Challenges for the implementation of the Pharmaceutical review 2005/06 in Bulgaria – an industry perspective

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- The question today:

What is all about?

Back to the past

- **1992 – the first official regulatory body created (NILS)**
  - New activities in the scope (registration, control over drug manufacture, distribution, import
  - Development of the Bulgarian Pharmacopoeia
- **1995 - the first Pharmaceutical Act was published**
  - More responsibilities for NILS
  - New procedure for registration (2 steps)
  - Clinical trials
  - External bodies (commission for approval) with new roles
  - 32 related regulations adopting more than 10 EU directives
- **90s – development of the regulatory infrastructure through the local offices of MoH**
- **1997 - CADREAC (Collaboration Agreement of Drug Regulatory authorities in European Union Associated Countries as a step on the way of harmonization**:
  - Initiated in Sofia and renewed on 1 May 2006
  - Simplified centralized procedure introduced for the members
  - Safety and pharmacovigilance data exchange
  - Set-up of regulatory networking with MS

Year 2005/06

- 2005 – the working group started work on the new Pharmaceutical Act (both R&D and generic industry presented)
- 2006 – the most intensive year ever
  - Changes in regulation 17 on the information for registration (May 2006)
  - New format of applications
  - DMF for API introduced
  - CTD format for all new submissions and renewals
- No transition period, no closed doors
  - New registration procedure for national application (new application forms introduced – Feb 07)
  - CP – all national registrations terminated
  - Clinical trials – CTA format introduced
  - Bioequivalence – GLP requirements

Just like in survival reality show

Challenge No 1
The regulatory files

- Example
  - Analgin – Chinin (metamizole/chininum)

Registered in the 80s, renewal not submitted in 2002. New procedure started in 2004, but the fixed combination form was challenged, no existing records for well established use, procedure suspended.

- Lessons learned
  - "The sacrifice"

Files should be examined vs. the EU requirements and appropriate regulatory strategy selected well in advance before re-registration. Sometimes is more sensible to sacrifice some products rather than to wait for the regulatory rejection.

Challenge No 2
The clinical data

- Example
  - Tabex (cytisine)

Original product for smoking cessation, developed 30 years ago, registered in some CEE countries. Assessment for possible MRP or access in old Europe – clinical data not consistent, very few controlled clinical trials, long term Efficacy not well proven. Partnering in clinical development negotiated with multinational Pharma

- Lessons learned
  - "The Jewel"

The relevant expertise should sought to support development of original products. Clinical data should be assessed vs. GCP standards. Possible million worth investment necessary, better in partnership with R&D based phama company

Challenge No 3
The API supply/production

- Example
  - NaCl

  sterile solution for injection used in the hospital care. No DMF available from the supplier (Merck). The regulatory agency agreed after intensive discussions to accept the technical specification instead

- Lessons learned
  - "The co-operation"

  API supply should be checked for availability of COS or DMF. GMP to be ensured in production facility. In cases of objective difficulties a specific agreement with the Regulatory agency should be sought

Challenge No 4
The production

- Example:
  - The facilities

The manufacturing licenses granted under the national legislation should be transformed to EU format and scope. Some producers may be not compliant.

- Lessons learned
  - "The investments"

Long term investment should be planned well in advance, upgrading of the facilities may be very resource demanding and long process. Intensive collaboration with the regulatory authorities strongly recommended.

