Development of new pharmaceuticals in the Netherlands

Dr. Peter J.A. Bertens
Me and today’s story

• Nefarma

• Development of a new medicine

• Technological trends

• Business trends

• The (bio)pharmaceutical industry in NL
Where do I work...? Nefarma

• Represents (bio)pharmaceutical companies, which are devoted to inventing innovative medicines that allow patients to live longer, healthier and more productive lives

• Industry association with 37 members

• Need to spend at least 8% of their turn-over on R&D
Tasks of Nefarma

- advocacy (government, parliament)
- deal making
- sector and individual member support

Main advocacy subjects:
- fast market access for novel therapeutics
- obtaining a fair price
- recognition of the importance of innovation
- good business climate
- good R&D climate
The association

17 colleagues working in different fields:

- health economy
- pharmaceutical affairs
- medical affairs
- legal affairs
- communications
- innovation and life sciences
What is innovation?

Innovation: finding new and better solutions for medical problems

- New: not previously treatable
- Better, less side effects
A lengthy and costly gamble
Development in phases

Drug Discovery
- Preclinical: 3–6 years
  - ~5,000–10,000 compounds
  - 250

Clinical Trials
- Phase 1: 6–7 years
  - Number of Volunteers: 20–100
- Phase 2: 6–7 years
  - Number of Volunteers: 100–500
- Phase 3: 6–7 years
  - Number of Volunteers: 1,000–5,000

FDA Review
- NDA Submitted: 0.5–2 years
  - One FDA-Approved Drug

Scale-Up to Mfg.
- Post-Marketing Surveillance

Production

Lab scale production (mg scale) → Pilot scale production (gram scale) → Process scale production (100g - Kg scale)

R & D, initial product characterisation → Pre-clinical/clinical trials → Commercial product
Packaging
And distribution
Life cycle of an innovative medicine

**Fig. 22.4**
Typical cash flow for a marketed drug. (Based on Grabowski et al., 2002.)
The cost of innovation

Allocation of R&D Investments by Function (%)

- **Pre-human/Pre-clinical**: 27.3%
- **Phase I**: 7.4%
- **Phase II**: 13.1%
- **Phase III**: 28.5%
- **Approval**: 5.1%
- **Pharmacovigilance (Phase IV)**: 13.4%
- **Uncategorized**: 5.2%

Clinical trials

Source: PhRMA, Annual Membership Survey 2009 (percentages calculated from 2007 data)
Commercial success is not guaranteed

Total sales vs. average R&D costs

New Rx Drugs Introduced Between 1990 and 1994, Grouped by Tenths, by Lifetime Sales

Note: Drug development costs represent after-tax out-of-pocket costs in 2000 dollars for drugs introduced from 1990–94. The same analysis found that the total cost of developing a new drug was $1.3 billion in 2006. Average R&D Costs include the cost of the approved medicines as well as those that fail to reach approval.

A world that changes - new trends

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**From**

- Chemistry
- On Size fits all drugs
- Aging (just happens)
- Therapeutics/diagnostics/devices
- Treating sickness
- Food for survival

**To**

- Biochemistry
- Personalized medicine
- Aging is optional / controllable
- "Theranostics"
- Preventing Sickness
- Food for health
140 yrs of technological developments
The emergence of biotechnology

- New scientific knowledge (DNA, diseases)
- New technological possibilities (RT screening, bioinformatics)
- Lead to rising of drug targets from 500 to >5,000
- New products
  - Hormones / growth factors
  - Antibodies
  - Fusion proteins
- Lead to formation of special biotechnology companies
  - Characterized by specialization and focus
  - Tool companies at interface of academic and commercial research
  - Others develop novel medicines (antibodies)
  - Interest venture capital industry
Biotech is here to stay ...

