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Medicines
you can trust

EU Marketing Authorisation (MRP+DCP+CMD/h)

Challenges for Generics in the New European Environment

18 April 2007, Sofia / Bulgaria

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Industry Regulatory Perspective

Challenges for Generics in the new European Environment

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Industry Regulatory Perspective

Ø Why Generics?

- Industry Perspective: Successful Generics
- What is a „European“ Generic?
- Challenge for EU Generics:
  How does a Generic become available to patients in Europe?

Why Generics?

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Many generics enter the market upon patent expiry

Effects of Generic Competition:

- Continuous price decay after patent expiry results in
  - Financial buffer for innovative treatments
- „Price war“: A „war for the patient“ only, if there are
  - **Long-term** savings for health fund systems

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Why Generics?

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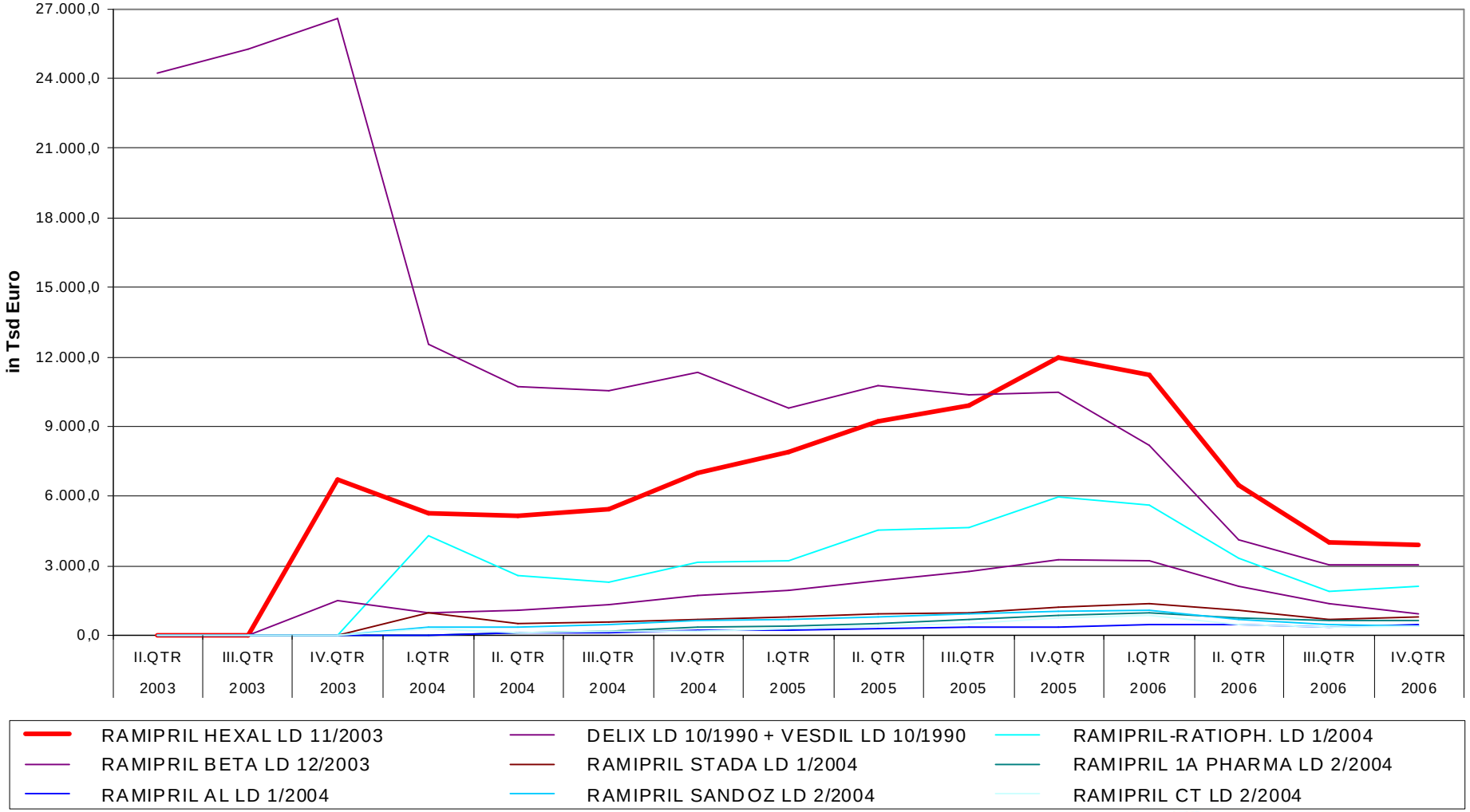
3 Years Off-Patent - Example ***Ramipril*** *(SPC/DE exp 10.01.2004)*:



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Why Generics?

