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Managing variations Current situation & Perspective

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Current Regulatory Challenges
Regarding Pharmaceuticals





BGPharmA

- **Bulgarian Generic Pharmaceutical Association** is the national representative body for the whole Generic industry in Bulgaria.
- **BGPharmA** aims at:
- Consolidating the Generic industry in its efforts to **develop and provide affordable medicines** for all patient groups, and
- Developing and assisting for the adoption and implementation of a **Coherent Generic Medicines Policy** by the government and health care institutions.



Challenges – past and future

- New rules for price setting and getting reimbursement status:
 - Two commissions (Pricing and PDL), two prices, no negotiation with MoH or NHIF
 - Lowest max. retail price from 9 countries, 20% price linkage for PDL (50% in draft)
- Strong opposition from ABPhM and EGA re 50% price linkage draft clause– letters to Prime Minister
- Lack of capacity in MoH to implement new PDL on time (April 2007) – delay to Jan 2009? – YES
- Delay to April 2009? – YES/NO



Challenges – past and future

Price linkage recent case:

- **Generics Bulletin, 10 January 2008 Issue 196**
- **“Bulgarian firms win pricing concession”**
 - Generic drugs in Bulgaria will be eligible for reimbursement provided they are priced at no more than 80% of the reference brand's cost, according to a positive list ordinance just published in the country's official gazette. A previous draft ordinance had proposed price linkage at 50%.
 - While the ABPhM remained opposed in principle to linking the price of generics to the price of reference products, the 80% limit at least provided a framework in which generics could compete.



Challenges – past and future

Price linkage recent case:

- **SCRIP, February 1st No 3332**
 - “...It has been agreed that generic medicines whose prices are no higher than 80% of their brand reference prices will be entitled to reimbursement. The ministry initially decided that the maximum price should be 50% of the reference price, but this was opposed by the industry led by the association of Bulgarian pharmaceutical manufacturers (ABPhM).
 - It received support from the European Generic medicines Association which wrote a letter to Bulgaria's prime minister and said the 50% restriction was anticompetitive and gave market advantages to producers of original drugs.



Challenges – past and future

- Companies still have to wait up to **90** days to have the prices of their Rx products approved by the health ministry's Pricing Commission and another 90 days **before** a reimbursement decision is made by the PDL Commission.
- Term too **long** and delays products entering the market, as price applications could only be submitted after receiving marketing authorizations.
- **Immediate inclusion** of Gx medicines in the PDL, after obtaining MA is needed – time and cost saved by government and patients!



Pharma Forum – barriers to Generic medicines

- Eric Gorka (Sandoz) – EGA president:
- *“Over €20 billion in savings is being secured for patients and healthcare systems by generic medicines competition, but this can only be effective, increased and sustainable on condition that generic medicines are ensured rapid market entry. A quick look at the market entrance of the top 35 off-patent molecules shows that in some cases the first generic medicine only entered the market up to 20 months after the patent expired.”*



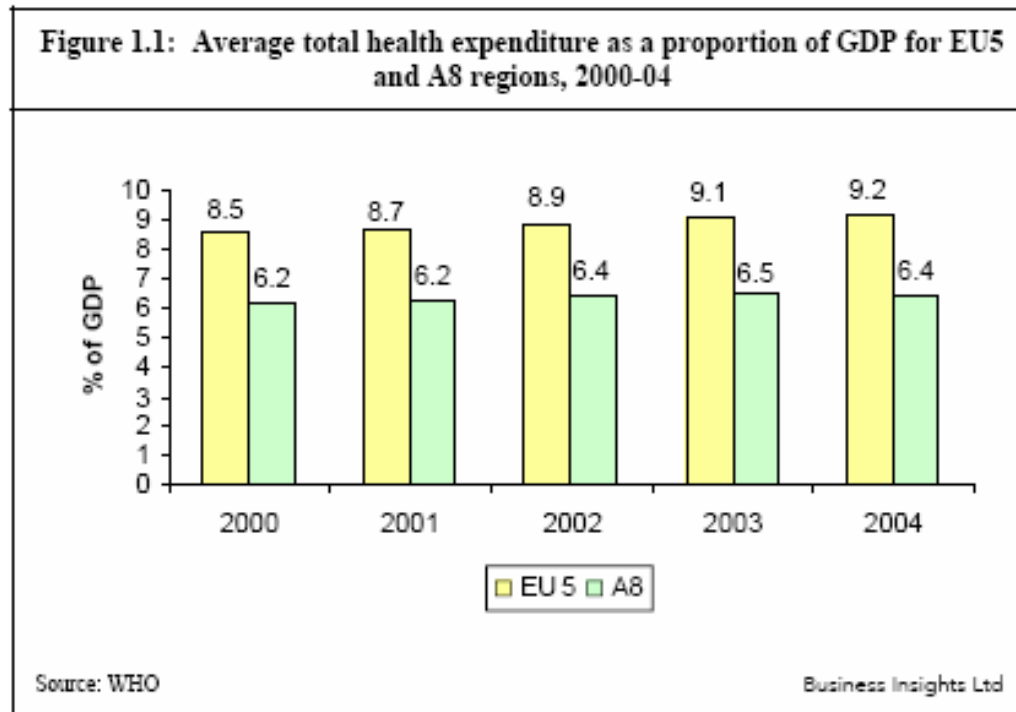
Highly cost-containment policy environment