Challenge No 5
Safety and pharmacovigilance

- Example
  - The PV system

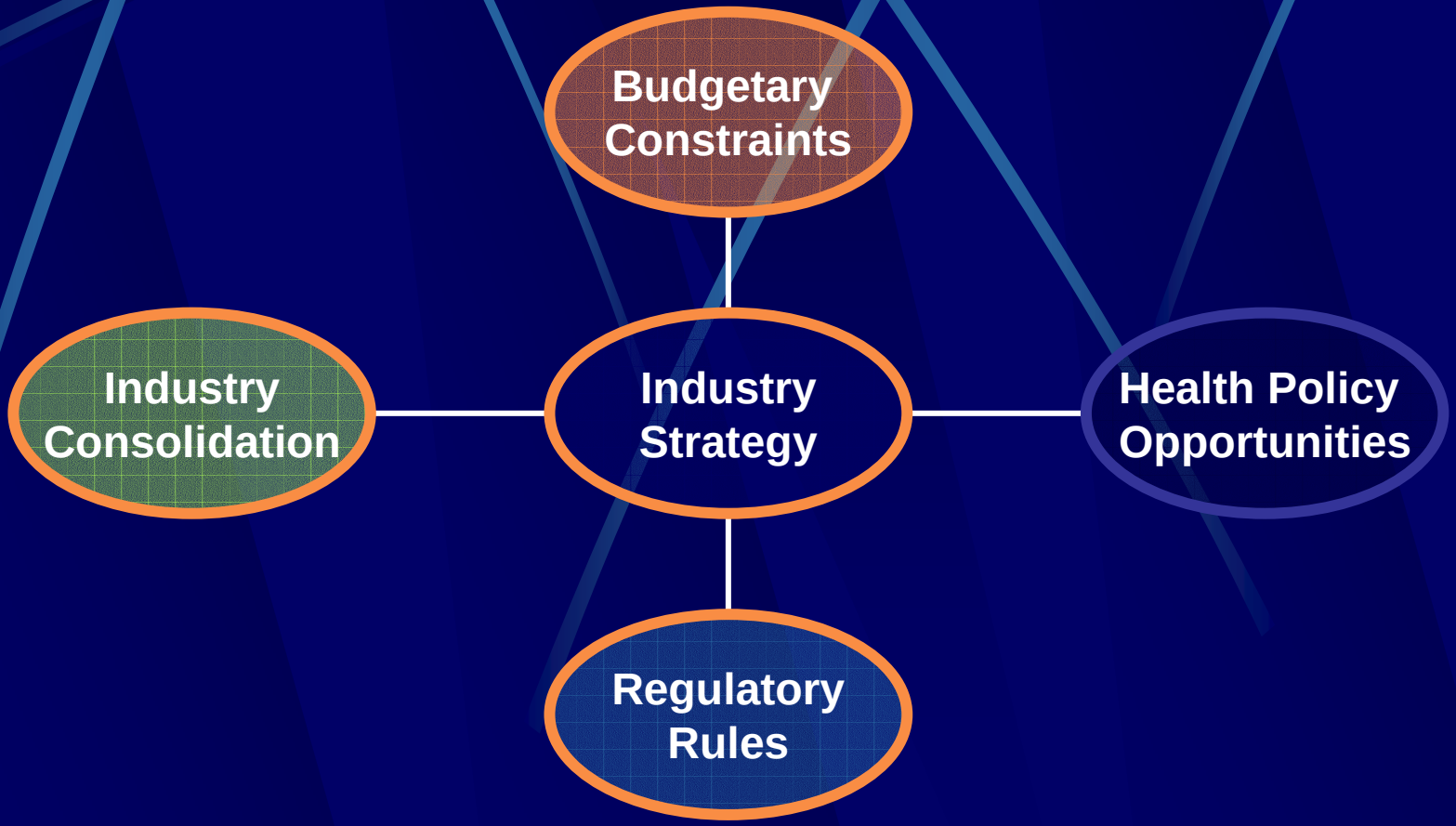
When negotiating in licensing deals, it appeared that existing SPv didn't fully correspond to the Volume 9A (EMEA) re data base, QP, assessment, CIOMS, PSUR's etc.

- Lessons learned
  - "The renovation"

Resources and money should be invested extensively in the upgrading of the SPv. Internal support should broadly Provided. People with experience should attracted from the multinational pharma.

Is it about the local industry?

Or maybe the environment?