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More Generic Competition Effects:

- Driver for „fresh“ innovation
  No eternal „cornucopia“ for innovator…
- New jobs in pharmaceutical and related industry
- ð ***More*** people than before will profit from pharma revenues

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Industry Regulatory Perspectives

ü Why Generics?

Ø **Industry Perspective:** „Successful“ Generics

- What is a „European“ Generic?
- Challenge for EU Generics:
  How does a Generic become available to all patients in Europe?

Industry Perspective

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Successfully making affordable Generics available to patients means:

- Ø Obtain many well „marketable“ marketing authorisations (e.g. product name, SmPC, proper trade dress for good compliance, etc.)
- Ø Offer an attractive price
  - ØPermanently optimize:
    - cost structures
    - supply chain structures
- Ø Build big portfolio (enabling for mixed calculation)

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Industry Perspective

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Successfully making affordable Generics available to patients means:

- Ø Reliably supply healthcare markets, i.e.:
- Ø Avoid „stock-outs“
  - Ø Achieve high manufacturing flexibility, regulatory flexibility, minimize batch failures
- Ø Ensure flexible, robust (mass) production processes granting consistent and commensurate quality

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Industry Perspective

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Successfully making affordable Generics available to patients means:

- Ø Comply with generic business laws, i.e.:
- Ø „Focus on Volume“ as compensation for low Margins:
  - ØBroad portfolio (many substances + dosage forms)
  - ØMultitude of Marketing Authorisations
  - Ø(e.g. Sandoz (2006): 3400 MAA‘s for 99 global „filings“
- Ø Gain & maintain high market share
- Ø Focus on „first to market“ („day-1-launches“)

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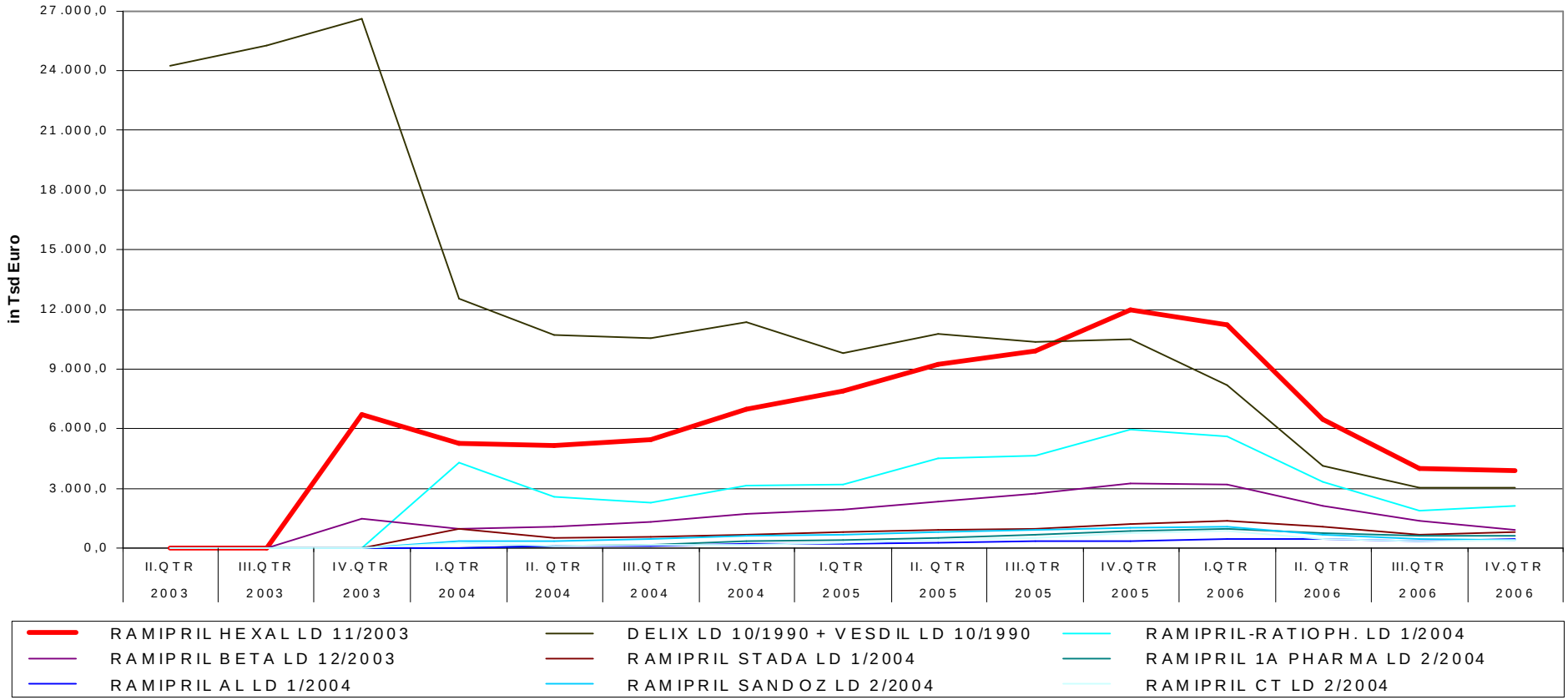
Why „**First** to market“ ?

