

Patient access to medicines: how to prevent medicine shortages?

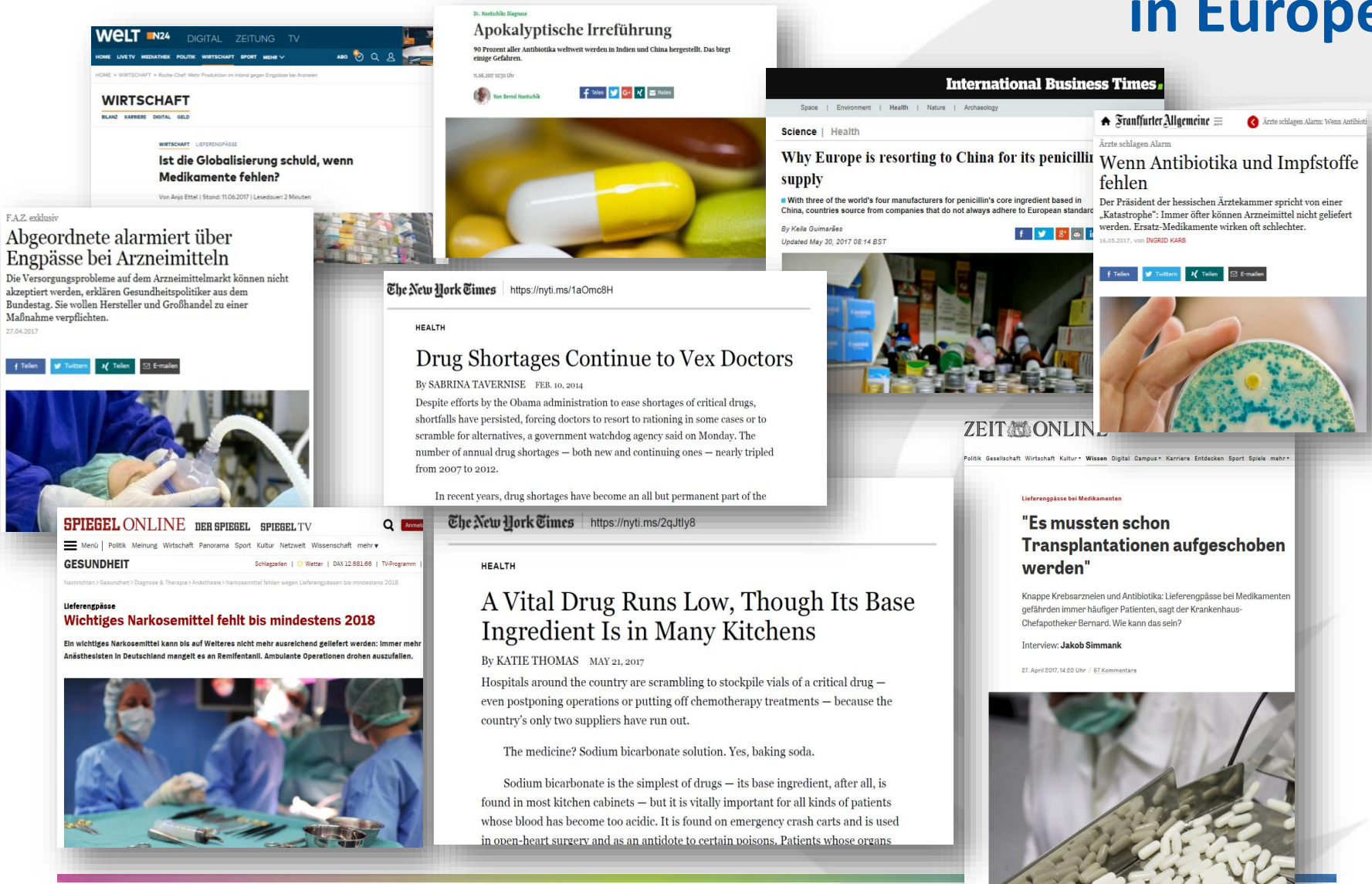
Brussels

6th December 2017

Patient access to medicines: how to prevent medicine shortages?