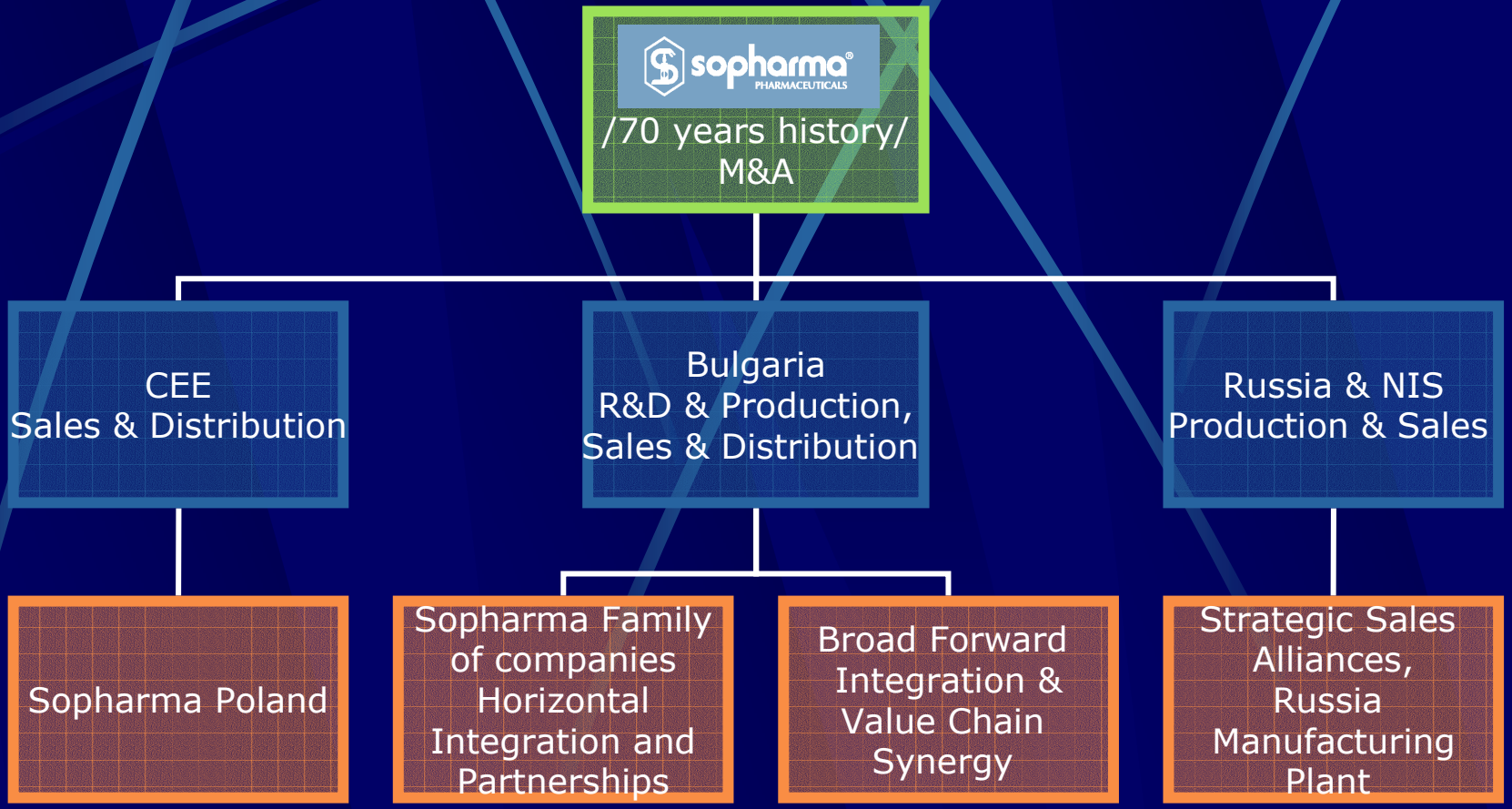
Is it about "Übermorgen"

- Regulatory compliance is a "must"
- The companies' portfolio should be shortened, optimized and prioritized
- New generic molecules will be developed or in-sourced from attractive suppliers (India)
- Great chance for local partnerships and license deals
- Consolidation of the local business (big companies will bigger, small ones will disappear)
- From national to regional market presence
- From local to international (EU) pharma players

What can we do for our future?

