Development of a Generic Agrochemical

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Presentation Coverage

- Global market for agrochemicals
- Why are generics so important to multinational companies?
- Getting a generic to market
Definitions

- **Generic** - an active ingredient that is off-patent in most of its major markets
- **Marketing companies** - strong in the development of ‘me-too’ products for a national or regional market
Global Sales of Conventional Agrochemicals (excluding ag-biotech) at Distributor Level ($bn)
Agrochemical Industry Restructuring

- mergers
- acquisitions
- alliances
- product line rationalisation
- marketing and distribution deals
- R&D collaborations
## Sales of top six in 2002

<table>
<thead>
<tr>
<th>Company</th>
<th>Crop Protection Sales ($m)</th>
<th>Market Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syngenta</td>
<td>5,240</td>
<td>21</td>
</tr>
<tr>
<td>Bayer</td>
<td>4,280</td>
<td>17</td>
</tr>
<tr>
<td>Monsanto</td>
<td>2,700</td>
<td>11</td>
</tr>
<tr>
<td>BASF</td>
<td>2,600</td>
<td>10</td>
</tr>
<tr>
<td>Dow</td>
<td>2,550</td>
<td>10</td>
</tr>
<tr>
<td>DuPont</td>
<td>1,800</td>
<td>7</td>
</tr>
</tbody>
</table>
Generic/Marketing Companies

- Major generic companies with significant global presence, include: Makhteshim-Agan, Nufarm, Cheminova
- Small generic manufacturers (ca. 300)
- Marketing companies (> 1,000)
Product Range Rationalisation

- forced by anti-trust commissions
- internal strategic rationalisation
Acquisition of Aventis by Bayer

- global fipronil business (sold to BASF)
- global acetamiprid business or, if this cannot be achieved, the thiacloprid neonicotionid insecticide
- tribufos business, (sold to Amvac)
- flucarbazone wheat herbicide business in the US to an FTC-approved buyer or, if this cannot be achieved, the production plants for flucarbazone and propoxycarbazone
- European rights to: cypermethrin, ethiprole, phosalone, acrinathrin, cyfluthrin, beta-cyfluthrin, fenamiphos, oxydemeton-methyl, linuron, metamitron, iprodione, prochloraz, pyrimethanil, triticonazole and fluquinconazole
- European licences for thiodicarb and to develop combination products with propoxycarbazone
Syngenta Divestments

- In 2000, combined number of active ingredients = 121
- By end of 2002, reduced to 89
- Target is to reduce this to just 76 by 2005
- Phasing out/divestment of these less profitable brands across the product range is likely to reduce sales by approximately $220 million
- 3,000 jobs from a total work force of 20,000 and 12 plant closures
Why Are Generics So Important To Multinational Companies?

- Decline in New Chemical Entities (NCEs)
- Increasing R&D costs
- Future generic products
Decline in Agrochemical New Chemical Entities (NCEs)

The number of active ingredients receiving ISO (International Standards Organisation) common names indicates the decline in NCEs.

* Data only available for half year.
R&D Costs

- **R&D costs** for the agrochemical industry typically **9-12%** of revenue
- Not far behind pharmaceutical industry’s **14-16%**
- Combinatorial chemistry and high throughput screening
- Significant increase in candidate molecules being screened
Recent US Fast-track Approvals

- fludioxonil
- azoxystrobin
- mefenoxam
- S-metolachlor
- cyprodinil
- pymetrozine
- mesotrione
- thiamethoxam
# Future Generics

<table>
<thead>
<tr>
<th>Company</th>
<th>% Sales Subject to Patent Expiry in Next 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer (incl. Aventis)</td>
<td>22</td>
</tr>
<tr>
<td>BASF</td>
<td>18</td>
</tr>
<tr>
<td>DuPont</td>
<td>14</td>
</tr>
<tr>
<td>Syngenta</td>
<td>12</td>
</tr>
<tr>
<td>Dow</td>
<td>5</td>
</tr>
<tr>
<td>Monsanto</td>
<td>0</td>
</tr>
</tbody>
</table>
## Syngenta’s “New” Future Generics

