GABA California
German American Business Association

LIFE SCIENCES **MARCH 2006 SPECIAL EDITION**

Sheer Facts

GABA'S NEWSLETTER FOR THE LIFE SCIENCES COMMUNITY

ABOUT GABA

BECOME A MEMBER

EVENT CALENDAR

CONTACT US

DECISION MAKING CRITERIA IN EARLY DRUG DEVELOPMENT

HIGHLIGHTS FROM THE PANEL DISCUSSION AT KIRKPATRICK & LOCKHARDT, SAN FRANCISCO

The goal of the panel discussion was to highlight challenges of early drug development and to share approaches to overcome them.

PRESENTER AND PANELISTS:

from far right:
Juan A. Leal, PhD, Senior Director Translational Medicine, Exelixis Inc

Arndt Schottelius, PhD., Director Immunology Non-clinical Drug Development, Genentech

MODERATORS:

Bahija Jallal, PhD., Vice President, Translational Sciences, Chiron

Sanuj Ravindran, MD, Director, Burrill & Company

Ulrike Ruppelt, Ticular – Market Access, and Chair GABA Life Sciences

Heike Abeck, Chiron and Co-Chair GABA Life Sciences

BACKGROUND:

Genentech South San Francisco, world's second largest Biotech firm, >10,000 employees, Sales $6.6 billion, 25 drugs in clinical trials or awaiting FDA approval and 4 in Pre-IND stage.

Chiron Emeryville, top biotech firm - soon to be Novartis, 5,400 employees, Sales $1.7 billion, 13 drugs in clinical trials or awaiting FDA approval, 1 in pre-clinical stage.

Exelixis, South San Francisco, 517 employees, Sales $76.0 mil, 8 drugs in clinical trials, 6 in pre-clinical stage

Burrill & Company is a life sciences merchant bank focused exclusively on companies involved in biotechnology, pharmaceuticals, diagnostics, devices, human healthcare and related medical technologies, nutraceuticals and wellness, agricultural biotechnology, and industrial biotechnology (biomaterials/bioprocesses).

THE CHALLENGE:

With more and more targets and drug candidates available, it is becoming increasingly challenging to make the right decisions about which drugs to take into full development. To overcome these challenges, more emphasis is being put on the early stages of drug development to establish signs of efficacy earlier and make better-informed go-/ no go decisions. One of the main challenges is the effective translation of preclinical studies in animals into the design of clinical studies in patients.

Arndt Schottelius gave the introductory presentation and offered insights into decision-making in early drug development.

PHARMACEUTICAL COMPANIES' R&D SPENDING IS INCREASING, BUT RESEARCH PRODUCTIVITY IS NOT (1983-2003*)

- R&D Spending peaked 2003 at $33 billion
- Estimated cost for a new drug development increased by $95 mil from 2001 to 2003 to $897 mil whereas the number of new drug applications has plummeted from 343 in the early 80ties to 127 in 2003
- Main driver for cost increase thought to be clinical trial cost.
- A 2001 study showed the price for pre-clinical trial per drug at $121 mil out of pocket plus Cost of Capital $336 mil

To enhance the research productivity decision makers need to carefully consider if the drug candidate can be used for more than one indication. This could lead to a drug for the use in several markets and thus multiply the return on invests for the drug development.

Source: PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2004/2005, pages 1 and 188
*2003 Pharmaceutical R&D spending estimate; Number of NDAs pending is not available

DRUG DEVELOPMENT CYCLE TIME

The drug development cycle times vary widely per pharmaceutical company. A statistic illustrates how much time pharmaceutical companies need in average to develop a new compound from research to the filing of an IND approval (FDA approval of an investigational new drug).
It shows that the fastest company only needs 4.6 years and therefore is 4.3 years faster than the slowest company who needs 8.9 years.

A comparison between biopharmaceuticals and conventional drugs shows that the development time for biopharmaceuticals is 3.5 years shorter than for chemical drugs – probably because the toxicity of chemical drugs is higher and it takes more time to proof that the compound is safe for humans.
Source: PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2004/2005

The goal is to achieve a time to market average of 8 years for biopharmaceutical and chemical drugs

R&D Productivity Parameters

Quantity - Quality - Value
Quantity stands for Cycle time and number of target indications;
Quality stands for attrition rates to be expected and Value for Return on Invest

WHAT IMPACTS THE SPEED OF THE CYCLE TIME?

Basically every stage of drug development: Idea –Leads – Development Candidates – Clinical Testing Phases to Product has an impact. Each of these stages has a number of challenges: *Idea and lead phase*: How to increase the rate of quality targets of currently 25% and valuable distinctive chemotypes of currently only 2 or 3 types?

Lead optimization: How to find more oral compounds for easier administration and how to improve the predictability of animal models for the disease?

Development Candidates: Hurdles to overcome in this phase are selectivity, safety, drug distribution; delivery & pharmacokinetics and predictivity of toxicology models.

Clinical phases are challenged by clinical safety and drug delivery formulations and it might turn out that metabolic and distributional characteristics are unsatisfactory.