- Operations management – building new production facilities and maintaining GMP and other quality assurance standards
- Human resources management – cutting costs and raising the standard of professional expertise
- Financial management – raising the value for shareholders
- Market consolidation, growth & synergy
  - M&A and strategic partnerships – local and international scale
  - Backward & Forward Integration – from API to wholesalers and pharmacy franchise
  - Geographical expansion & pipeline development
  - Outsourcing R&D and production

Is it about synergy?



Actually it is mainly about our country Bulgaria

But at the end of the day…

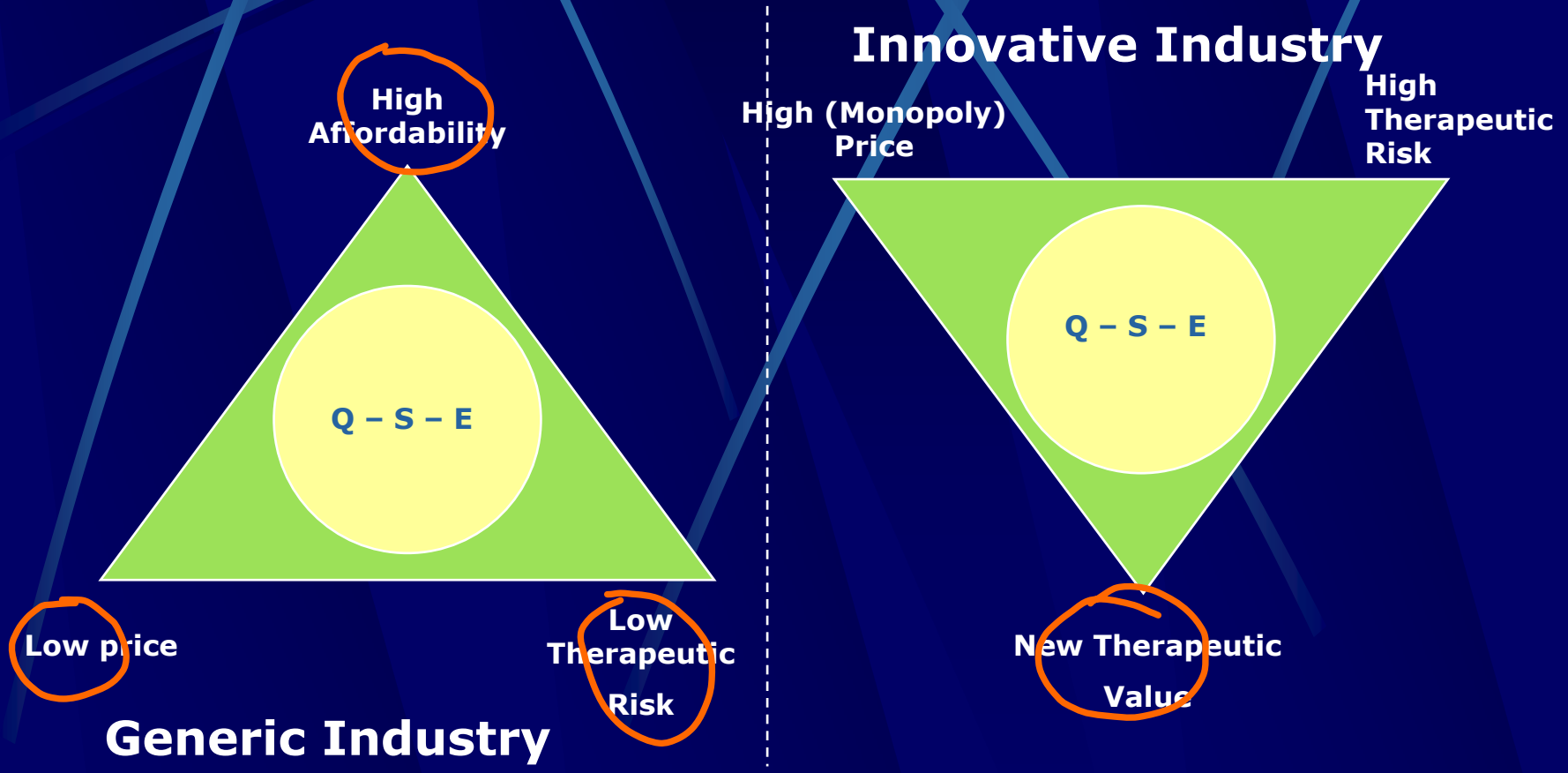
Thank you for your attention!
Danke fur Ihre Aufmerksamkeit!