Let‘s look at Ramipril again:



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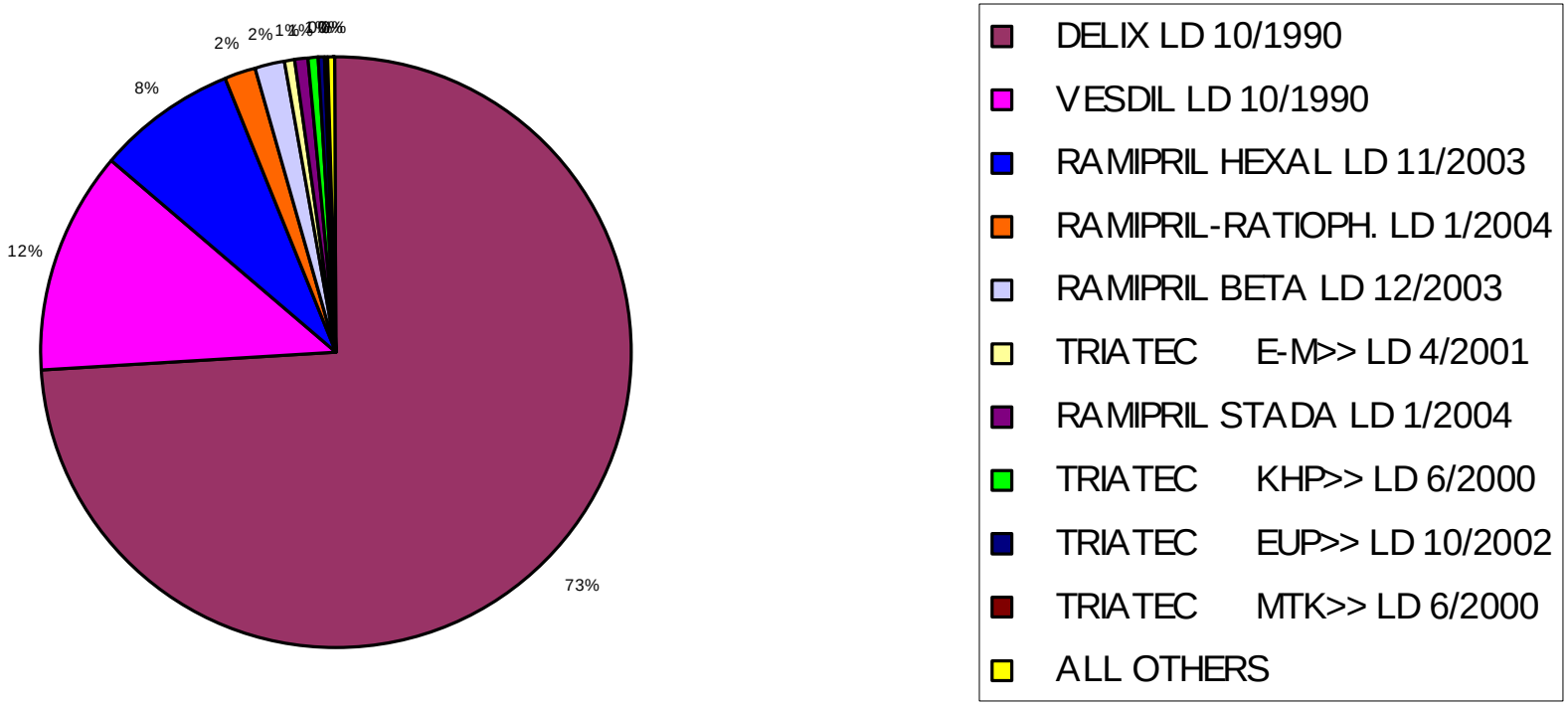
Why „**First** to market“ ?