- Lack of budget resources continues – 4.3% from GDP.
- Global Economic Crisis appeals more than ever to the rational and optimal use of medicines and resources!
- Still no incentives from the state to promote generic consumption, which can bring more savings to the budget and the healthcare system.



Highly cost-containment policy environment

- Policy and healthcare financing in CEE





Highly cost-containment policy environment

- No free pricing for non-reimbursed drugs, except OTCs (G10 Rec. 6)
- Reference pricing system – good or bad?
- Co-payment increases by lowering levels of reimbursement.
- Pressure on prices of both generics and brand medicines.
- No price/volume negotiations.



Final Recommendations of the High Level Pharmaceutical Forum

Recommendation 9: Optimal use of resources



2nd October 2008

9.1 Optimal use of national budgets should take into account patients' needs.

9.2 National pricing and reimbursement policies should ensure an efficient use of price control, a consistent package of supply- and demand-side measures and the right environment for price competition. Member States should secure the principle that a Member State authority to regulate prices in the EU should extend only to those medicines purchased by, or reimbursed by, the State. Full competition should be allowed for medicines not reimbursed by State systems or medicines sold into private markets.



Communication from the Commission - A Call for Action

e) *Competitive generic market*

The increased use of generic medicines is an important factor in improving the sustainability of health care financing for pharmaceuticals. Health care costs across Europe are rising. Increased use of generic medicines can improve the sustainability of financing. Generic medicines can provide significant savings to healthcare providers, however, their use must be balanced with sufficient incentives to develop innovative products.

Key actions

Brussels, 1.7.2003

- Introduction of a "Bolar-type" provision allowing generic testing, as well as the consequential practical requirements, before the end of the patent protection period in order not to delay the introduction of generics on the market after the expiry of the patent;
- Following political agreement in the Council, the introduction of a marketing authorisation application for a generic and to grant this authorisation in the last two years of the data protection period of the reference product for all products except those falling in the mandatory scope of the centralised procedure. This will allow these products to come on to the market immediately after the end of the ten years data protection period;
- Providing a clearer Community definition of generics;
- Introducing greater flexibility for generic producers to supply generic medicines to member states where the reference product is not on their market; and



The situation today

- **EGA WELCOMES THE ADOPTION OF THE REVISED VARIATIONS REGULATION:**
- Considering it a “positive step” toward simplifying and optimising the system of changes to Marketing Authorisations, the EGA welcomes the European Commission’s adoption of the EU Regulation on the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.



The situation today

- Bulgarian pharmaceutical act fully harmonized with the EU legislation
- Bulgaria is EU member since 1 Jan 2007
- Since mid 2006 the industry is in constant process of:
 - Changing the API suppliers
 - Upgrading the production facilities
 - Improving the quality management
 - Optimizing the product portfolio
 - Improving the dossiers (CMC) via **variations**

