Pharmaceutical industry in CEE Region

Perspective from Regulatory Point of View

Miroslav Janoušek, Zentiva

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Agenda

- CEE pharmaceutical market overview
- Zentiva - a case study
- Recent trends and drivers
Central and Eastern Europe developing pharmaceutical market

- History
- Economical basics
- EU enlargement impact
- Generic perspective
- Strong local development and manufacturing capacities
Pharmaceutical MARKET EUROPE

WE R&D 60-90% GENERICS 10-40%
CEE R&D 10-40% GENERICS 60-90%

RETAIL BUSINESS
Commodity generics

Originators products dominance

PRIMARY CARE undedeveloped
Branded generics
Commodity generics
<table>
<thead>
<tr>
<th>Generics market share in value</th>
<th>Country Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>A,B,FI,F,GR, IR, I,PT, SP</td>
</tr>
<tr>
<td>10-40%</td>
<td>DK,EE, NL, SK,SL, S, TR, UK</td>
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<tr>
<td>&gt; 40%</td>
<td>HR, CZ, D, LV, LT, H, PL</td>
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CEE area - opportunities in Attractive Growth Markets

Growth through Closing the Gap in spending per capita
ZENTIVA

case study of important regional player
TOP GENERIC COMPETITORS ON CEE REGION (selected markets)

- ZENTIVA A.S. 482,243,566 USD
- GEDEON RICHTER 474,053,150 USD
- KRKA 376,715,167 USD
- SANDOZ 342,006,359 USD
- TEVA 281,792,362 USD
- POLPHARMA 259,531,121 USD
- RATIOPHARM 158,235,480 USD
- STADA 63,403,785 USD
What is common to regional key players?

- history
- long tradition in pharmaceutical competencies
- strong backward integration
- branded generics concept
- portfolio development
- international with regional focus
- quality as driving value and strong change management dynamics
ZENTIVA case study

1857 – 1945  from pharmacy to industrial perspective
1945 – 1993  governmentally managed production of medicines
1993 – 2004  European quality standards implementation
from 2004  from local to regional player
from pharmacy in historical Prague center to industrial enterprise

Privat company from pharmacy – to industrial enterprise

- 1857 pharmacy in Praha center, Benjamin Fragner
- 1930 start of industrial pharmaceutical production in Dolní Měcholupy, Jiří Fragner
- 1948 – nationalisation of enterprise

Company as state owned enterprise

Modernisation and standardisation with industrial and management practices

- Ambitious investment programme to renovate all key facilities on international cGMP standard
- QS based on TQM principles and GxPs implementation
- Overall change to company managed in accordance to international standards
- Key financial and ERP Information systems implementation

History from 1998

Creation of a Leading Generic Pharmaceutical Company

**Business Rationalisation**
- Management and Warburg Pincus completed successful MBO of the company

**Positioned for Regional Growth**
- Increased product diversification
- Transformed organisational processes, particularly commercial
- Introduction of key performance indicators corporate-wide
- Invested in building a leading product portfolio and deep pipeline

**Leading CEE Player Expanding Internationally**
- Zentiva is one of the largest CEE pharmaceutical players
- Zentiva rapidly expands presence in Poland and Russia
- Zentiva was the first corporation raising share capital among the new EU countries
- IPO has provided financial flexibility for further growth
- Zentiva acquired additional #1 generic market position
- Improved BS via debt & accumulated cash acquisition financing
- Zentiva enters Hungarian market via acquisition of products, employees and other operating assets from sanofi-aventis
- Announcement of acquisition of a leading Turkish company

- Zentiva acquired 24.9% of shares from Warburg Pincus and Zentiva management
- sanofi-aventis acquired 24.9% of shares from Warburg Pincus and Zentiva management
- sanofi-aventis became Zentiva’s largest shareholder

1998
- Zentiva completed modernisation programme
- IT systems implemented
- Fully GMP compliant

1999 - 2002
- Zentiva is one of the largest CEE pharmaceutical players
- Zentiva rapidly expands presence in Poland and Russia

2003
- IPO and listing on PSE and LSE
- Launch of Zentiva corporate brand

2004
- Acquisition of Romanian pharma company Sicomed
- Zentiva acquired additional #1 generic market position
- Improved BS via debt & accumulated cash acquisition financing

2005
- sanofi-aventis became Zentiva’s largest shareholder

2006
- sanofi-aventis
- Acquisition and full oper. integration of Slovakofarma
- Launch of Zentiva corporate brand
- sanofi-aventis acquired 24.9% of shares from Warburg Pincus and Zentiva management
- sanofi-aventis
- Acquisition in Turkey

2007
- Zentiva entered Hungarian market via acquisition of products, employees and other operating assets from sanofi-aventis
- Announcement of acquisition of a leading Turkish company
Zentiva – Leading Generic Player in CEE