RAMIPRIL MARKTANTEILE
MAT/01/2004



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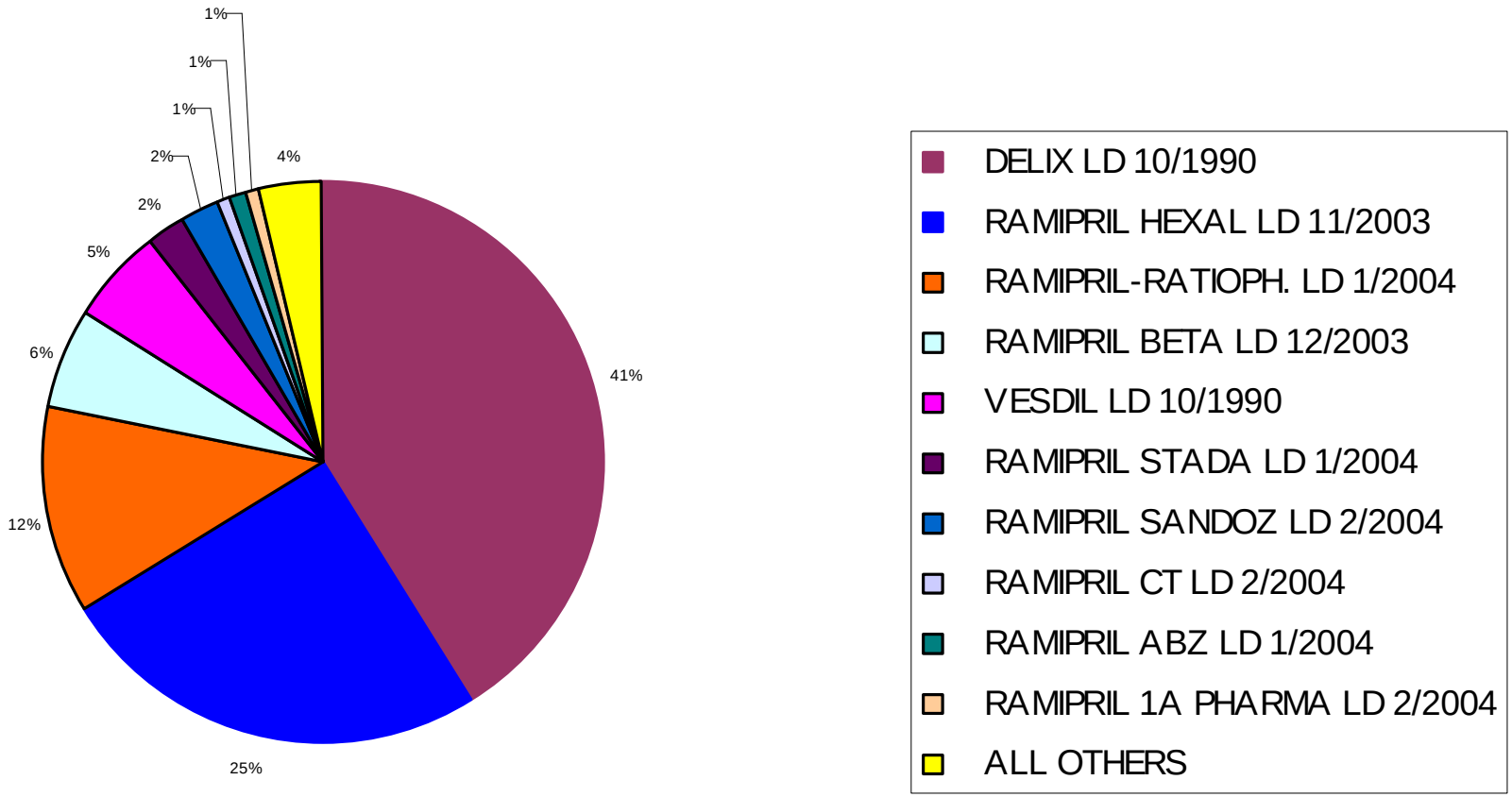
Why „**First** to market“ ?