<table>
<thead>
<tr>
<th>Biotechnology Medicines in Development—By Product Category</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisense</td>
<td>16</td>
</tr>
<tr>
<td>Cell Therapy</td>
<td>23</td>
</tr>
<tr>
<td>Gene Therapy</td>
<td>38</td>
</tr>
<tr>
<td>Growth Factors</td>
<td>5</td>
</tr>
<tr>
<td>Interferons</td>
<td>16</td>
</tr>
<tr>
<td>Interleukins</td>
<td>10</td>
</tr>
<tr>
<td>Monoclonal Antibodies (mAb)</td>
<td>192</td>
</tr>
<tr>
<td>Recombinant Hormones/Proteins</td>
<td>66</td>
</tr>
<tr>
<td>Vaccines</td>
<td>223</td>
</tr>
<tr>
<td>Others</td>
<td>44</td>
</tr>
</tbody>
</table>
... in several disease conditions

<table>
<thead>
<tr>
<th>Biotechnology Medicines in Development—By Therapeutic Category*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Disorders</td>
</tr>
<tr>
<td>Blood Disorders</td>
</tr>
<tr>
<td>Cancer/Related Conditions</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>Diabetes/Related Conditions</td>
</tr>
<tr>
<td>Digestive Disorders</td>
</tr>
<tr>
<td>Eye Conditions</td>
</tr>
<tr>
<td>Genetic Disorders</td>
</tr>
<tr>
<td>Growth Disorders</td>
</tr>
<tr>
<td>HIV/AIDS Infection/Related Conditions</td>
</tr>
<tr>
<td>Infectious Diseases</td>
</tr>
<tr>
<td>Neurologic Disorders</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
</tr>
<tr>
<td>Skin Disorders</td>
</tr>
<tr>
<td>Transplantation</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

*Some medicines are listed in more than one category.*
### Scientific knowledge leads to better definitions and care and ...

<table>
<thead>
<tr>
<th>60 years ago</th>
<th>50 years ago</th>
<th>40 years ago</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Sickness of the blood’</td>
<td>Leukemia or lymphoma</td>
<td>Chronic leukemia</td>
<td>Indolent lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute leukemia</td>
<td>Aggressief lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-leukemia</td>
<td></td>
</tr>
<tr>
<td><strong>~38 Leukemia types identified:</strong></td>
<td></td>
<td><strong>~51 Lymphomas identified:</strong></td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia (~12 types)</td>
<td></td>
<td>Mature B-cell lymphomas (~14 types)</td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia (2 types)</td>
<td></td>
<td>Mature T-cell lymphomas (15 types)</td>
<td></td>
</tr>
<tr>
<td>Acute promyelocytic leukemia (2 types)</td>
<td></td>
<td>Plasma cell neoplasm (3 types)</td>
<td></td>
</tr>
<tr>
<td>Acute monocytic leukemia (2 types)</td>
<td></td>
<td>Immature (precursor) lymphomas</td>
<td></td>
</tr>
<tr>
<td>Acute erythroid leukemia (2 types)</td>
<td></td>
<td>(2 types)</td>
<td></td>
</tr>
<tr>
<td>Acute megakaryoblastic leukemia</td>
<td></td>
<td>Hodgkin's lymphoma (5 types)</td>
<td></td>
</tr>
<tr>
<td>Acute myelomonocytic leukemia (2 types)</td>
<td></td>
<td>Immunodeficiency associated</td>
<td></td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td></td>
<td>lymphomas (~5 types)</td>
<td></td>
</tr>
<tr>
<td>Chronic myeloproliferative disorders (5 types)</td>
<td></td>
<td>Other hematolymphoid neoplasms</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndromes (6 types)</td>
<td></td>
<td>(~7 types)</td>
<td></td>
</tr>
<tr>
<td>Mixed myeloproliferative/myelodysplastic syndromes (3 types)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>syndromes (3 types)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Source: Mara G. Aspinall, former President, Genzyme Genetics
... a paradigm shift in treatment

 Patients are different

 Medicines are not differentiated

~ 30% of patients do not benefit from medicines\(^1\)
(100,000 deaths and 2.2 million nonfatal events from ADR in the US in 1994)

\(^1\)JAMA 1998, 279: 1200

Source: Bayer HealthCare Diagnostics and Burrill & Company
Drugs do not work as envisioned

And ... 2 million ADRs in the U.S. annually, with 100,000 deaths
Personalised medicine in theory

**Patient selection and treatment by trial & error**

- Treatment
- Diagnosis
- Treatment failure
- Treatment success

**Patient selection by profiling**

- Biomarker selection
- Diagnosis
- Treatment with personalised medicine
- Higher rate of treatment success
Traditional 20th Century Pharma

- Tracing their roots back many decades, often to the nineteenth century chemical industry
- Large enterprises, fully integrated from drug discovery through clinical development, regulatory affairs, manufacturing and marketing
- Most drug discovery conducted in house
- Large-scale ‘random screening’ programs with limited requirements for deep knowledge about fundamental physiological processes
- Leading to pipeline with relatively small number of internally developed blockbuster drugs

- This is a dead track
The innovation gap

Current industry
Time for change
Diversification
Rise of biotechnology
R&D in transition

Diversifying business
Consolidation

Drug Industry Consolidation
A series of mergers has winnowed the drug industry to a few major players.

