Regulatory Perspectives on Diabetes Drugs & Devices
Pharma and Device Perspective

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Head Medical & Scientific Affairs, CMO Roche Diabetes Care

Keystone Conference 2012, Practical Ways to Achieve Targets in Diabetes Care
- Facts and Trends to Consider
- Industry Perspective(s)
- Needs / Requests and Wishlist
Facts and Trends to Consider

- Industry Perspective(s)
- Needs / Requests and Wishlist
FACT I  Many Different Products (Medical Devices)

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>NMEs Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>22</td>
</tr>
<tr>
<td>2007</td>
<td>18</td>
</tr>
<tr>
<td>2008</td>
<td>24</td>
</tr>
<tr>
<td>2009</td>
<td>26</td>
</tr>
<tr>
<td>2010</td>
<td>21</td>
</tr>
</tbody>
</table>

*Represents applications for New Molecular Entities (NMEs) filed under New Drug Applications (NDAs) and therapeutic biologics filed under Original Biologic License Applications (BLAs)

<table>
<thead>
<tr>
<th>Clearance or Approval Type</th>
<th>Total Number of Devices Cleared or Approved Since 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devices - PMA</td>
<td>2,825$^1$</td>
</tr>
<tr>
<td>Devices - 510(k)</td>
<td>46,690</td>
</tr>
</tbody>
</table>

1 Includes 180-day supplements (excluding “no user fee” supplements) and panel track supplements.
FACT 1  High Product Diversity

Medical Devices Cleared or Approved by FDA in 2012

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Category</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access® Hybritech p2PSA on the Access Immunoassay Systems - P0900026</td>
<td>PSA Test</td>
<td>06/14/12</td>
</tr>
<tr>
<td>PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) - P110010/S001</td>
<td>Stent</td>
<td>06/01/12</td>
</tr>
<tr>
<td>Presilien Plus CoCr Coronary Stent on RX System - P110004</td>
<td>Stent</td>
<td>05/01/12</td>
</tr>
<tr>
<td>BOND™ ORACLE™ Human Epidermal Growth Factor Receptor 2 (HER2) Immunohistochemical (IHC) System - P0900015</td>
<td>Breast Cancer Test</td>
<td>04/24/12</td>
</tr>
<tr>
<td>Epic™ Vascular Self-Expanding Stent System - P110035</td>
<td>Stent</td>
<td>04/24/12</td>
</tr>
<tr>
<td>ARCHITECT HBsAg - P110029</td>
<td>Reagents</td>
<td>04/12/12</td>
</tr>
<tr>
<td>Zenith™ Fenestrated AAA Endovascular Graft (with the adjunctive Zenith Alignment Stent) - P020018/S040</td>
<td>Endovascular Graft</td>
<td>04/04/12</td>
</tr>
<tr>
<td>LINX™ Reflux Management System - P100049</td>
<td>GERD</td>
<td>03/22/12</td>
</tr>
<tr>
<td>Sientra Silicone Gel Breast Implants - P070004</td>
<td>Breast Implants</td>
<td>03/09/12</td>
</tr>
</tbody>
</table>

FDA Approved Drugs for Endocrinology

Drugs Approved in 2012

- **Bio-T-Gel (testosterone gel)**: Teva Pharmaceuticals; For the treatment of hypogonadism
- **Eleyso (taliglucerase alfa)**: Pfizer Inc; For the treatment of Gaucher disease, Approved February 2012
- **Jentadueto (linagliptin plus metformin hydrochloride)**: Eli Lilly; For the treatment of type II diabetes, Approved September 2012
- **Korlym (mifepristone)**: Concept Therapeutics; For the control of hyperglycemia in patients with pancreatic endocrine or exocrine insufficiency due to cystic fibrosis or other conditions, Approved March 2012
- **Ultresa (pancrelipase) delayed-release capsules**: Aptalis Pharma; For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, Approved March 2012
- **VioKase (pancrelipase) tablets**: Aptalis Pharma; For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, Approved March 2012

Drugs Approved in 2011

- **Afinitor (everolimus)**: Novartis; For the treatment of advanced pancreatic neuroendocrine tumors, Approved 2011
- **Juvisync (sitagliptin and simvastatin)**: Merck; For the treatment of type II diabetes, Approved 2011
- **Sutent (sunitinib malate)**: Pfizer; For the treatment of pancreatic neuroendocrine tumors, Approved 2011
- **Tradjenta (linagliptin)**: Boehringer Ingelheim; For the treatment of type II diabetes, Approved 2011
FACT II Many Different Regulatory Requirements (1)