RAMIPRIL MARKTANTEILE
MAT/01/2005



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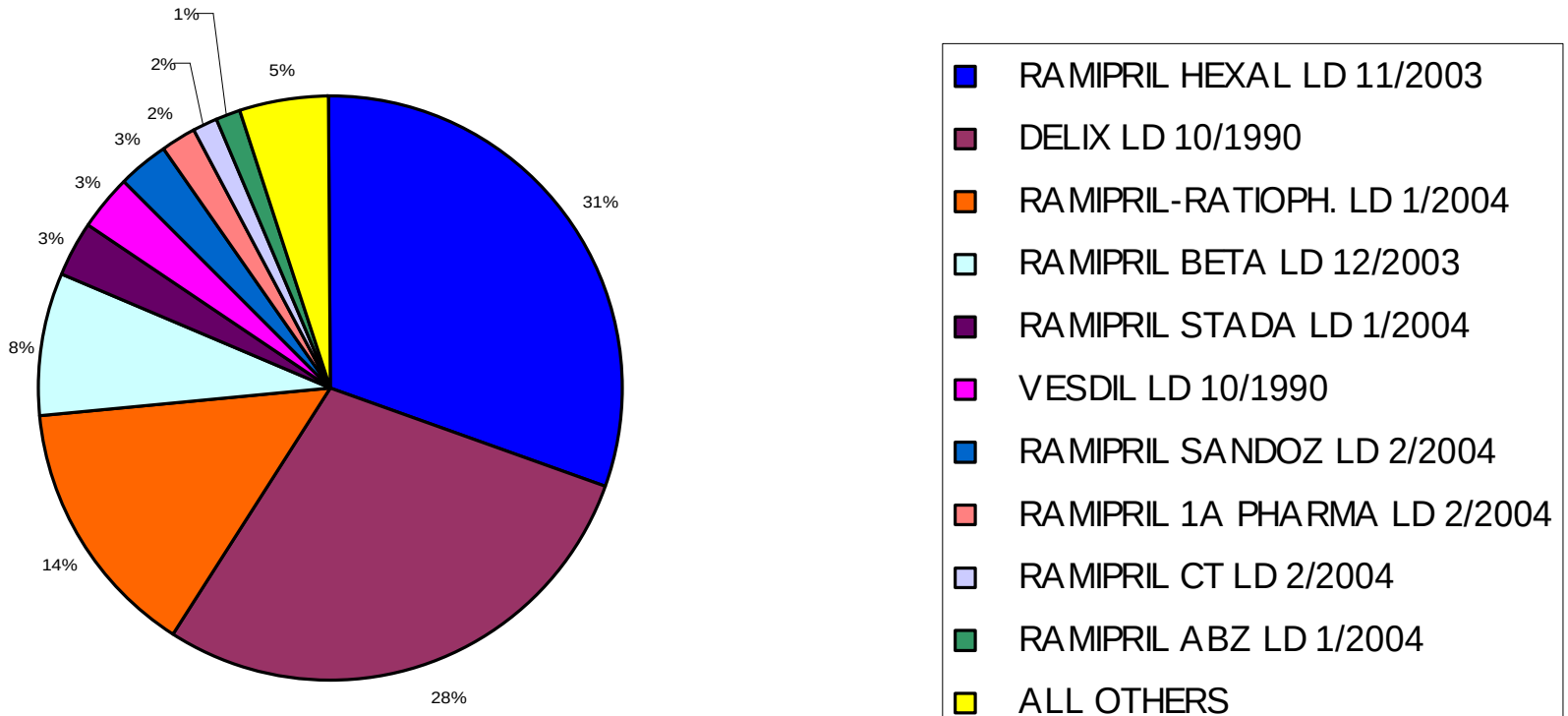
Why „**First** to market“ ?

RAMIPRIL MARKTANTEILE
MAT/01/2006



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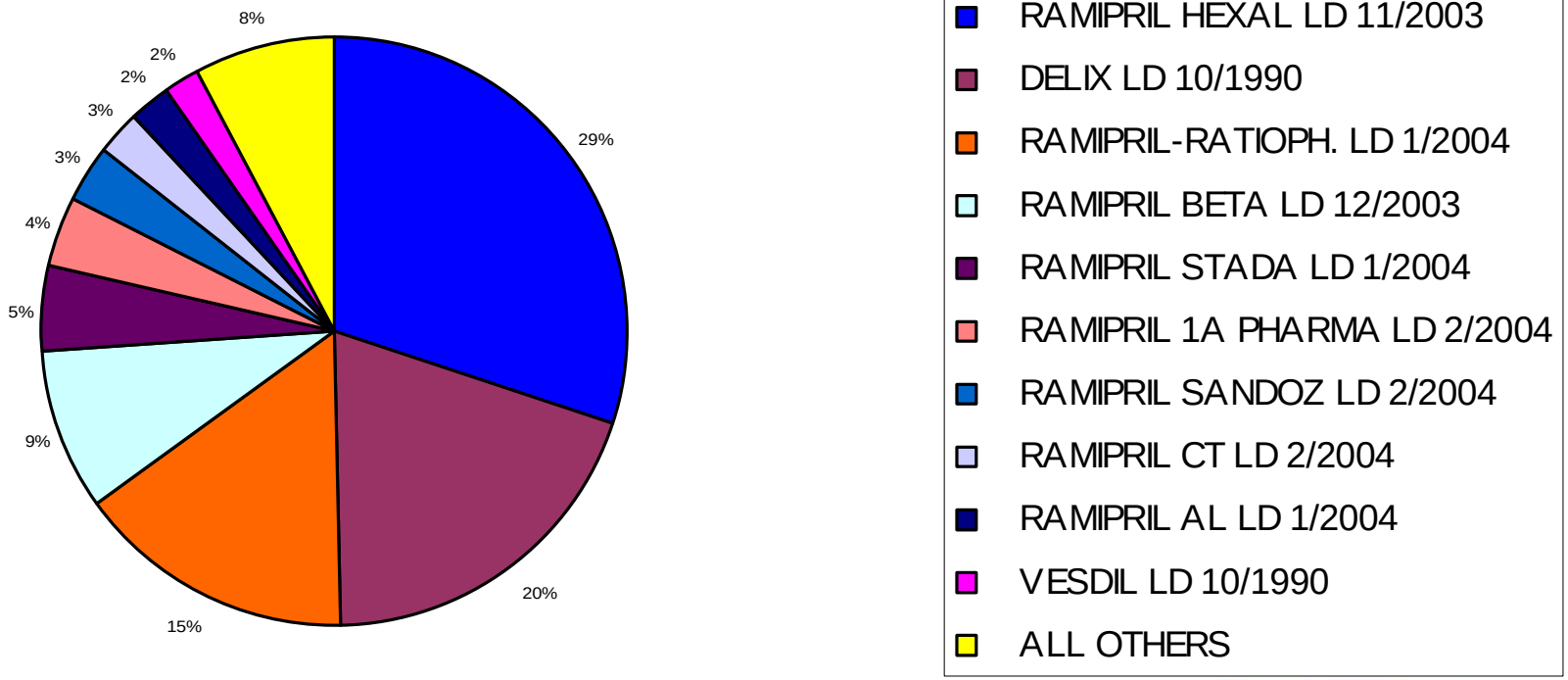
Why „**First** to market“ ?