DATES DEALS WERE ANNOUNCED

'93  '95  '97  '99  '01  '03  '05  '07  '09

American Home Products
American Cyanamid

Pfizer
Warner-Lambert
Pharmacia & Upjohn

Monsanto was spun off as an agricultural products company.

Glaxo Wellcome
SmithKlineBeecham
Synthelabo
Sanofi-Aventis

Rhône-Poulenc
Hoechst

Merck
Schering-Plough
Zeneca
AstraZeneca

Sandoz
Novartis
Ciba-Geigy

Roche
Genentech (Roche bought most of the company in 1990, but has announced a deal to buy the rest)

Sources: Credit Suisse; company reports; Bloomberg
And reorganizations

<table>
<thead>
<tr>
<th>Date announced</th>
<th>Company</th>
<th>Number of jobs at risk</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2009</td>
<td>Pfizer</td>
<td>19,200</td>
<td>Global</td>
</tr>
<tr>
<td>March 2009</td>
<td>Merck</td>
<td>15,900</td>
<td>Global</td>
</tr>
<tr>
<td>September 2009</td>
<td>Eli Lilly</td>
<td>5,500</td>
<td>Global</td>
</tr>
<tr>
<td>November 2009</td>
<td>Pfizer</td>
<td>1,300</td>
<td>South Brunswick, New Jersey; Chazy and Rouses Point, New York; Sanford, North Carolina; and Gosport and Slough, UK</td>
</tr>
<tr>
<td>January 2010</td>
<td>GlaxoSmithKline</td>
<td>5,201</td>
<td>Tonbridge, UK; Verona, Italy; Zagreb, Croatia; Poznan, Poland.</td>
</tr>
<tr>
<td>February 2010</td>
<td>AstraZeneca</td>
<td>8,550 total (3,500 in R&amp;D)</td>
<td>Leicestershire, UK; Lund, Sweden. End of discovery in Wilmington, Delaware</td>
</tr>
<tr>
<td>January-September 2010</td>
<td>Pfizer</td>
<td>8,480</td>
<td>New Jersey, Pennsylvania, New York, Puerto Rico, Ireland, UK and Germany</td>
</tr>
<tr>
<td>May 2010</td>
<td>Takeda</td>
<td>1,600</td>
<td>North America and 20% of staff at Lake Forest, Illinois</td>
</tr>
<tr>
<td>September 2010</td>
<td>Abbott Laboratories</td>
<td>3,000</td>
<td>Hannover, Germany, Weesp, The Netherlands</td>
</tr>
<tr>
<td>October 2010</td>
<td>Sanofi-aventis</td>
<td>2,500 (including sales, mostly pharma operations division)</td>
<td>Great Valley, Pennsylvania and Bridgewater, New Jersey</td>
</tr>
<tr>
<td>November 2010</td>
<td>Bayer</td>
<td>4,500</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>November 2010</td>
<td>Roche</td>
<td>4,800 (including sales jobs)</td>
<td>Global</td>
</tr>
<tr>
<td>December 2010</td>
<td>Novartis</td>
<td>1,400 (sales jobs)</td>
<td>United States</td>
</tr>
<tr>
<td>February 2011</td>
<td>Pfizer</td>
<td>3,500</td>
<td>Sandwich, UK and Groton, Connecticut</td>
</tr>
<tr>
<td>March 2011</td>
<td>Novartis</td>
<td>550</td>
<td>West Sussex, UK</td>
</tr>
</tbody>
</table>
R&D via open innovation (1)

- Drug companies open-up their R&D
  - Collaboration
  - Publication
  - Exchange of (precompetitive information)
- Exploit external sources of technology
  - In-licensing
  - Strategic partnerships with specialist research firms
- Big pharma: 20-30% R&D budget allocated external parties
R&D via open innovation (2)

Current industry
Time for change
Diversification
Rise of biotechnology
R&D in transition
More cooperation
Life Sciences in the Netherlands
NL- strengths

- Pockets of excellence in biomedical research (universities, institutes), also attractive for companies (funding)