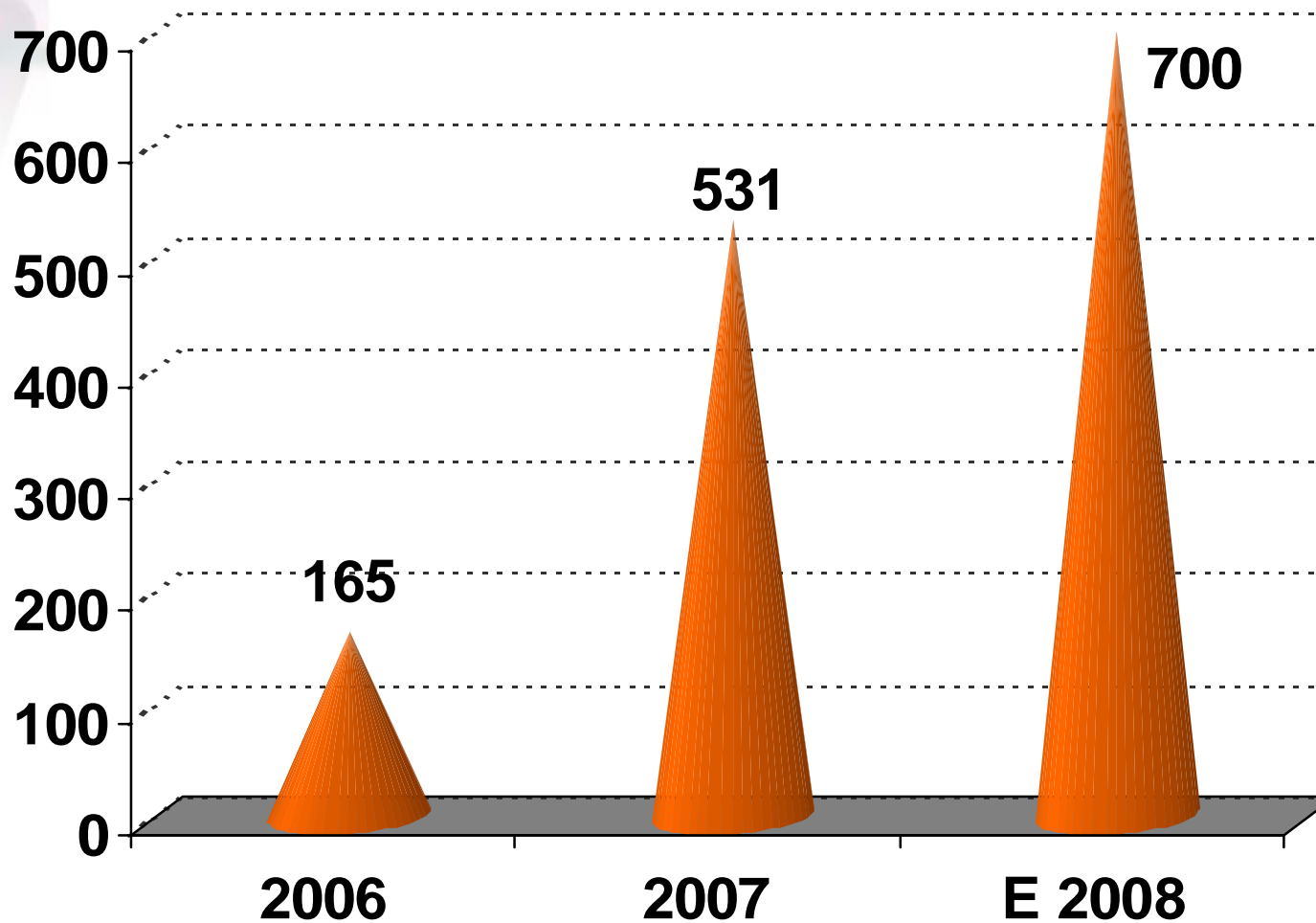


Variations – clearly the very difficult part

- For old products with deficiency of API supply
- For transition to validated API suppliers
- For related variations (more than one at a time)
- For different compositions on different markets
- For administrative purposes (packs, PIL, blisters)
- For further harmonization (readability, Braille, blisters in BG etc.)
- For whatever reasons