RAMIPRIL MARKTANTEILE
MAT/01/2007



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Challenges for Generics

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è Conclusion:

„Day-1-Launch“ into market is the

ý ð Challenge No 1

for succesful generics. „Day 1“ is the day when patent protection in any country has expired, 0.00 h!

6-3 months before launch, supply chain organisation needs „ready-to-use“, valid marketing authorisation!

- But there are obstacles…

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Challenges for Generics

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Bottlenecks and stumbling blocks for generic product development:

- **API Sourcing:** Commercial availability at project start
  - Circumvent increasing complexity of **IP landscape:**
  - Formulation Patents ↔ Bioequivalence
    - Synthesis patents, polymorphism patents
    - Protection of shape and colour ↔ substitution
    - Usage patents
    - ð Availability of complete submission dossier (incl. ICH stability data)

- **Vigilant & flexible project management is mandatory !**

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Challenges for Generics

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Stumbling blocks for generic launches:

- **Transfer to off-patent manufacturing site**
  (Roche-Bolar no provision for launch batches)
- **Follow-on patents**
- National original product changes SmPC or dosage form, just around patent expiry (ð may affect generic interchangeability)

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Challenges for Generics

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Find your Path through EU Patent Jungle and against „Defense Strategies“

- Creative innovators postpone generic market entry with:
  - Usage patents (intravenous use of emulsified cytostatic)
  - Indication patents („nausea and vomitus“ for ondansetron…)
  - Formulation patents (use of protective layer between acidic gastro-resistant film and acid-sensitive API)
  - „Second generation“ patent strategies (enantiomers, salts)

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Submission and Approval Planning under „Day-1-Pressure“

Early dossier availability is not merely a matter of good (or poor) planning. Surprises during development are not uncommon.
You may always come too late!

Reliablility of estimated overall approval times (i.e. including all possible delays and „lead times“, such as pre-validation, pre-submission-hearings, clock-stops, national MA issues, pricing, etc.), is essential for generic project & launch management.

If regulatory time frame looks „d-1-launch-critical“ (*for a country*):

Ø Search for *(national)* **license offer**!

Challenges for Generics

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ý ð Challenge No 2

License Management

- Ø In a licensor‘s network with many licensees, price reduction options are few (limited flexibility with COG*s, royalties, suppliers, manufacturers, etc.…). :
- Ø Increasing economical pressure leads to search for opportunity to decrease dependence on competitors and/or suppliers by **switch** to a (late) ***in-house*** development (after merger: product harmonisation).
- Ø Variations do not serve this purpose very well, as there is an entirely new dossier involved. Often connected with entry into additional markets.
- Ø New application with new dossier. Challenge: Resources in RMS.

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Industry Regulatory Perspectives

- ü Why Generics?
- ü Industry Perspective: Successful Generics
- ü **What is a „European“ Generic?**

- Challenge for EU Generics:
  How does a Generic become available to all patients in Europe?