Annotations

- Bulgarian Drug agency - presentations dedicated to the 100 years anniversary
- Association of Bulgarian Pharmaceutical Manufacturers
- My company SOPHARMA PLC
- All colleagues from the department "Medical and regulatory affairs"

- Back-up slides

Strategic Values



Key Socio-Economic Factors to Affect Industry

- High social demand for effective cost containment policies for pharmaceuticals.
- Deficiencies in health care budgets in 'transition' countries – e.g. Bulgaria & Romania, etc.
- The EU accession harmonization of national legislation and its impact on P&R policies towards cross-national convergence.

Health Policy and Legislation Harmonization

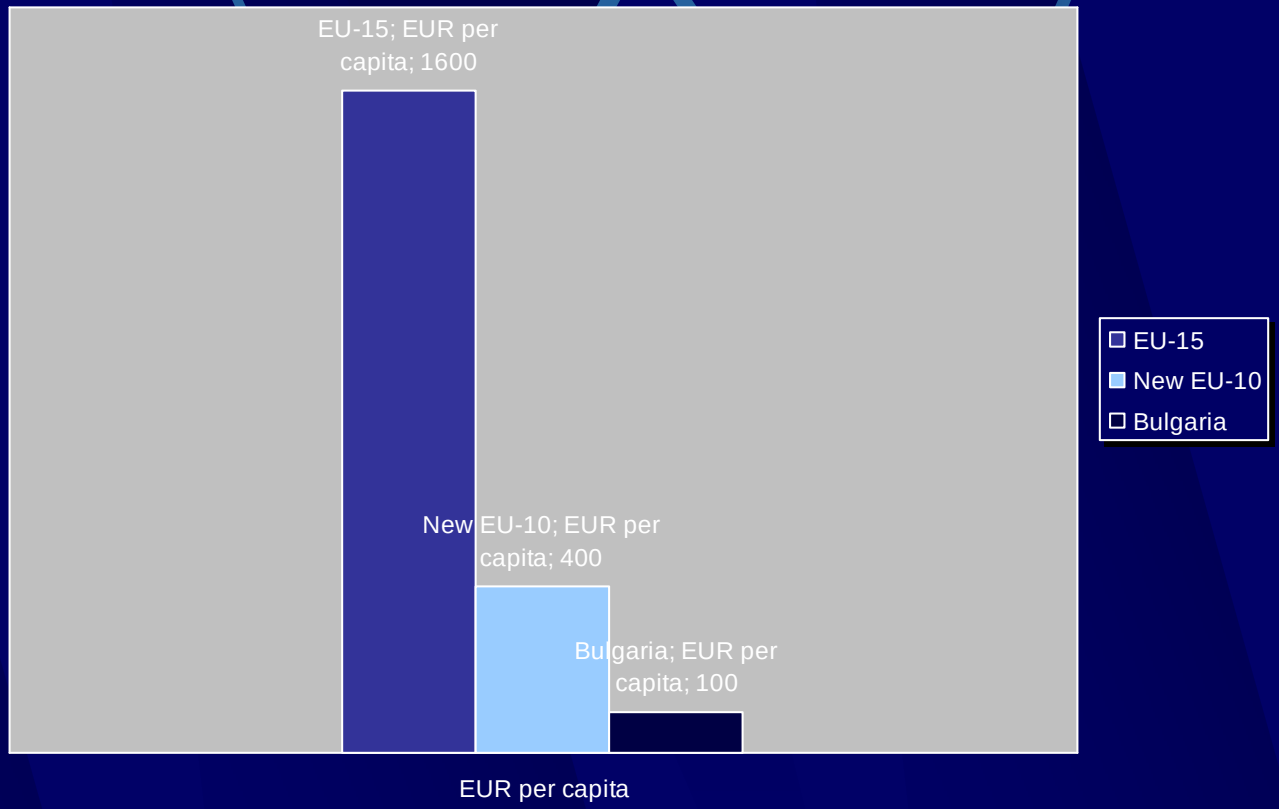
- New Pharma Law – still on 2nd reading in Health Commission – fully harmonized with EU (Directive 2001/83/EC, 2004/27/EC, EU Regulations).
- 8 + 2 +1 Data exclusivity & Bolar provisions.
- No Patent Linkage.
- Positive and Reimbursement Lists will merge in a single formulary.
- NHIF becomes the only funding body to administrate drugs budget.