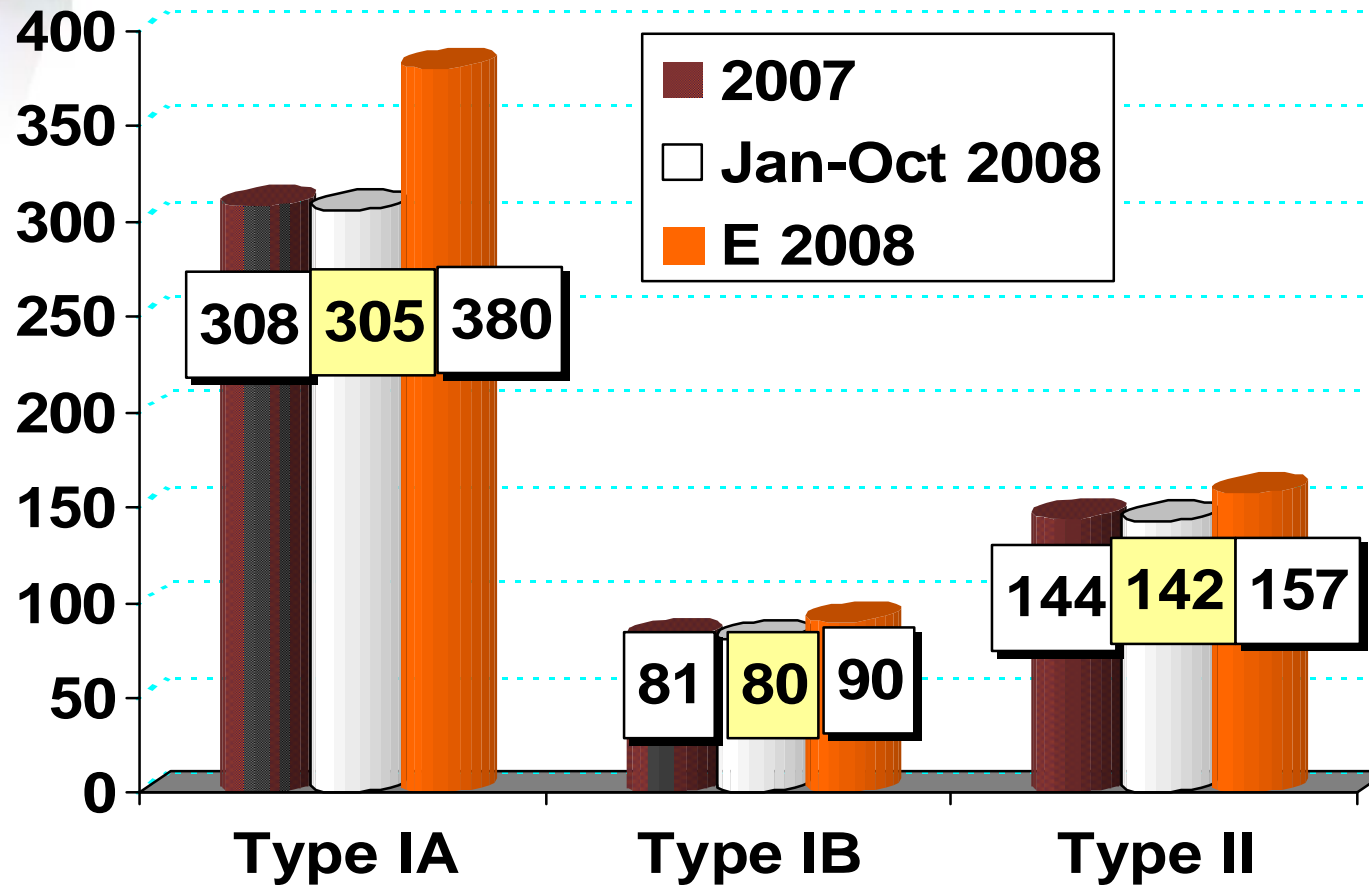


Actavis Bulgaria Variations 2006-2008



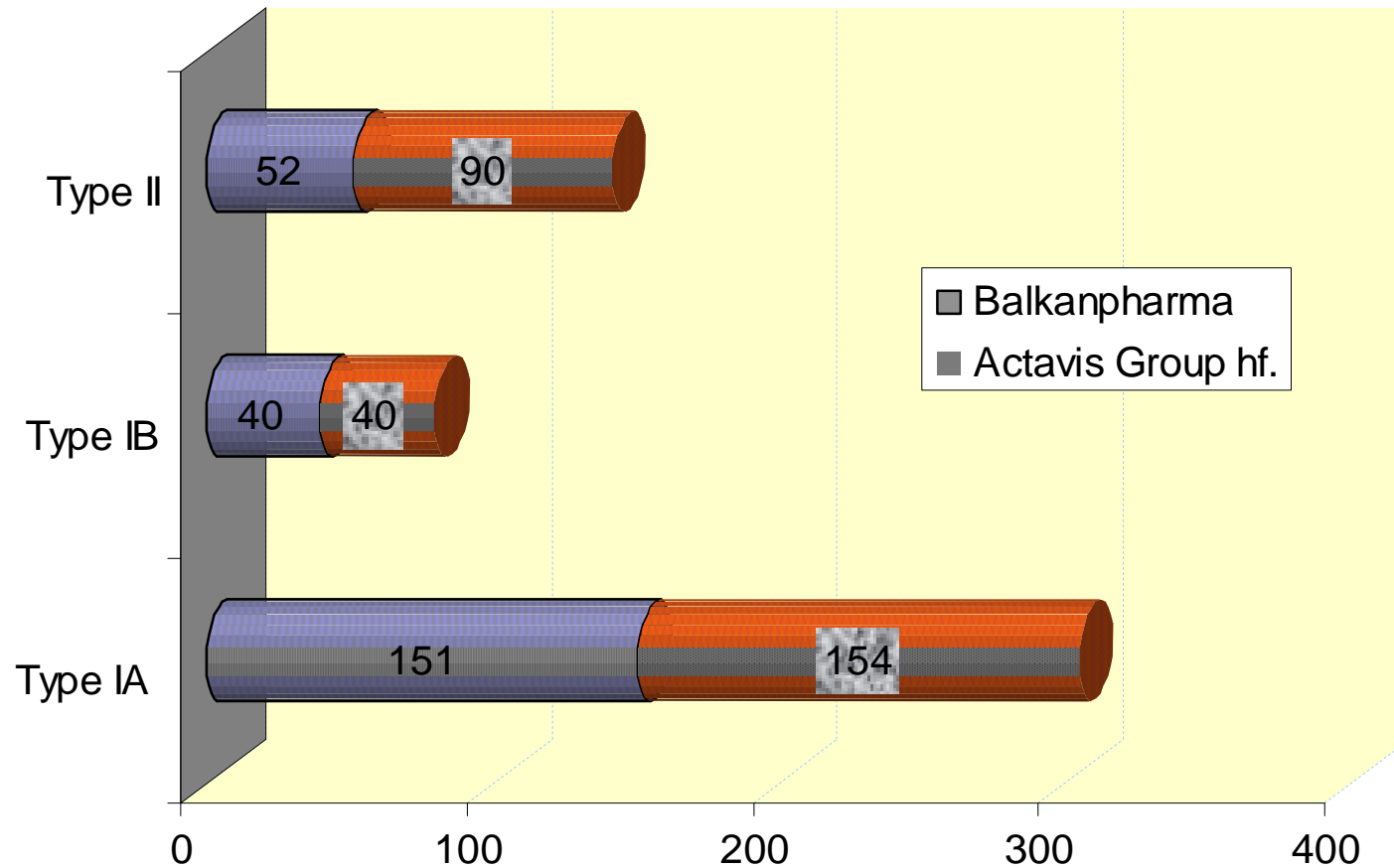


Actavis Bulgaria Variations split 2007-2008





Variations split Domestic-Imported products





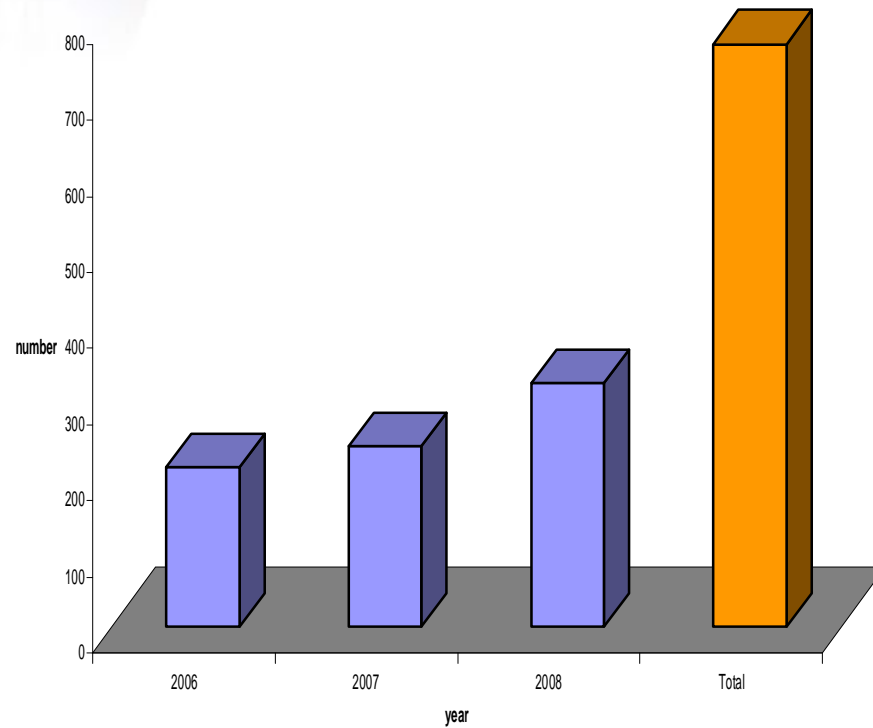
In our case

- No of registered products in Bulgaria – 155