- Zentiva is leading generic player in its five core markets with 2006 Sales CZK 14.3 bn (USD 619 m)\(^{(1)}\) and current market capitalization of CZK 48.2bn (USD 2.2bn)\(^{(2)}\):
  - #1 generic player in the Czech Republic, Slovakia, and Romania
  - Fast growing pharma company in Poland and Russia
  - Leading OTC franchise in the Czech Republic, Slovakia and Romania
- Zentiva is successfully positioning in some of its new markets such as Ukraine, Baltic's and Bulgaria
- Zentiva has grown rapidly in the last 4 years focusing on extension of modern treatment in primary care, utilizing its modern product portfolio and efficient production processes:
  - 2003-2006 CAGR of 16.6% in Sales, 19.0% in Gross Profit, and 24.9% in Net Profit
- Zentiva has a successful acquisition track record in Slovakia and Romania
- Zentiva recently announced entrance to Hungary and an acquisition of third largest domestic pharma company in Turkey (Eczacibasi)
- Upon the closing of Turkish aquisition Zentiva will rank among the top producers in Europe in terms of output

\(^{(1)}\) Average Exch. Rate for 2006 of 22.609 CZK/US$; \(^{(2)}\) As at March 6, 2007, Exch. Rate 21.507 CZK/US$0
Central and Eastern Europe
quality and regulatory view in last decade

- Adoption of pharmaceutical regulatory standards in safety, efficacy and quality of medicines
- Industry driven (GxPs)
- Politics – accession procedure and adoption of EU standards
  - Intellectual property
  - Data exclusivity
  - Safety, Efficiency and Quality evidence of registered older products
  - Adoption of registration standards
  - Participation on harmonised procedures
  - Pharmacovigilance systems
Central and Eastern Europe
still a lot of specifics in regulatory and quality

• Still important role of older products – demanding requirements on their up-date to european level of the evidence of Safety Efficacy and Quality
  – CZ, HU, EE, LV, SK no transition period, since 2004 done
  – new accession countries ROM, BG no transition period – 2007
• Differences in quality development of state authorities
  – CZ (SÚKL), HU (OGYI) among leading european agencies as reference country for EU harmonised procedures (MRP, DCP)
  – some of them have started (EE, SLO, SK(?)
  – Some not yet prepared (legal-institutional reason, lack of qualification)
Quality management in pharmaceutical industry – challenging trends
Pharmaceutical industrial process is under strong Quality systems regulations

- **product registration**
  - Product development
    - GMP, regulatory compliance
      - GMP facilities a QA system
      - Manufacturing process
      - Vendor and contractors management
      - Change control
      - QP role
    - Quality of API
    - Quality of DF
    - Up-scale
  - GDP
  - Pharmaco vigilance
    - Quality of healthcare system, pharmacoepidemiology, medication errors
Quality systems in pharmaceutical industry

- SAFETY
- EFFICACY
- QUALITY

strong focus on product quality, patient / end user view and very detailed and demanding systems mostly based on legal and regulators requirements
opinions to meet often across the industry

• ISO family standards are not giving added value, our GxP based systems are more robust and focused
• risk management is broadly and deeply implemented in pharmaceutical industry processes
• regulators view is not in line with business ( and sometime also healthcare systems economics ) needs
• industry is overregulated and its business flexibility and cost effectiveness are influenced negatively
• product quality certification is much more advanced then Quality management certification
• product quality design is specific due to science base, selective research approaches and is very much influenced by IP protection rules and strong regulation defending patients
Why pharma industry is not pioneer in quality management and risk management approaches?

- due to strong focus on intellectual rights, complicated and non-harmonised price-reimbursement concepts for medicines there is not fully competitive environment for all players (monopolistic situations)
- critical end-customer view and evaluation is not fully applicable and developed
- cost and industrial/systematic view is not the prime intention when regulations are established and most of the organisations are focused on „to meet regulation“ then on „built-in quality and improvement“
- demanding change control is freezing most of systematic and continuous technical improvements
Quality systems in pharmaceutical industry
- key trends

- Cost and flexibility parameters will be more stressed as important future source of competitiveness
  
  (Increasing cost of innovation, decrease number of registered innovative products, what is innovation to be paid for?, generic – cost competitive approach to be applied widely)

- Regulations are moving towards application of overall Quality system principles
  
  (FDA initiatives, International Conference of Harmonisation (ICH) guides – ICH Q8, Q9 and Q10, new inspection approaches, active monitoring of product safety programmes,..)

- Complex view on healthcare quality parameters
  
  (Healthcare system quality measurements, pharmaepidemiology issues, medication errors, misuse of medicines, anti-counterfeiting measures, quality measures applied on regulators, objectivisation of innovation benefits,..)
Authorities Pharmaceutical GMP Initiative:

“seeks to integrate quality systems and risk management approaches into the existing programs and encourages adoption of modern and innovative manufacturing technology.”

“intended to enhance the integration of pre-approval review and cGMP programs and achieve more consistent application across agency organization components.”

“use existing and emerging science and analysis to ensure that limited resources are best targeted to address important quality issues, especially those associated with predictable or identifiable health risks.”

*Lester M. Crawford, FDA Deputy Commissioner, 21- August- 2002*