<table>
<thead>
<tr>
<th>COUNTRY/REGION</th>
<th>PRE-MARKET</th>
<th>PLACING ON-MARKET</th>
<th>POST MARKET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product control</td>
<td>Medical device establishment control</td>
<td>Advertising control</td>
</tr>
<tr>
<td></td>
<td>Tools for acknowledging product cleared for the market</td>
<td></td>
<td>Vendor after-sale obligations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Examples of common requirements</td>
</tr>
</tbody>
</table>

WHO Global Forum on Medical Devices (Bangkok 2010)

- ~30% of countries have a developed regulatory framework for Medical Devices
- ~30% of countries only have "partial regulation of Medical Devices"
- ~remaining countries are either developing a framework or do not yet have any regulations

Harmonization of Regulation – Challenges and Benefits, http://www.who.int/medical_devices/00_co_chair_brief_noboru_takamura_reg.pdf

* Australia’s new medical devices legislation was passed by the Australian Parliament in April 2002 (see www.health.gov.au/tga/)
** Japan’s PAL (Pharmaceutical Administration Law) revision is scheduled for 2005.
**FACT II**

Many Different Regulatory Requirements (2)

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**Table 1: Biosimilars approval pathways**

<table>
<thead>
<tr>
<th>Country</th>
<th>Inception</th>
<th>Approval pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>September 2009</td>
<td>Administracion Nacional de Medicamentos, Alimentos y Tecnologia (ANMAT) published biologics and biosimilar approval guidance</td>
</tr>
<tr>
<td>Australia</td>
<td>June 2006</td>
<td>CHMP/437/04 Guideline on Similar Biological Medicinal Products</td>
</tr>
<tr>
<td>Brazil</td>
<td>December 2010</td>
<td>Resolution 55/2010 regulates all biologic products</td>
</tr>
<tr>
<td>Canada</td>
<td>March 2010</td>
<td>Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics</td>
</tr>
<tr>
<td>China</td>
<td>-</td>
<td>All biologics, original or copy biologics, undergo the same pathway</td>
</tr>
</tbody>
</table>

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**Table 2: Comparison of biosimilars guidelines across major markets, 2011**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>EU and Australia</th>
<th>US</th>
<th>Japan</th>
<th>Canada</th>
<th>South Korea</th>
<th>India</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar pathway status</td>
<td>Pathway established</td>
<td>Pathway not established</td>
<td>Pathway established</td>
<td>Pathway established</td>
<td>Pathway established</td>
<td>Draft preclinical pathway issued; similar biologics currently approved as new drugs</td>
<td>No pathway, copy biologics approved as new drugs</td>
</tr>
</tbody>
</table>

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Source: Datamonitor; European Generic medicines Association, 2010; European Generic medicines Association, 2010a; Simmons, 2010; Chen, 2009; Dicocco, 2010; Alexander, 2011; GaBi, 2009a; GaBi, 2011a; GaBi, 2011b; GaBi, 2011c; GaBi, 2011d
FACT I & II  Considerations

- **Different regulatory processes** and requirements from regulatory bodies (!)
  
  --- Drugs ... FD&C Act, Section 201, [21 USC 321(g)(1)] ... (IND, NDA)
  
  --- Medical Devices ... FD&C, section 201(h) ... 510(k) [class I, II] PMA [class III], section 520(m) Humanitarian Device Exemption (HDE)
  

- … in combination with **high number** of Medical Devices, results in **complexity and cost** (!!)
  
  --- choosing (prioritizing) between a FDA approval/clearance (US) or a CE Mark (conformity mark) (EU) can be a Strategic Business Decision

- **Differences in nomenclature** call for consistency & harmonization

  Global Harmonization Task Force (GHTF)
  1992: US, EU, Japan, Australia and Canada
  2006: in addition, AHWP, Organization for Standardization (ISO)

  and International Electrotechnical Commission (IEC)
FACT III  Drugs and Medical Devices Are Different Species (!)

... with different “Mode of Action” (!)

► In **pharmacology**, the term mechanism of action (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect.