- No of countries with market presence – over 25, incl:
 - EU countries
 - Russia
 - Ukraine
 - Ex-Soviet Union countries
 - RoW (Tunisie, Vietnam, Algerien etc.)
- Therefore – diverse picture with many icebergs

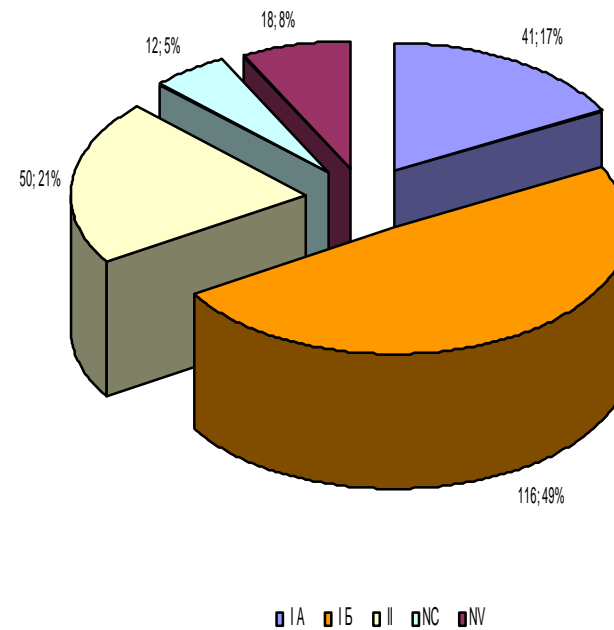


No of variations (BG only)