The „European Generic“

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1. EU Legislation: „Regulatory“ Definition of

- ü **Generic:** Dir 2001/83/EC, Art 10(2)b:
  (same active ingredient, strength, dosage form, bioequivalence)
- ü **„Hybrid“**: Art 10(3): Additional Data
- ü Biosimilar: Art10(4)
- ü European Reference Product: Dir 2001/83/EC, Art 6

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The „European Generic“

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2. Additional „Definitions“ in National EU Markets:

Ø **<u>Rating</u>** of product as (truly) „generic“ is determined by (subsequent) national qualification for

- Substitution („interchangeability“) and/or
- Reimbursement

ð 2nd „marketing approval“ (hurdle beyond EU law)

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Types of Procedures in the EU

1. Centralised registrations	validity:
community procedure	community
2. National registrations	validity:
a) national procedures	member
b) MRP and DCP	state

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National registrations in one single member state

Only possible if a pharmaceutical company (including subsidiaries and licensees) wishes to market a medicinal product in
<u>one single member state.</u>

ð for “local” generics only

<u>Time lines:</u>
Very different, depending on the country.

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Legal Situation

A pharmaceutical company (includ. subsidiaries and licensees) wishing to market a medicinal product in more than one member state must either use the *centralised procedure* for medicinal products falling under the scope of this procedure or the *mutual recognition procedure* resp. the *decentralised procedure*.

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Scope of the centralised procedure

Optional for:

1. New active substance
2.a. Medicinal products with significant therapeutic, scientific, technical innovation
2.b. Where authorisation is in interest of patients
3. **Generics to centrally authorised medicinal products**

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Challenges for Generics

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Centralised Procedure:

ØPro Generics:

- Short, reliable time schedule
- **Validity in all MS**

ØContra Generics:

- High cost
- Translations into all MS
- Single name

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Theoretical maximum duration of DCP vs. MRP

DCP days		MRP days	
X + 14	„Timely notification“ + validation phase	X	national validation RMS
120 + X	Assessment step I + clock-stop	210(?) + X	RMS phase + clock-stop
		X + 90	Update dossier and assessment report between RMS approval and start of MRP
90	Assessment step II	14 + 90	CMS validation + MRP (international phase)
(30 +) 60	(start of) CMD referral	(30 +) 60	(start of) CMD referral
30 (?)	nat. MA phase	30 (?)	nat. MA phase
344 + XX	Total	**524 + XXX**	Total

Challenges for Generics

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Selected Sandoz numbers from 2006:

DCP	**43**
MRP	**35**

- Ø RMS: AT, DE, DK, FI, NL, SE, UK
- Ø Mean validation period: about 30 days
- Ø Draft answer assessment (clock-off): 3 weeks to 3 months
- Ø Mean clock-stop period: 140(+) days:
  - ØDE: 110; DK: 136; NL: 155; SE: 131; UK: 100

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Challenges for Generics

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ý ð Challenge No 3

„Find your RMS“

- **v** Out of **27** MS, max. **8** MS are currently acting as Reference Member State „routinely“
- **v** Clinical expertise for therapeutic fields relevant in some cases: complex hybrids [phase III in Module 5], biosimilars
- **v** Resources are an issue
- **v** Same RMS for dossier switch from license plus application in additional CMS may also become an issue
- **v** With 20+ RMS, the capacity situation should improve

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„Find your RMS“

During 2006, Sandoz experienced increasing „lead times“ before obtaining a definite „time slot“ from RMS to start a DCP:

- DK, SE: ca. 12 months
- NL: ca. 6 months
- FR: Detailed „pre-filing“ assessment - if dossier will be acceptable for DCP
- FI: 6-12 months, only selected cases
- AT: selected cases, pre-submission meeting
- DE, UK: 3-6 months

- Repeat-use procedures: Last priority (wait for 9–12 months)

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Challenges for Generics

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ý ð Challenge No 4

Plan your Approval Date

- DCP is clearly superior (but still two „X“ remain)
- Time target for validation (14 days) seems unrealistic (average 30)
- Clock-stop periods in DCP and time required for reviewing draft responses are unpredictable. No obvious link with quality and quantity of issues raised by MS.

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ý ð Challenge No 4

Plan your Approval Date

- Criteria for Potential Serious Risks to Public Health (PSRPH) not commonly interpreted by all MS
  ð CMD-referral, arbitration ð further delay
- Option to end „uncomplicated“ DCP already after 105, 120 or 150 days should be used more freely.
- National phase: 30 days to issue nat. MA still far from realization with some MS (some countries can take up to 2 years).
  Same issue with national procedures, but not so transparent.

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ý ð Challenge No 5

Variations

v Typical „Optimisation“ Changes:

- Alternative manufacturer of active substance
- Optimisation of the manufacturing process
- Additional bulk manufacturer
- Change of the formulation

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Variations

Timelines for Changes in EU (calendar days)

- **Type IA notifications:** 14 days
- **Type IB notifications:** Min. 44 - Max. 104 days
- **Type II variations:** Min. 104 - Max. 224 days
- **Extension applications:** Approx. 1 year

Variations

- For 2006, Global DRA Sandoz has reported **23102** variations worldwide (in total)
- **20845** of which were done in the EU
- Given a stock of **8000** EU marketing authorisations, this is still enormous

What is the reason for that?