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand Name</th>
<th>Activity</th>
<th>Sales ($m)</th>
<th>Approx. Patent Expiry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tralkoxydim</td>
<td>Grasp</td>
<td>Selective herbicide</td>
<td>65</td>
<td>2002</td>
</tr>
<tr>
<td>Tefluthrin</td>
<td>Force</td>
<td>Insecticide</td>
<td>80</td>
<td>2004</td>
</tr>
<tr>
<td>Primisulfuron</td>
<td>Beacon</td>
<td>Selective herbicide</td>
<td>120</td>
<td>2004</td>
</tr>
<tr>
<td>Cyproconazole</td>
<td>Alto</td>
<td>Fungicide</td>
<td>60</td>
<td>2004</td>
</tr>
<tr>
<td>Flauzinam</td>
<td>Omega</td>
<td>Fungicide</td>
<td>70</td>
<td>2004</td>
</tr>
<tr>
<td>Difenconazole</td>
<td>Score</td>
<td>Fungicide</td>
<td>60</td>
<td>2005</td>
</tr>
<tr>
<td>Lufenuron</td>
<td>Match</td>
<td>Insecticide</td>
<td>40</td>
<td>2007</td>
</tr>
<tr>
<td>Clodinafop</td>
<td>Topik</td>
<td>Selective herbicide</td>
<td>140</td>
<td>2007</td>
</tr>
</tbody>
</table>
Getting a Generic to Market ...

.... or ‘how to walk through a minefield without being blown up’
## New Generic Agrochemicals Post 2002

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>bensulfuron-methyl</td>
<td>flusilazole</td>
</tr>
<tr>
<td>clethodim</td>
<td>imazaquin</td>
</tr>
<tr>
<td>clodinafop-propargyl</td>
<td>imazethapyr</td>
</tr>
<tr>
<td>clomazone</td>
<td>imidacloprid</td>
</tr>
<tr>
<td>cyproconazole</td>
<td>kresoxim-methyl</td>
</tr>
<tr>
<td>cyprodinil</td>
<td>mefenacet</td>
</tr>
<tr>
<td>difenoconazole</td>
<td>nicosulfuron</td>
</tr>
<tr>
<td>diflufenican</td>
<td>primisulfuron-methyl</td>
</tr>
<tr>
<td>dimethenamid</td>
<td>sulcotrione</td>
</tr>
<tr>
<td>epoxiconazole</td>
<td>thifensulfuron-methyl</td>
</tr>
<tr>
<td>fipronil</td>
<td>tebuconazole</td>
</tr>
<tr>
<td>fluazinam</td>
<td>tralkoxydim</td>
</tr>
<tr>
<td>fludioxonil</td>
<td>tribenuron-methyl</td>
</tr>
</tbody>
</table>
How to Choose the Right Generic to Develop

- Market potential
- Synthesis/technology/manufacturing issues
- Intellectual Property Rights (IPR) status
- Registrations issues
- Economics
Market / Competition
Patents (SPCs)
Process Chemistry
Impurity Profile
Protected Data
Toxicology Data
Field Trials
Environmental Data
Environment
Market / Competition

Impurity Profile

Protected Data

Toxicology Data

Environmental Data

Field Trials

Generic Manufacturer

Process Chemistry

Patents (SPCs)
Market Potential

- Straight or mixtures
- Market price
- Competition from other products
- Geographic spread
- Market Segmentation
Market Segmentation

- Mixture products
- Branded products
- Extended branded products
- Distributor deals
What is the available market?

For example: the UK tebuconazole market

- Tebuconazole was protected by EP 0040345, expired 01.05.2001 but extended by SPC until 01.06.2003
- 35 registrations in total by 6 companies
- 25 mixture products, 10 straight products
UK Tebuconazole Registrations

- Co-mixture a.is. - carbendazim, fenpropidin, imidacloprid, prochloraz, propiconazole, spiroxamine triadimenol, triazoxide.
- Triazoxide, triadimenol, imidacloprid and spiroxamine are Bayer products and not available to generic manufacturers from other sources or are still covered by patents.
- Propiconazole and fenpropidin are Syngenta products and unavailable from other sources.
- Thus only mixture products with carbendazim and prochloraz are possible.
- Of the ten straight tebuconazole registrations, six are registered under Bayer’s name.
- The remaining four Barclay Chemicals, Clayton Plant Protection, ME2 Crop Protection Ltd. and Standon Chemicals Ltd. are parallel imports or the tebuconazole used in these products is supplied by Bayer.
Manufacturing Aspects

