From Marine Expeditions to New Drugs in Oncology
26 June, 2007

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A Biopharmaceutical Company

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PharmaMar & Zeltia

- Founded 1986
- Wholly owned by Zeltia Group (Market Cap €1.2 Bn)
- Over 270 employees
- Headquarters Madrid (Spain)
- Pre-clinical Cambridge, MA (US)

“To advance Cancer Care through the discovery and development of new marine derived drugs”

PharmaMar Business Model

- Marine Expeditions
- Preclinical Testing
- Medicinal Chemistry
- Clinical Trials
- Production
- IP & Trademarks
- Marketing & BDL

Build a Library
New chemical scaffolds & New MoAs
Synthesis of identified NCEs
Activity improvement
International clinical dev. in Europe, US & Canada
Keep last steps of purification or synthesis
Keep EU rights
License US & RoW
Generate profits

Generate profits
### PharmaMar: Facts & Figures

- **Bio-pharmaceutical company** (20 years; Investment € 400 M)
- **Unique library** (> 42,000 marine samples)
- **Broad network of collaborations** (> 50 international centers)
- **Over 110 inventions** (660 patents granted; 700 on prosecution)
- **Five compounds from marine sources in clinical development.**

### Goals

- **Launch Yondelis®** in STS in 2007 and in Ovarian by 2008/09
- **Increase pipeline:** one new compound in the clinic every 24 months
- **New strategic alliances** for drug development & commercialization
- **Become a profitable biopharmaceutical company.**

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### BioDiversity: The Business Case

**PharmaMar**
A Biopharmaceutical Company

**BioDiversity: The Business Case**
The Current Research Environment

**Value Creation: The R&D Process**
From BioDiversity to Final Product
BioDiversity: Strong Track Record as Drugs

> 60% of the 877 new chemical entities that reached the market over the last 20 years have origins in nature *

Advantages | Difficulties
--- | ---
Structural Diversity | Sourcing (political hurdles)
Potency (inherent activity) | Legal uncertainty (patents)
*Evolution* against challenges | Scientific (isolation, synthesis.)

Successes in Cancer

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
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</table>
| Paclitaxel (TAXOL) | Roots of bush *Taxus brevifolia*
| Irinotecan (CAMPTOSAR) | Leaf of plant *Camptotheca acuminata*
| Etoposido (VEPESID) | Roots of plant *Podophyllum peltatum*
| Doxorubicina (ADRIAMICINA) | Bacterium *Streptomyces peucetius*

* DJ Newman et al. 2003, Journal of Natural Products 66, 1022-1067
Advantages of Marine Biodiversity

- Sea has higher biodiversity than land
- High Biodiversity = High chemical diversity

**Opportunity:** Marine exploration for pharmaceutical purposes < 20 years old.

- 0.01% of terrestrial samples show anti-tumor potential vs 1% of marine samples*

* US National Cancer Institute (NCI) Estimates

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Value Creation: The R&D Process

PharmaMar
A Biopharmaceutical Company

**BioDiversity: The Business Case**
The Current Research Environment

**Value Creation: The R&D Process**
From BioDiversity to Final Product
The R&D Process: Value Creation

Deliverables

- Natural Product Library
- Bioactive Molecule
- Drug-like Molecule
- Oncology Medicine

Activities

- Worldwide Expeditions
- Drug Discovery
- Lead Optimisation
- Clinical Development

Value Creation

Expeditions (Access & Benefit Sharing)

Macro-Organisms (mainly invertebrates)
Taxonomic classification, limited material, no control of metabolites present.

Micro-Organisms
Associated with macros, possible to change metabolites, potential for fermentation

Environmental DNA
Obtained from non-cultivable organisms

<table>
<thead>
<tr>
<th>Monetary Benefits</th>
<th>Non-Monetary Benefits</th>
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<tr>
<td>Access Fees, Fee per sample</td>
<td>Sharing of Research results</td>
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<td>Milestone payments</td>
<td>Collaboration in Education &amp; Training</td>
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<td>Royalties &amp; Licensing Fees</td>
<td>Collaborative R&amp;D Projects</td>
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<tr>
<td>Special Fees to support conservation &amp; sustainable use of biodiversity</td>
<td>Transfer of technology &amp; expertise for conservation or study of biological resources</td>
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<tr>
<td>Research funding for local initiatives</td>
<td>Resources to protect biodiversity</td>
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<tr>
<td>Joint ventures</td>
<td>Joint ownership of intellectual property</td>
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</tbody>
</table>

Non-Monetary Benefits

- Joint ownership of intellectual property
- Collaboration in Education & Training
- Transfer of technology & expertise for conservation or study of biological resources
- Resources to protect biodiversity
- Sharing of Research results
- Special Fees to support conservation & sustainable use of biodiversity
- Collaborative R&D Projects
Drug Discovery

BioDiversity
- Macro-Organisms
- Micro-Organisms
- Environmental DNA

Drug Discovery
- Extraction & Bio-Assay
- Guided Purification

Supply
- Bioactive molecules < $10^{-6}$ % wet weight of marine organisms!
- Synthesis, Fermentation, Biotechnology

Bioactive Molecule
- Chemical structure
- In Vitro Activity
- Intellectual property
- Small Quantity

Lead Optimisation

Bioactive Molecule
- Defined chemical structure
- In Vitro Activity
- Intellectual property evaluation
- Small Quantity

Lead Optimization *
- Metabolic Stability
- Safety
- Drug-drug PK
- Toxicity
- Solubility
- Selectivity
- Absorption
- MoA 1
- MoA 2

Drug-like Molecule
- Potential to reach the Site-of-Action in Man, at the required concentration, for the necessary duration & with an adequate safety window

Structural Modification (analogs)
- Drug Delivery Technologies
- Dose, Frequency & Route of Administration

* Fundamental to minimize risk of downstream failure.
Clinical Development

Clinical Development & Regulatory Approval

Drug-like Molecule

Oncology Medicine

Ready for Clinical Trials

Phase I, Safety, Dose, Pharmacokinetics
Phase II, Efficacy, Tumour Type
Phase III, Large-scale, Comparative studies

Demonstrated Quality, Safety & Efficacy

The Drug Development Process

BioDiversity

Bioactive Molecule

Drug-like Molecule

Oncology Medicine

Discovery

Pre-clinical

R&D (2-10 years)

3.4 years

9.6 years

CLINICAL STUDIES & APPROVAL

MARKET

11 years

Paclitaxel (TAXOL): > 20 years from Structural Determination (Bioactive molecule) to FDA approval

Cost ~ $ 802 mill.*

Only 2 in 5 Marketed Drugs recover costs

* Di Massi 2003

10000

100

5 Failures

1

Sales

Di Massi 2003

16
New Medicines from BioDiversity

- "Orphan Drug" for Soft Tissue Sarcoma & Ovarian Cancer
- More than 3500 patients treated
- Novel MOA; Manageable toxicity
- Ovary, Breast, Prostate Cancers (plus paediatric & combination).
- Licenced to Johnson & Johnson outside EU
- Dossier submitted (July, 2006) to the European EMEA for STS Registration

Conclusions

BioDiversity offers enormous potential for discovery and yields very interesting, highly potent BioActive Molecules.

Conversion of BioActive Molecules to Medicines requires a long-term commitment (10-15 years), significant financial (800 M $) & human resources & expertise (multi-disciplinary). Success is not guaranteed.

Without research investment, there will be no benefits or commercial rewards to share.

Legal certainty is required to protect research investment.

Access and Benefit-Sharing are equally important if benefits of nature to be shared by all.
Thank You

www.pharmamar.com

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