Main Reasons for Variations

1.) Process optimisation variations:

Change in batch size, manufacturing process, IPC parameters, specifications

ð This block could be diminished by implementing the design space concept

Main Reasons for Variations

2.) Administrative Variations:

Product name changes, address changes, CEP updates

ð This block could be diminished by implementing the annual reporting system

Main Reasons for Variations

3.) Flexibility Increasing Variations:

e.g. additional API sources, bulk manufacturing sites:

- ð many are not minor and need approval
- ð but cannot be avoided, since they are a direct consequence of the dynamic generic business

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Industry Regulatory Perspectives

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Ø Challenge for EU Generics:

How does a Generic become available to all patients in Europe?

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Challenges for Generics

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Successful
EU Generics

are those that will become actually available, without delay, to all patients in all member states

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Challenges for Generics

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TODAY, Successful EU Generics have to:

- ü be „compliant“ with various ***national*** healthcare systems
- ü qualify for reimbursement in ***national*** healthcare systems
- ü be interchangeable with ***national*** originator products

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The „European Generic“

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National Health Systems

For Substitution and/or Reimbursement of Original by Generic Product

- Some countries need **100% identicality** with **national originator** SmPC
- diverse other HS-specific national rules have to be observed across Europe (Name rules: INN+C. , „EFG“ Status in Spain, etc.)

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The „European Generic“

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If more than 1 Member State is involved for the „same product“:

- Mandatory use of **MRP** or **DCP**
  (CP also possible, if originator‘s route was central)

- Result:
  HARMONIZED „Generic“ SmPC

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Challenges for Generics

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Mandatory result of **EU-HARMONIZED** „Generic“ Marketing Authorisation leads to

ý ð **Challenge No 5:**

Meet the Needs of 27 National Health Systems

Without a really synchronised SmPC harmonisation for original products and generics (e.g. immediately upon submission of generic application).
Systematic SmPC harmonisation acc. Dir. 2001/83, Article 30 is slow, meanwhile many „EU generics“ are not reimbursed.

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Challenges for Generics

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On „Equal Terms“?

EU Regulatory Legislation & Procedures:	National Health Systems :
Designed **for innovator products** (***pro****spective* view), superficially revised for generics in 2005: Definition of „Generic“ provided; but same ***procedural*** rules apply.	Generic definition not translated into NHS. Provision for substitution and good compliance: Generic **follows** originator (***retro****spective* view)
„Harmonisation“ of „generic“ SmPCs required, independent of originator	**No** EU-focussed harmonisation of originator
Immediately applicable for all „new“ applications, **incl. Generics!**	**But no immediate** changes of registered reference products
Harmonized, but not with sufficient „retrospective“ effect.	**Not harmonized**

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MAJOR DILEMMA:

HARMONISED EU Generic Marketing Authorisations are actually **worthless,** (no market share) if they do not qualify for national

- Substitution (Interchangeability) and
- Reimbursement

in the **NON-EU-HARMONISED** healthcare environment

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Generics in Europe

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Example:

Second wave MRP for antibiotic **with aim to achieve CHMP referral** on claim of CMS to include the indication „community acquired pneumonia“ (CAP), which is not included in the originator‘s SmPC in the RMS.

CMD referral **was not favoured by the applicant**, because the outcome of same is considered a result of the generic MRP, whereas a „CHMP harmonised“ EU SmPC resulting from arbitration may, in a few systems, be granted reimbursement, even though different from the originator.

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Generics in Europe

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Best solution for the patient:

All SmPCs **for any medicinal product with the same INN-strength-pharmaceutcal form** (including the originator) should, at the same time, always be the **same** (i.e. **really** harmonised) **throughout the EU**.

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Generics in Europe

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To achieve fast penetration of the European market with affordable generics TODAY, there is still a dynamic for

NON-HARMONIZED national generics

in a

NON-HARMONIZED market

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On „Equal Terms“?

It would save European Healthcare Systems millions, if generic SmPCs were respected as what they are, i.e. copies of the originator SmPC. As long as unharmonised original products are reimbursed, **for the sake of the European patient, generic SmPCs should not be harmonised before the national originator SmPC.**

Generics with a valid marketing authorisation should be reimbursed in all systems, without further prejudice.

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On „Equal Terms“?

Q: How much sense does it make to treat generic SmPC (applications) as „independent“?

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Conclusion

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A Successful EU Generics Industry needs a strong and effective Regulatory Agency Network, but also:

HARMONIZED ***national*** healthcare systems

and

HARMONIZED ***national*** innovator products

or

(intermediate) tolerance to supply markets quickly with affordable EU generics on a „purely national“ SmPC basis, i.e., as long as the „purely national“ master SmPC of the originator product is tolerated

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Thank you 

for your attention !!!