Usual Success Rates:

The Reality is that only 1 out of 100 research projects results in a successful product.

THE CRUCIAL QUESTION: WHAT CAN BE DONE TO ACCELERATE THE CYCLE TIME?

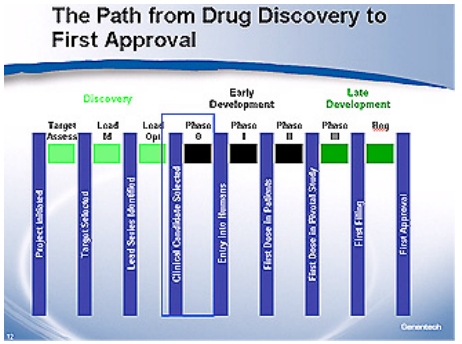
Building on each other the key steps are:

- Research (the right targets and molecules)
- Diagnostics (the right patients)
- PD/Bio (the right markers)
- AAT/BARD/BA (the right analytics)
- PKPD, SA (the right studies, analyses, and interpretations)

These steps are the prerequisite to the right molecule, dose route, regimen and trial design.

At Genentech diagnostics is introduced early on in drug research. With predictive specific biomarkers Genentech tries to make sure to deliver these drugs to the right patients.

Early Drug Development spans various stages and has several definitions in literature. At Genentech it reaches from Lead Optimization to Late Development starting with Phase III of Clinical Trials



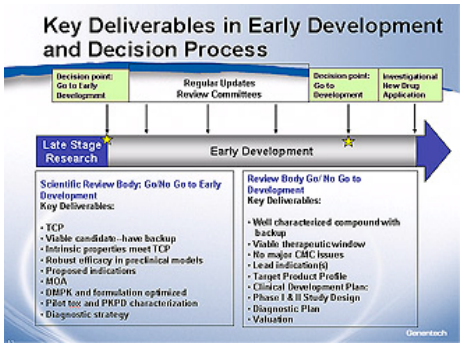
DECISION MILESTONES AT GENENTECH

The first decision milestone occurs at the late stage research phase.
The Scientific Review Body decides if certain criteria are met.

- Does a TCP exist? The Target Candidate Profile TCP is a precursor to the target product profile. It incorporates epidemiology data, market assessments, medical needs information etc.
- The intrinsic properties of the new compound should meet the TCP.
- The viable drug candidate should come with a back up especially if it is a small molecule drug candidate.
- Taking into account that the predictivity of clinical models for the actual disease is limited one should have at least two clinical models that show good efficacy.

- A drug candidate can treat potentially more than one indication – but what are the most promising and therefore porposed indications?
- What are the Mechanisms of Action MOA? Are there insights into the real works of the molecule? However, it is accepted that MOA data are not always obtainable.
- DMPK - Distribution, Metabolism, Pharmacokinetics and Formulation – are they known and optimized?
- Has a pilot tox been conducted and is the Pharmacokinetic and -dynamic PKPD characterized?
- Has the diagnostic strategy been decided - when to use which biomarkers?

The Scientific Review Body committees are updated on a regular basis about the progress of the development. They make sure that the development is on track.



REVIEW BODY: GO - NO GO TO DEVELOPMENT

Before the drug candidate is taken into the clinical Phase I it has to undergo another rigorous review. From here on the drug development begins to be really costly – GOP toxicology studies can easily amount to $1 million – $1 ½ million or the FDA / GMP manufacturing of the material for putting the compound into humans can cost $2-3 million.

KEY DELIVERABLES FOR GO-NO GO DECISION:

- Well characterized compound with backup
- Viable therapeutic window
- No major Chemistry Manufacturing Control CMC issues
- Lead indication(s)
- Target Product Profile
- Clinical Development Plan:
  - Phase I & II Study Design
  - Diagnostic Plan
- Valuation – Probable Peak Sales – Market Success

FINAL GO – NO GO DECISION

Beyond core factors there are other factors that influence a GO/NO GO decision to development–

- is it a good fit for
  - the overall company strategy
  - the existing drug pipeline or franchises,
- is it better than the standard of care,
- is there a meaningful, approvable experiment to test the hypothesis (to hit Target Product Profile),
- does it have a strong scientific rationale,
- is there a significant unmet medical need,
- is it commercially viable?

The decision to full development can be enabled by selecting the indication, establishing a target product profile, conducting market research and analysis of the internal and external competition, creating a clinical development plan, timelines, costs, peak revenues and net present value for a program.

WHAT ARE LIMITING FACTORS FOR THE SUCCESS RATE OF DRUG DEVELOPMENT?

Arndt: The pharmakokinetic/pharmacodynamic characteristics, target selectivity and the safety profile of a compound often limit its success in drug development.

HOW DO YOU DECIDE TO FUND?

Sanuij: We look at the exit point – like 5 years from now and how much money we are likely to spend up to this milestone. We match our funding to the market potential of the drug – depending on how many patients have the disease to be treated by the envisioned drug; how much can be charged for it and the revenue to be expected. We compare this with the cost of the development and the risk involved.
Preclinical development is riskier than late stage development because the drug candidate can fail to pass several approvals.