Total No 2006-2008



Variations by category - 2007





Most common reasons for variations

- Minor variations IA

IA1 - Change in the name and/or address of the MAH

IA 15 - Submission of a new or updated CEP for an active substance

IA 25b - Change to comply with an update of the relevant monograph of PhEur

IA 36b - Change in the shape of container/closure

IA 38a - Minor change to an approved test procedure



Most common reasons for variations

- Minor variations IB
 - IA 18** – Replacement of an excipient with a comparable excipient
 - IB 26 & 27**- Changes in the specifications/test procedures of the immediate packaging of the finished product
 - IB 33** – Minor change in the manufacture of the finished product
 - IB 37 & 38** – Change in the specification/test procedure of the finished product



Most common reasons for variations

- Major variations - Type II
- Safety reasons** - update of SPC & PIL
- Changes in module 3** referring to:
- API supplier
 - manufacturing in-process control
 - release & shelf-life specifications
 - composition, etc.



Main reasons for variations

- **Process optimisation variations**

batch size, manufacturing process, specifications
(implementing the design space concept)

- **Administrative variations**

name, address, CEP updates
(annual reporting system)

- **Flexibility Increasing variations**

API sources, bulk manufacturing sites



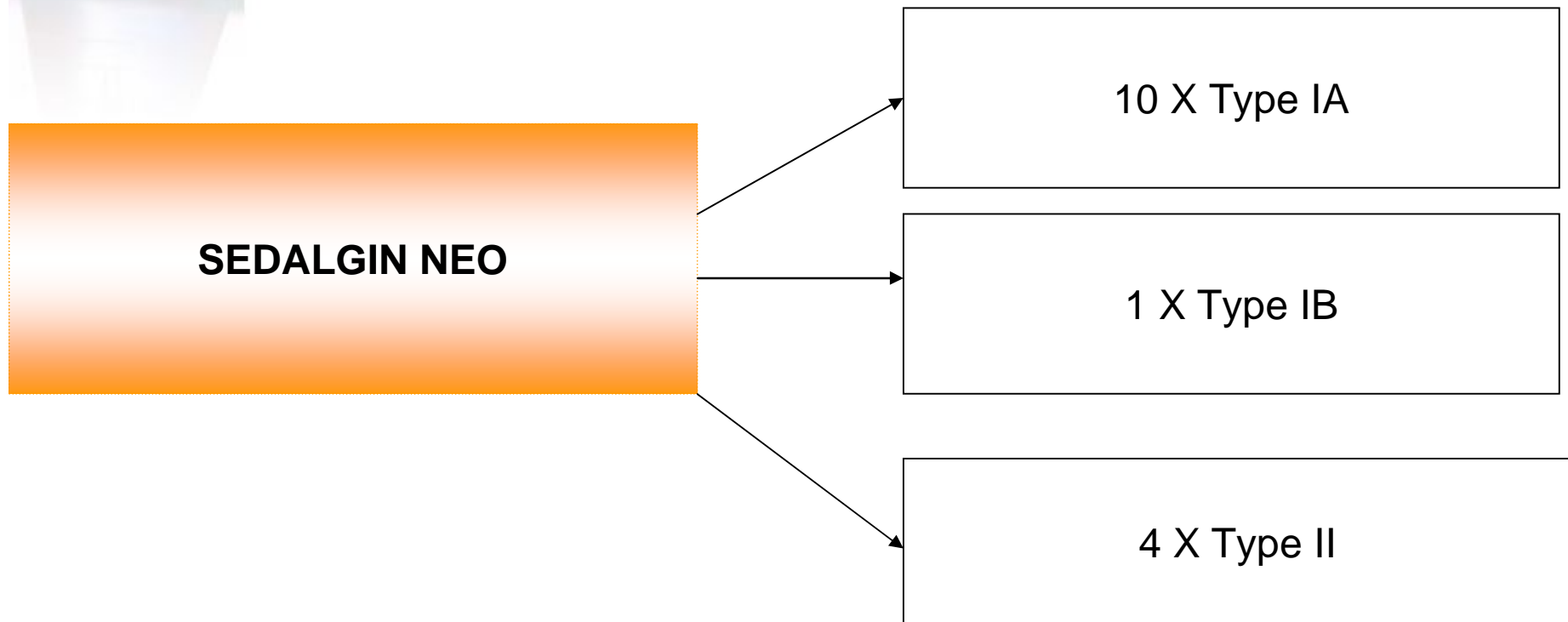
The worst - related variations



- Variation upon variation
- Champion products
- Related variations
- Etc.