Health Policy and Legislation Harmonization

- Implementing a cost-containment system based on pharmaco-economic evaluation of drugs with reference pricing system (fixed to the lowest bid).
- Application for price and reimbursement - processed by one "single step". (HC decides this week)
- Directive 89/105/EC – price setting and decision time frame and transparency implemented.
- New Patent Law fully in effect from 1st January 2007! Implementation of SPCs - only for products first registered in EU after 1st January 2000 (Bulgaria & Romania Accession Agreement)

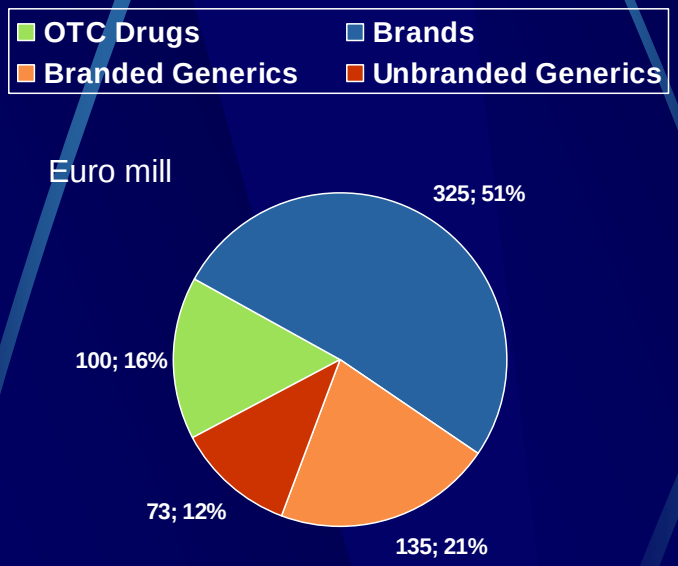
Health Policy and Legislation Harmonization