We are expecting ten times our investment as return on invest when investing in preclinical development. When we fund later stage development – for example from phase III on – we expect three times our investment as ROI.

DOES BIG PHARMA ONLY STRIVE FOR BLOCKBUSTER PRODUCTS?

Arndt: Genentech believes that the science should be the strongest driver in drug development. The company invests into diagnostics that enable the identification of those patients that respond well to a drug or do not respond. And Genentech believes that if a drug candidate is extremely effective in a sub-population of patients that it is worthwhile to develop the drug even though the initial commercial value seems to be decreased by the smaller market segment. Further down the road this smaller market segment might be served so well that the increased market penetration makes up for the smaller patient population. The driving force is here not the blockbuster to be expected but the benefit for the patient.

Bahija: Gleevec is a good example for a drug that initially seemed to serve a market segment that was too small to be profitable- a patient population with the rare cancer Chronic Myeloid Leukemia CML.

If it hadn't been for one MD who pushed it, Novartis wouldn't have developed it any further. And now it is the number one blockbuster for Novartis. The trend is that companies recognize this may not be an issue anymore, since we understand more about drug mechanism and potential patient population.

HOW IMPORTANT IS STRUCTURAL BIOLOGY IN THE EARLY DECISION POINTS?

Bahija: At Chiron we won't start a program without the knowledge of the biological structures. For the optimization of the molecule, having the crystal structure is extremely helpful.

Juan: We are learning to know nowadays in oncology why drug resistance is acquired. The drug fits in one specific pocket and when the target molecule changes its structure the drug won't be effective anymore
That is why existing drugs are failing.

HOW DO YOU FIND A NEW INDICATION FOR AN EXISTENT DRUG?

Bahija: Based on expression profile, mechanism and clinical data, new indications may emerge.

Sanuj: It can happen that a drug shows interesting side effects while in clinical trials. For example it happened that patients started growing hair. That led to a hair-growing agent.

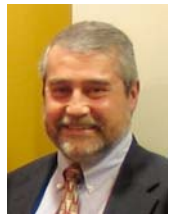
Juan: I think Viagra was discovered in that way – the drug was originally meant for heart disease and showed some strange side effects.

Arndt: Rituxan is a good example that a new indication can be found through an investigator-sponsored trial. Originally explored for NHL-Non-Hodgkin Lymphoma it then showed exceptional results of improving rheumatoid arthritis. As part of the life cycle management for a marketed drug the project team constantly thinks about possible new indications based on the science behind the product and the medical need in a disease.

WHAT MODELS ARE USED IN PRECLINICAL TESTING?

Arndt: At Genentech we have a model for every indication we pursue. We do rigorous testing and compare the data with results from clinical studies. We have a database that facilitates the correlation. You want to compare the pathophysiology of the model with the pathophysiology of the disease. As a second step we employ a panel of models because we know that some models are not fully predictive for a certain disease.

Juan: There is a high correlation between a weak animal model and drug failure as shown in oncology and central nervous diseases drug development. Transgenic mice provide a good animal model but it really hurts the oncology research to have to pay the high fees to license the use of the patented transgenic mice.



ISN'T IT CHEAPER TO FIND NEW INDICATIONS FOR A DRUG THAT HAS BEEN ALREADY APPROVED?

Arndt: Interestingly enough it is not necessarily so. Again – Rituxan is a good example – it had already been tested in thousands of patients, but additional safety testing was still required for the new indication.

Bahija: In the case of Rituxan the use of the drug has been expanded from oncology to Rheumatoid Arthritis RA. The tox studies required are different from oncology, since RA is a more chronic disease that requires long term treatment. If the indication would have been for cancer as well - the existing tests had sufficed.

FOR THE ALLOCATION OF LIMITED RESEARCH FUNDS: DO YOU USE PORTFOLIO MANAGEMENT?

Arndt: Again, it is the science that drives our decision-making. If the science is solid and the molecule has good efficacy with little side effects then this is a good measure for funding.

Juan: In oncology the funding should be based on the knowledge of the tumor – the biology – and the evidence of a definite endpoint of the drug development – the practicality.
For example, prostate cancer endpoints are very unclear. It could mean 20 years of investigation into the drug – that is why not many firms choose prostate cancer as a target indication.

ARE THERE ANIMAL MODELS FOR ONCOLOGY AND CNS DISEASES?

Juan: It depends on asking the right questions when you work with an animal model. If you grow human prostate cancer cells on the back of a mouse and then test your drug, you do not heal the prostrate cancer of the mouse. But when we see that the receptor in the tumor is inhibited; when we see the intracellular changes we expect to see, when the pathway is related to the target then it was a good animal model.

WHAT IS TRANSLATIONAL MEDICINE?

Bahija: Everything we have touched so far. Translational medicine forms a bridge between preclinical and clinical development and facilitate a bidirectional use of data.