- Strong technological position in imaging, medical informatics, vaccines

- Attractive country for clinical trials

- Recognition by government as top sector
  - financial incentives for SMEs
  - improvement of legislation
  - faster reimbursement procedures
NL- opportunities in R&D

• About 20% of total private R&D expenditures in the Netherlands is invested in the LS&H domain

• Biotech sector is young so there is potential for further growth and development

• The (pre-clinical) pipeline of drugs companies in the Netherlands is promising

• Leading multinationals DSM and Philips have put health and life sciences at the centre of their corporate strategy

• But ... almost no pre-clinical research in traditional pharma (closure Organon facilities)
The number of companies increased with 5.4% from 298 (2008) to 314 (2009).

- Source: The Decision Group database -
Employment

Number of companies Dutch life sciences & health cluster
Listed and non-listed companies

- Source: The Decision Group database -
# Largest employees

<table>
<thead>
<tr>
<th>Company</th>
<th>Location / division</th>
<th>Employment 2009 (in NL)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MSD</td>
<td>MSD</td>
<td>8675</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td></td>
<td>Organon</td>
<td>5841 (-2175 expected)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervet</td>
<td>1361</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schering-Plough</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (Nobilon, etc)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>2. Philips</td>
<td>Philips Healthcare</td>
<td>3353</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td>3. Johnson &amp; Johnson</td>
<td>Johnson &amp; Johnson</td>
<td>1329</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td></td>
<td>Centocor</td>
<td>495</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medtronic</td>
<td>1084</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td>5. Abbott</td>
<td></td>
<td>958 (-500 expected)</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td>6. Teva Pharmachemie</td>
<td>Teva Pharmachemie</td>
<td>643</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td>7. Astellas Pharma</td>
<td>Astellas Pharma</td>
<td>575</td>
<td>R&amp;D, manufacturing, marketing &amp; sales</td>
</tr>
<tr>
<td>8. DSM</td>
<td>DSM pharmaceuticals</td>
<td>403</td>
<td>R&amp;D, specialized research supplier, specialized research service provider</td>
</tr>
<tr>
<td>9. Novartis</td>
<td></td>
<td>400</td>
<td>R&amp;D, marketing &amp; sales</td>
</tr>
<tr>
<td>10. PURAC biomaterials</td>
<td>PURAC biomaterials</td>
<td>354</td>
<td>R&amp;D, marketing &amp; sales</td>
</tr>
</tbody>
</table>

Source: Dutch Life Sciences Outlook 2011. The Decision Group,
Activities

Core value chain of the Dutch life sciences & health cluster
Listed and non-listed companies

- Source: The Decision Group database

Source: Dutch Life Sciences Outlook 2011. The Decision Group,
Large (bio)pharmaceutical companies

- Merck (MSD) (development, vaccines, manufacturing)
- DSM (biologicals)
- Centocor (antibodies, manufacturing)
- Amgen (packaging & distribution)
- Janssen/Crucell/Centocor (R&D vaccines, manufacturing)
- Abbott (vaccines, manufacturing)
- Apprx. 20 companies (clinical research)
A powerhouse in clinical research

Top European Institutions in Clinical Medicine, based on Jan. 1998 – Dec 2008 data*