► **Medical Devices** belong to a group of products whose main effect is based on physical mechanisms, ..., they do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means.
FACT III  Considerations

- Stand-alone Medical Devices often don’t meet clinical requirements – **product solutions can be „systems“**  
  --- regulatory challenge for „systems“ or „combination product“ approval

- **Combination products** which combine two products in different regulatory categories, e.g. device and biological product become complex regulatory challenges

- Innovative „**Medical Device Systems**“ may include “physicians” activities, e.g. „decision support functionality“ / automated advice processes  
  --- regulatory challenge for all stakeholders
Fact IV: Innovation, Technical Developments and Translation into Product Solutions is going fast.

Prof. Barry Marschall
Australia

Prof. Marshall has proven that the bacteria Helicobacter pylori is the cause of most stomach ulcers.

GENE GEN
Prof. Barry Marshalls Lifetime Risk

- Macular degeneration: 3 times
- Alzheimer's Disease: 2 times
- Heart attack: marginally
- Type 2 diabetes: marginally
**FACT IV**  Innovation, Technical Developments and Translation into Product Solutions is going fast

<table>
<thead>
<tr>
<th>Automated Pancreas</th>
<th>Healthcare in the „Cloud“</th>
<th>Implantable Medical Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Automated Pancreas" /></td>
<td><img src="image2.png" alt="Healthcare in the „Cloud“" /></td>
<td><img src="image3.png" alt="Implantable Medical Devices" /></td>
</tr>
</tbody>
</table>
FACT IV Innovation, Technical Developments and Translation into Product Solutions is going fast
FACT IV  Considerations

- Search for innovation, new technologies and new applications of known technologies result in new product types

  - e.g. “borderline products”, … between a medical device and a medicinal product …
    --- ... results in the question if a product actually falls within one of the (EU) Medical Device Directives, or is it subject to another regulatory regime, such as pharmaceuticals, cosmetics or aesthetic products.

  - e.g. “telemedicine solutions”,
    --- medical device manufacturers expand the scope of usage of devices from a patient’s home to make medical data available to a doctor or a nurse providing primary health care

  - e.g. “software” … becoming a differentiator of Medical Devices …
    --- the rewards of software innovation are balanced by the risks and challenges of regulation ...
    --- Software used as a component of a medical device
      Software that is a medical device
      Software in the production of a medical device
      Software used to manufacture a medical device
      Software used in the implementation of a quality system

--- Software Validation, FDA, 2002

**call for clear guidance and abiding to international standards**
FACT_V  There Is Still Significant (Medical) Need For Better Drugs & Medical Devices (Diagnostics)

Achievement of therapy goals

Prevention of acute complications

Prevention of long-term complications

Reduction of health-care cost
FACT VI Industry Provides Solutions for many Unmet Medical Needs and to many Stakeholders
Considerations

- Diabetes is currently managed, not cured. Breakthrough therapies which could slow, stop, or cure disease come from innovation. **Innovation** (in Diabetes) need to be accelerated, not braked.

- Improvement in the management of Diabetes comes from technology but, in future, even more from functionality (like [automated] decision support) to empower the patient/healthcare team collaboration.

- „Personalized Health Care” products face specific challenges ...because Medical Devices / Diagnostics „meet“ Pharma
  --- because Diagnostics (Medical Devices) „meets“ Pharma, which results in the need to apply different regulatory frameworks and processes
  --- because of the need of new quality of products, e.g. composite biomarkers (in vitro diagnostic multivariate index assays [IVDMIAs])
Industry Perspective(s)

- Facts and Trends to Consider
- Needs / Requests and Wishlist
Industry Perspective: Regulatory Challenges

- Highly complex and diverse processes
- Long approval times / periods
- High regulatory approval cost
  - Regulatory Affairs departments exceed staffing of Medical / Development departments
  - Post-market vigilance ... post-market surveillance and adverse event reporting procedures
- Trend (!): Regulatory approvals become more unpredictable and overall requirements continue to increase
  - cardiovascular (CV) outcomes evaluation for non-cardiovascular drugs
  - increased frequency of inspections ... in many different countries
  - increased requirement of post market surveillance (10,483 citations in 2011)
Industry is Key Driver of Innovation

