of patenting – protecting what you might want to do in the future
- Potential for any patent extensions

Questions answered by groups of participants from organisations with products in the marketplace

How do we optimise the building of sales rapidly?

1. Regulatory approvals
 - 1.1. Prioritize:
 - a) market size
 - b) Ease of registration
 - 1.2. Quick as possible

2. Marketing > Business Development
 - 2.1. Market knowledge
 - 2.2. Market share
 - 2.3. Market penetration
 - 2.4. Sales and marketing investment
 - 2.5. Off label use
 - 2.6. Customer/market feedback
 - 2.7. License agreements
 - 2.8. Pricing
 - 2.9. Patient advocacy

3. Longer term planning
 - 3.1. Line extensions
 - 3.2. Formulations – convenience
 - 3.3. Optimise population – longer term administration
 - 3.4. New indications
 - 3.5. Patent
 - 3.6. LCSP
 - 3.7. Dose

How can we best maximise peak sales?

Markets

- Low hanging fruit
- Early dialogue with players
- Emerging markets
- IP
- Trademarks
- Market presence
- Supply chain
- Planning for differentiation claims

Populations/Indications

- Paediatric
- Outcomes studies

- Plan for QOL/health outcomes measures
- Geriatric
- Focus on diagnostics

Formulations

- Speed of action
- Adjunctive therapy
- Need for differentiation
- Thinking with the patients' needs in minds
- Focus on the strategy

- Internal expertise challenges
- co-promotion activities
- Order onto the market

- Partnerships/out-licensing

How can we best defend against patent expiry?

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- Strong IP
 - Non-obvious
 - IP strategy
 - Patent thicket
- Regulatory strategy
 - Data exclusivity (Hatch-Waxman)
- Orphan status
- Biologics
- New indication
 - Follow on- transfer patients
- Fixed combination/product kits
- New formulation – build IP
- Paediatric extension (6m/2yr)
- CMC – tighten specs
- Brand loyalty
- Legal challenge – citizens petition (US)
- Authorised generic
- Team continuity
 - 'seamed'/seamless