<table>
<thead>
<tr>
<th>Rank in Europe</th>
<th>Rank in world</th>
<th>University</th>
<th>Papers</th>
<th>Citations</th>
<th>Citations per paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Erasmus University Rotterdam</td>
<td>7,108</td>
<td>166,015</td>
<td>23.36</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>University of Cambridge</td>
<td>4,795</td>
<td>107,088</td>
<td>22.33</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>University of Oxford</td>
<td>6,706</td>
<td>149,545</td>
<td>22.30</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>University of Glasgow</td>
<td>4,908</td>
<td>104,245</td>
<td>21.24</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>University of Helsinki</td>
<td>10,169</td>
<td>206,196</td>
<td>20.28</td>
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<tr>
<td>6</td>
<td>50</td>
<td>Imperial College London</td>
<td>7,550</td>
<td>145,914</td>
<td>19.33</td>
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<tr>
<td>7</td>
<td>59</td>
<td>University of Amsterdam</td>
<td>8,123</td>
<td>150,269</td>
<td>18.50</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>Karolinska Institute</td>
<td>12,787</td>
<td>236,174</td>
<td>18.47</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>Humboldt University of Berlin/Charité</td>
<td>6,097</td>
<td>112,420</td>
<td>18.44</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>Leiden University</td>
<td>8,150</td>
<td>149,851</td>
<td>18.39</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>University College London</td>
<td>16,761</td>
<td>302,182</td>
<td>18.03</td>
</tr>
<tr>
<td>12</td>
<td>77</td>
<td>Uppsala University</td>
<td>6,327</td>
<td>105,962</td>
<td>16.75</td>
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<tr>
<td>13</td>
<td>79</td>
<td>University of Milan</td>
<td>8,722</td>
<td>145,331</td>
<td>16.66</td>
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<tr>
<td>14</td>
<td>80</td>
<td>Utrecht University</td>
<td>8,418</td>
<td>137,602</td>
<td>16.35</td>
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<tr>
<td>15</td>
<td>81</td>
<td>Aarhus University</td>
<td>6,340</td>
<td>103,629</td>
<td>16.35</td>
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<tr>
<td>16</td>
<td>82</td>
<td>University of Vienna</td>
<td>8,579</td>
<td>140,063</td>
<td>16.33</td>
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<tr>
<td>17</td>
<td>84</td>
<td>King’s College London</td>
<td>8,359</td>
<td>136,382</td>
<td>16.32</td>
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<tr>
<td>18</td>
<td>85</td>
<td>Maastricht University</td>
<td>6,247</td>
<td>100,910</td>
<td>16.15</td>
</tr>
<tr>
<td>19</td>
<td>88</td>
<td>University of Zurich</td>
<td>8,638</td>
<td>137,050</td>
<td>15.87</td>
</tr>
<tr>
<td>20</td>
<td>89</td>
<td>Lund University</td>
<td>8,041</td>
<td>127,533</td>
<td>15.86</td>
</tr>
</tbody>
</table>

* The Essential Science Indicators database, Thompson Reuters (May 2009)
Listed medium-sized

- Pharming (transgenic animals, orphan diseases)
- OctoPlus (drug delivery, hepatitis C, manufacturing)
- Galapagos (drug targeting)
- Genmab (antibody therapies and treatments for cancer, rheumatoid arthritis)
- AMT (gene therapy, orphan diseases)
SMEs

• Kiadis: prevention of acute Graft versus Host Disease in blood cancer treatments
• Pepscan Systems: cancer immunotherapeutics
• AM Pharma: acute kidney injury
• Prosensa: RNA-based treatment of Duchenne disease
• To-BBB: drug delivery to the brain
• IQ Corporation: biodefense, infectious diseases
• Agendia: molecular cancer diagnostics
Foreign Investments
The Netherlands Foreign Investment Agency (NFIA) has been set up to help and advise foreign companies that wish to take advantage of the Dutch business environment as their gateway Europe. The NFIA is a subdivision of the Dutch Ministry of Economic Affairs. The NFIA provides information and practical assistance free of charge on basis of confidentiality. more

Why Choose The Netherlands
The relative small size of the Netherlands forced the Dutch to be outward looking and open minded. As a small nation, it had to be smart and innovative in order to claim its corner. The pragmatic and entrepreneurial spirit of the Dutch made them to become one of the big see-faring nations and their innovative thinking turned the hostile sea into fertile land. more

Cooperation is in our genes

Integrated Life Sciences
The Netherlands is home of first-rate academic research organizations, hundreds of small and medium sized life science companies and an array of multinational biotech and pharma corporations.
So much diversity within a 120-mile radius offers magnificent opportunities for knowledge creation and innovative product development. The Netherlands is leading a trend towards public-private collaborations and is open to partners worldwide.

Hundreds of companies and organizations
This website offers instant access to all the Dutch life sciences sector has to offer. An interactive company database provides leads to hundreds of companies and research organizations working in health, agro-food and industrial biotechnologies or in medical technology. more

Science shapes our minds

Red, green and white life sciences
Life sciences help address the main socio-economic challenges facing the world:
- Delivering health to an ageing population with an increasing prevalence of chronic diseases
- Feeding the world and its growing population
- Securing resources for generating energy, chemicals and materials needs
- Sustaining the environment.
This website focuses on the first topic: 'delivering health', and how the biomedical sciences can contribute to this.
For the agro/food sector please visit Top Institute Food & Nutrition and Ti Green Genetics. For the chemical/energy sector

Govermental Support
Finding support
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