Gap in Health Care Budget



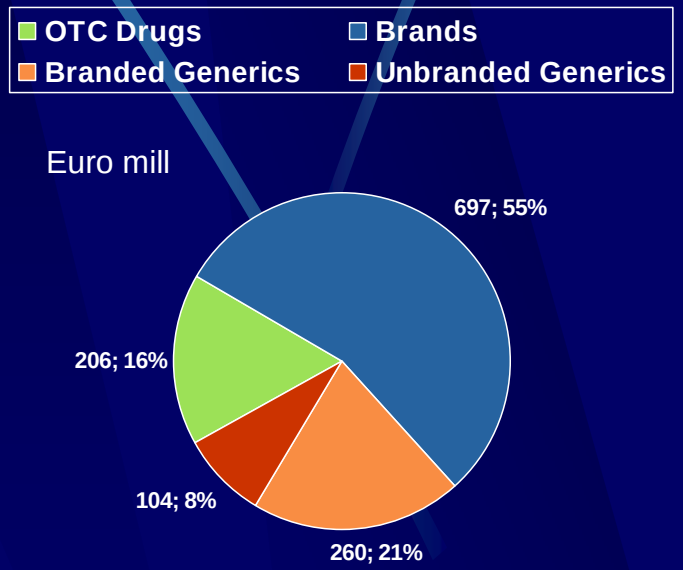
Bulgarian & Romanian Market

Bulgaria



Total Euro 638 mill

Romania



Total Euro 1,268 mill

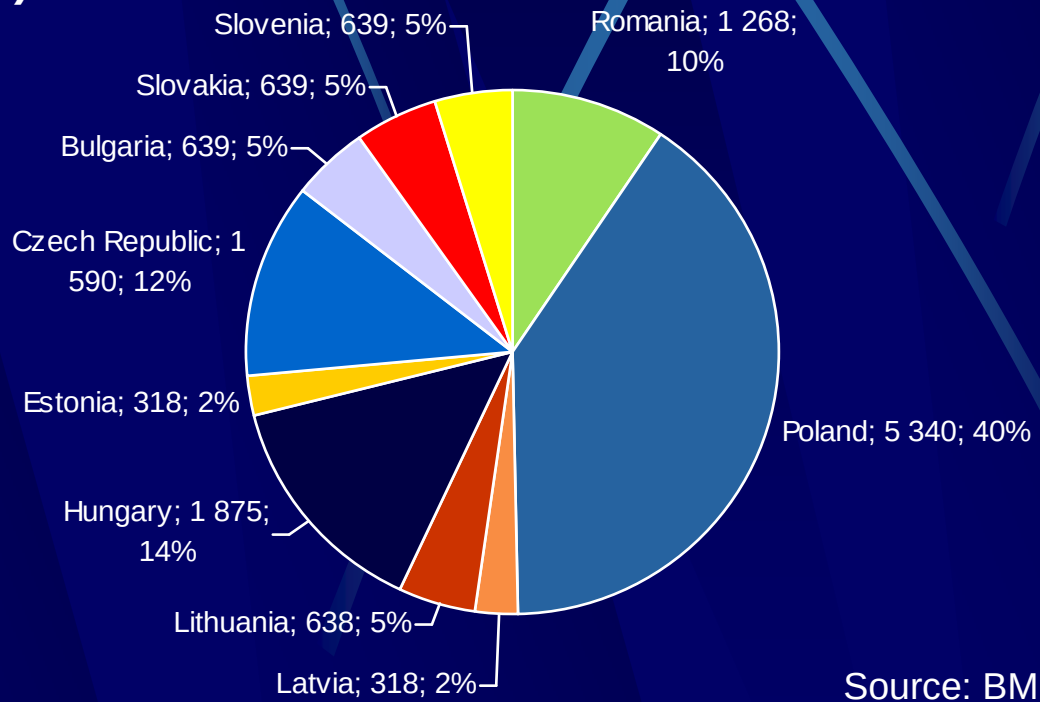
Source: IMS/ABPhM

EU CEE Drugs Market

Euro 13 190 mill

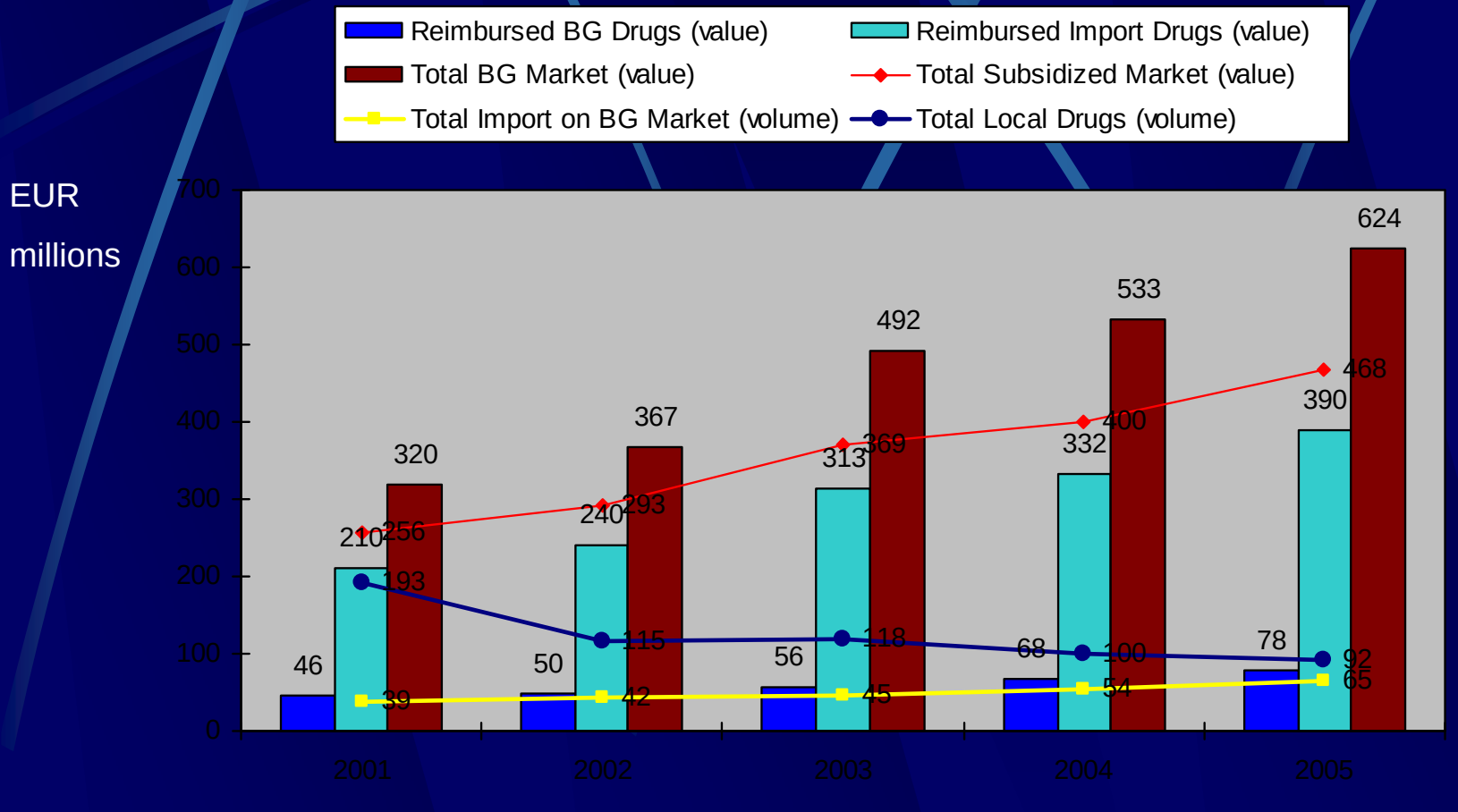
(41.5 %)

EU CEE Regulated Market



Source: BMI/ABPhM

Bulgarian Drugs Market



Source: BDA/ABPhM

Opportunities & Threats

- Predictive EU Regulatory & IP environment 10+1 Data Exclusivity & Bolar provisions
- Health Policy on P&R favors prescription generic volumes but cuts price margins.
- Pharmaco-economic evaluation favors both Rx generics and true innovative products.
- “me-too products”, life-style and OTCs are out of the lists.