- Manufacturing process – easy or difficult?
- IPR – process patents etc
- Intermediates – available or restricted?
- Synthetic pathway – same as originator?
- Know-how
Patents (IPR)

- Active ingredient – patent term extensions
- Novel formulations
- Synergistic mixtures of active ingredients
- Methods of manufacture
- Key intermediates
- Resolution of racemic mixture to the optically active isomer
Patent Term Extension

- Hatch-Waxman
- SPCs
- “Data (field trials) for registrations”
Hatch-Waxman

- 5 year period of data exclusivity for innovator products
- Patent term extensions for the active ingredient if the date of first marketing of the drug was delayed as a result of the regulatory review
- Abbreviated New Drug Application (ANDA)
- 180 days of marketing exclusivity for the first generic
Supplementary Protection Certificates

- European patents post 1\textsuperscript{st} January 1985
- Initially for pharmaceuticals, then extended to plant protection products
- SPC is for a product from within a patent and grants a maximum term of exclusivity of 15 years from first market approval in a European member state
Registration Data and IPR Issues

- Field trials during the life of a patent deemed to be infringement
- Field trials during the life of an SPC anticipated to be infringement
Patent Term Time-line For Pharmaceuticals And Agrochemicals

- **AGROCHEMICALS**
  - Date of filing of patent
  - 20 years standard patent term
  - 2 years - time taken to generate registration data (field trials)
  - Patent Term Extension Supplementary Protection Certificate (SPC)/Hatch Waxman
  - 6 months
  - Market entry for generic agrochemicals

- **PHARMACEUTICALS**
  - Exclusive US market entry for 1st generic pharmaceutical
  - US market entry for other generic pharmaceuticals
  - 25 years standard patent term

0 - 27 YEARS
Registration and Data Protection Issues - Timescales

- List 1
  - 90 products being reviewed
  - 34 to be completed by 2005

- List 2
  - 148 products supported
  - Review complete by 2005

- List 3
  - 197 products supported
  - Review complete by 2008
Registration and Data Protection Issues

- Pre-Annex 1 listing
  - prove product comparability
  - field trials
Registration and Data Protection Issues

Post-Annex 1 listing

- negotiate for animal tox data under data protection
- negotiate for eco-tox data under data protection
- generate own eco-tox data under data protection
- develop own product once Annex II data loses protection
Registration barriers to market entry for generics

- Lack of transparency
- Time factors
- No system for data compensation
- Inconsistencies in requirements at country level
- Cost of data
Lack of transparency

- AS product profiles confidential to the registration authorities
- Advanced Analytical techniques result in more complicated profiles than submitted by originator
- Process methods not declared in detail except for hazardous impurities, product profiles can differ from those registered
- Interpretation of recipes inconsistent and sometimes inaccurate
Time factor

- Post Annex 1 listing the monograph list is often inaccurate.
  - Takes time to check out and establish true list at member state level.
- Some studies take 2 years to generate, revocation can occur before data list and new data is complete.
- Requirements escalate year on year.
Data compensation

- USA - data compensation exists with an arbitration system, no EU equivalent

- Directive 92/32/EEC and 86/609/EEC requires that animal toxicology data is not duplicated

- No such Directive for eco-tox studies
Cost of getting a generic product to market – pre Annex 1

- Simplest data package and registration fees for 2 /3 countries will cost Euros 80,000 to 100,000
- Field trial data may be required – additional cost Euros 150,000 to 250,000
- Market research costs
- Process development costs
- Registration consultancy and fees
Cost of getting a generic product to market – post Annex 1

- Data compensation for protected animal tox data
- Data compensation for protected eco-tox data
- Generate own eco-tox data
- Risk assessment and modelling
Summary

- Maturing agrochemical market, agrochemical innovation declining, GM innovation increasing
- A greater percentage of the market is open to generic competition
- Major consolidation has occurred
- Large % of sales by multinationals are off patent products
- Recent IPR changes have assisted R&D sector
Summary

- Registrations increasingly more complicated and costly – favours R&D sector
- Registration of agrochemicals is more complicated in the EU than in the US
- Registration of agrochemicals in the US is harder than registration of pharmaceuticals
- Rewards for generic pharmaceuticals is much greater than that of generic agrochemicals
- Fragmented generic segment with little influence on legal and registration framework
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