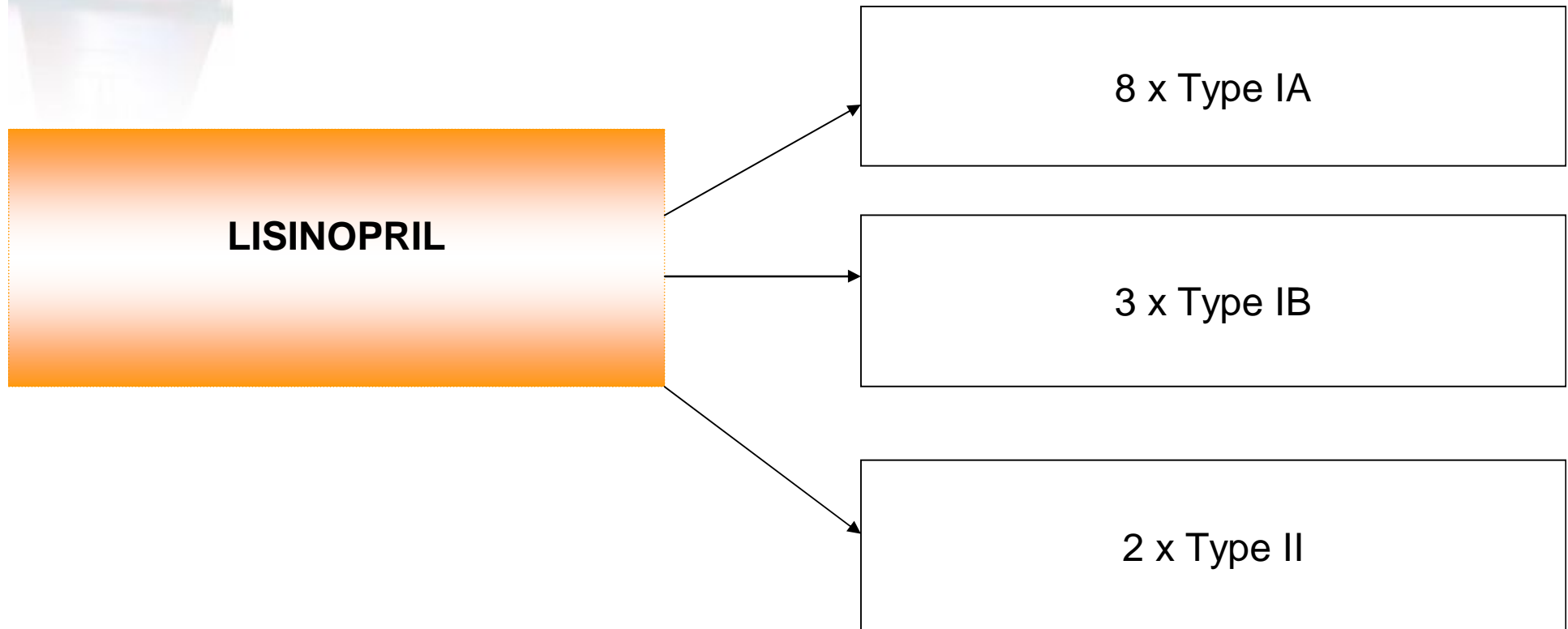


Variation upon variation champions in variations 2007



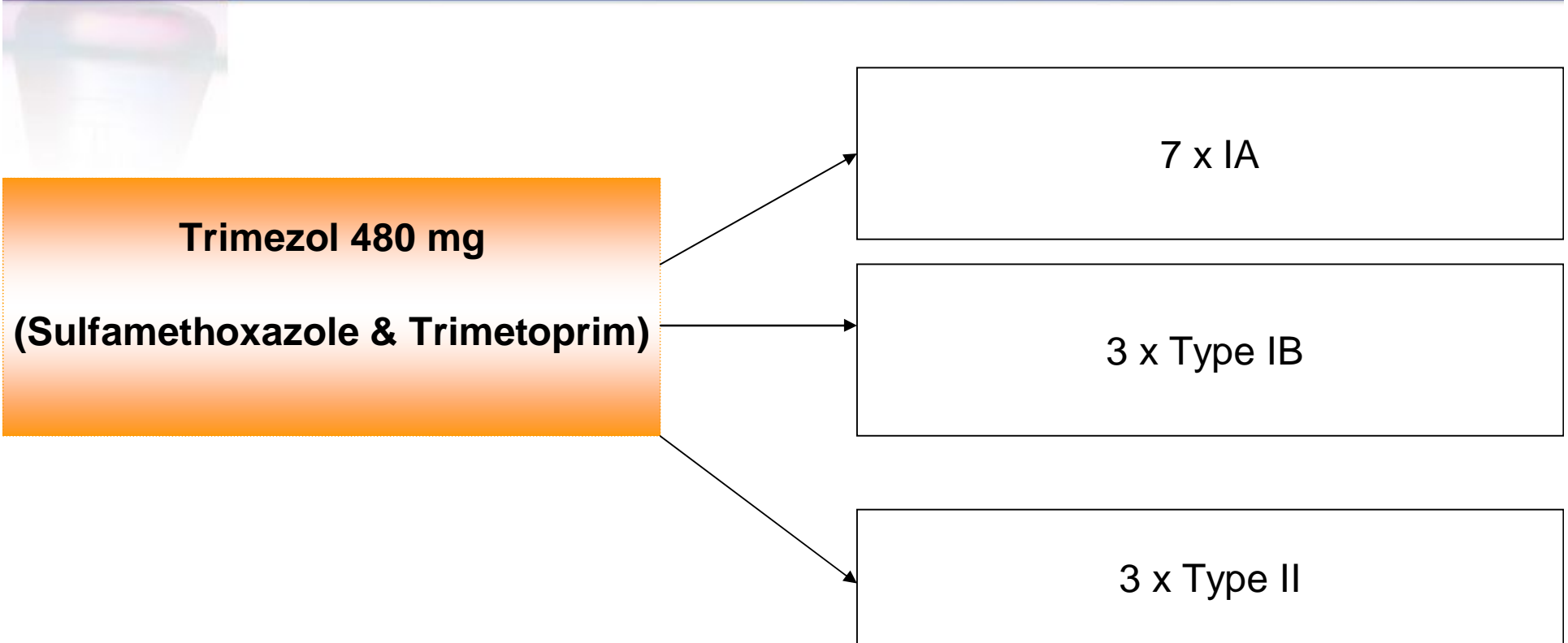


Variation upon variation champions in variations 2007





Variation upon variation champions in variations 2008





Do we manage this?

- Workload?
- Resources?
- Internal co-ordination?
- Uniformity across markets?
- Expenses?



Variations Administrative & financial burden

- Cir. 3,5 variation applications filed every working day

Expenditures per year

- 2007 - BGN 324,500
- Jan-Oct 2008 - BGN 466,000



Conclusions

- National MAs represent the vast majority of authorizations in the EEA (more than 80%)
- Community rules not harmonized
- Administrative burden for both agencies & industrial operators
- Logistic complications



Conclusions

- Both agencies and companies will benefit from facilitating the preparation and review of the variations
- Tell & do approach for minor variations requiring immediate reporting
- Introduction of annual reporting system for minor variations that should not require any prior approval and be notified within twelve months following implementation (do & tell approach)



Conclusions

- Transitional period to be allowed for implementation of Type II variations
- Introduction of grouping of variations in case of several variations for one MA or more than one MA affected by the exact same group of variations
- Worksharing procedure will be beneficial for globally operating companies



Our part

- Optimization of the internal communication
- Specialized task force for managing variations (different from new submissions)
- Better planning
- Uniform approach
- Time ruling



Hence our support

- For revision of the variation regulation
- For “DO and Tell” concept (type IA)
- For default variations (type IB)
- For grouping of variations into single submission
- For optimizing the workload of the agencies:
 - Common rules with national variations
 - Work sharing in CMD
 - Application for extension in the scope of variations



Variations system Germany

- Variations of national German MAs follow a national system, different from the EU one
- The majority of the national German Type IA variations does not need official approval
- Transition period for implementation of Type II variation announced in the application form
- Grouping of variations belonging to one and the same MA in one application form - for example changing of test procedure, batch size increase, shelf-life extension and inclusion of new ADR in the SPC/PIL would be one application form only



Variations system The Netherlands

- Type IA are implemented after confirmation of receipt and validation by the authorities
- Type IB - transition period for implementation is indicated by the applicant in terms of production after approval
- Type II – if not related to specific batches – 6 month transition period for implementation; if related to specific batches - than indicated by the authorities;



Variations system Portugal

- Type IA – tacitly approved in 20 days, no official approval issued
- Type IB – implementation period pointed out in the application form
- Type II – the same as IB's



Variations system Romania

- Type IA – official approval is issued
- Type IB – implementation period pointed out in the application form
- Changes in printed materials must be implemented within 6 months following approval