…but success and progress need an innovation friendly environment

Owning the disease: A new transformational business model for healthcare

By Dr. Christopher L. Wasden,
Global Healthcare Innovation Leader, PwC, and
Brian S. Williams, Global Healthcare,
Director Clients and Markets, PwC

“… from generating profits by increasing volume to winning by delivering greater value …”

PricewaterhouseCoopers 2011
Industry Perspective towards Innovation / Development Decisions

Attractiveness / Hurdles

- Likelihood of success and resources needed to get regulatory approval for a new drug / medical device / diagnostic product / medical device system PHC system … to translate innovation into a marketable product

- Time to market for new (innovative) products
  --- drugs lose patent protection (!)
  --- ongoing increase in R&D investment / cost (!)

- Intracompany competition !!! regarding development decisions between diseases / disease areas (indications) and single molecules / medical devices / diagnostic products …

- Incentives to increase developments for specific diseases and/or patient populations
  --- pediatric indication, ..., have resulted in updated pediatric labeling for more than 120 drugs
  --- under the Orphan Drug Act, nearly 1,700 medicines have been designated orphan drugs, and 249 have been approved for use
Industry Perspective towards Innovation / Development Decisions

Attractiveness / Hurdles

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of U.S. Clinical Trials</th>
<th>NME Approvals</th>
<th>Approvals per Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>3,663</td>
<td>27</td>
<td>8.7</td>
</tr>
<tr>
<td>2001</td>
<td>3,883</td>
<td>24</td>
<td>8.2</td>
</tr>
<tr>
<td>2002</td>
<td>4,158</td>
<td>17</td>
<td>5.8</td>
</tr>
<tr>
<td>2003</td>
<td>4,544</td>
<td>21</td>
<td>8.6</td>
</tr>
<tr>
<td>2004</td>
<td>4,827</td>
<td>36</td>
<td>7.3</td>
</tr>
<tr>
<td>2005</td>
<td>5,029</td>
<td>20</td>
<td>5.2</td>
</tr>
<tr>
<td>2006</td>
<td>5,445</td>
<td>22</td>
<td>5.9</td>
</tr>
<tr>
<td>2007</td>
<td>5,826</td>
<td>18</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Source: FDA
Industry Perspective towards Innovation / Development Decisions

SMBG – Glucose information based Diabetes Management Solutions

1. The testing algorithm
2. The correct analysis and diagnoses
3. The appropriate therapeutic action

2008 | 2009 | 2010 | 2011 / 2012

Random Testing, "Structured Testing"
Industry Perspective towards Innovation / Development Decisions

SMBG – Glucose information based Diabetes Management Solutions
Industry Perspective towards Innovation / Development Decisions

(Semi-)closed loop system development

1. Continuous Glucose Monitor
2. Computer-Controlled Algorithm
3. Insulin Pump
4. Patient Effect
- Trends and Facts to Consider
- Industry Perspective(s)
- Needs / Requests and Wishlist
Industry Needs / Requests and Wishlist

Certainty & predictability

- **Consistency, clarity and predictability** on regulatory requirements (guidelines, regulatory framework, standards, etc.)
  - e.g. Draft Guidance for evaluating substantial equivalence under 510(k) program
  - Draft Guidance on companion diagnostics --- gaps so far e.g. in guidance on adaptive study design, cut-off
determination, treatment of false positives ...

- **Guidance** on regulatory needs and requests … (not single expert opinion)

- **Reliability** during the entire regulatory process *(pre-investigational device exemption process)*
  --- reliable feedback on regulatory path and the type of data appropriate to support the desired indication
Innovation friendly environment

Scientific excellence for discussions on new drugs, technologies, Medical Devices (systems), PHC solutions, (automated) Diabetes Management solutions

Efficiency of regulatory processes,
--- mutual recognition process
--- avoidance of (unexpected) delays … improve and widen Fast Track, Accelerated Approval and Priority Review processes
--- simplified processes
--- reduced time and cost to market!

Harmonization of regulatory requirements to lend efficiency and cost effectiveness to the process of product development, manufacturing and expediency to global access … international regulatory collaboration

Regulatory Predictability for the entire spectrum of product development process, registration, post-marketing and product lifecycle activities

Equal application of defined regulatory requirements and regulatory framework, i.e. to standards (ISO, CLSI) across companies
Regulatory Predictability and Equality
Thank you for your attention!