Marc-Alexander Mahl
Brussels, 06 December 2017

Reports about medicine shortages in Europe



Why are there multisource medicine shortages?

THE EVIDENCE THAT THE **ROOT CAUSE OF MEDICINES SHORTAGES** ARE ECONOMIC, INCLUDING UNSUSTAINABLE P&R POLICIES, IS OVERWHELMING



“It is time for health-care systems to recognize that such costs and economic drivers are essential elements”



“Cost-containment measures need to be applied with scrutiny to ensure that all players of the drug supply chain can undertake their activities in a sustainable way.”



“For generic medicines, internal or external reference pricing, tendering as well as price capping may affect drug shortages”

Generic medicines manufacturers offer maximum benefit to patients

Generic medicines manufacturers operate cost efficiently to deliver patient benefits



- **Generic drug competition is fierce** - Average price reduction after patent expiry **50%**, **increasing** over time
- Generic manufacturing is a **high-volume / low-margin** business (MS: 29% in value / 62% in volume)
- A single manufacturer can have **25 000** market authorizations in Europe
- **350 European** manufacturing facilities
- Complex supply chains for cost and flexibility (many supply chain partners)
- A manufacturer can ship to **50 000+** customers in Europe
- **R&D investment** to bring new devices, formulations and biosimilars to bring competition and access to specialty markets

Regulatory compliance impacts cost structure



Large manufacturer employ **up to few hundred** people in regulatory and Pharmacovigilance to cover Europe



More than 50% of Regulatory Activities dedicated to dossier maintenance only



75% of EU regulatory budget on **MA maintenance cost** e.g. renewals, Annual fees, PSUR's, Safety Variations, CMC Variations

Source: Medicines for Europe Regulatory Efficiency Report 2015



The ability to supply
negatively affected by:

- regulatory costs
- price pressure & tender rules



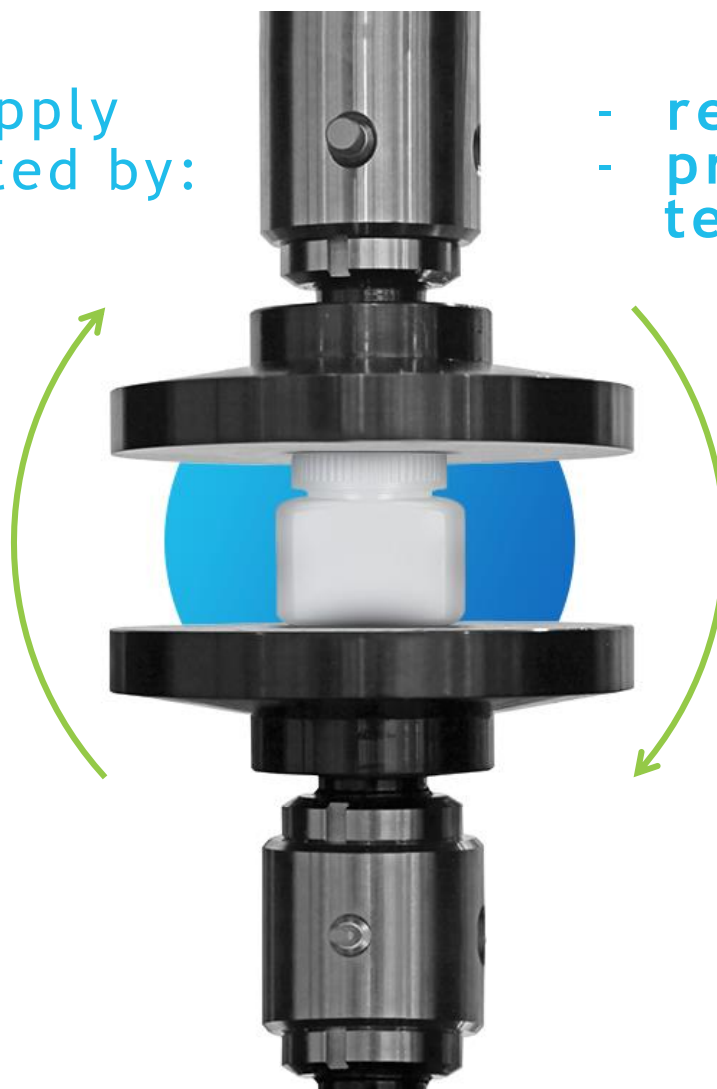
Regulatory compliance

- Falsified Medicines Directive
- GMP / GCP / ...
- Variations, notification
- Pharmacovigilance regulation



Price & tender rules

- Tendering (single-winner tenders, unbalanced penalties, lead-times,...)
- External Reference Pricing
- Price cuts
- Claw-back taxation



EXAMPLE OF PRICE PRESSURE

PORTUGAL: DRAMATIC REDUCTION IN HOSPITAL SUPPLIERS DUE TO PAYBACK

Código SPMS	Artigo SPMS	Nº Contrato Público	Número AIMS	Número Empresas SPMS	variação
G128	GLUCOSE 5% [20ML]	2012003	7	2	-5
A467	AMOXICILINA + ÁCIDO CLAVULANICO [2000 + 200 MG; IV; F/AMP]	2013005	10	5	-5
A466	AMOXICILINA + ÁCIDO CLAVULANICO [1000 + 200 MG; IV; F/AMP]	2013005	7	5	-2
C120	CEFTAZIDIMA [1G; IM-IV; F/AMP]	2013005	11	2	-9
C121	CEFTAZIDIMA [2G; IV; F/AMP]	2013005	12	2	-10
C1447	CEFUROXIMA [750 MG; IV; F/AMP]	2013005	5	2	-3
F128	FLUCLOXACILINA [500MG; IM-IV; F/AMP]	2013005	6	2	-4
M56	MEROPENEM [500 MG; IV; F/AMP]	2013005	17	5	-12
M55	MEROPENEM [1G; IV; F/AMP]	2013005	17	4	-13
P116	PIPERACILINA + TAZOBACTAM [4 + 0,5G ;IV ;F/AMP]	2013005	13	5	-8
D459	DOCETAXEL (CONC P/A SOL) [20 MG/1 ML; FRS]	2013006	10	3	-7
G46	GEMCITABINA (PÓ P/ SOL P/ PERF) [200MG; FRS]	2013006	16	2	-14
G256	GEMCITABINA [40 MG/ML; 5 ML; SOL INJ; FRS]	2013006	11	2	-9
G254	GEMCITABINA [40 MG/ML; 25 ML; CONC P/ SOL P/ PERF; FRS]	2013006	11	2	-9
P2	PACLITAXEL (CONC P/ SOL P/ PERF)[6 MG/ ML; 5 ML; FRS]	2013006	7	4	-3
P835	PACLITAXEL (CONC P/ SOL P/ PERF) [6 MG/ML; 16,7 ML; FRS]	2013006	7	4	-3
A15	ACARBOSE [50MG; CÁP/COMP]	2013007	15	5	-10
M910	METFORMINA [1000 MG; CÁP/COMP]	2013007	22	5	-17
O5	OCTEOTIDA [50MCG/1ML; F/AMP]	2013007	8	1	-7
M246	MIRTAZAPINA [30 MG; CÁP/COMP]	2013044	23	3	-20
M1104	MIRTAZAPINA [15 MG;COMP ORODISP]	2013044	15	5	-10
P396	PARACETAMOL [1 G; IV; F/AMP]	2013044	16	2	-14
T143	TRAMADOL [100MG/2ML;F/AMP]	2013044	7	2	-5
C224	CISATRACURIO (Besilato)[5 MG/2,5ML;F/AMP]	2013045	7	2	-5
I4	IBUPROFENO [200MG; CÁP/COMP]	2013047	12	5	-7

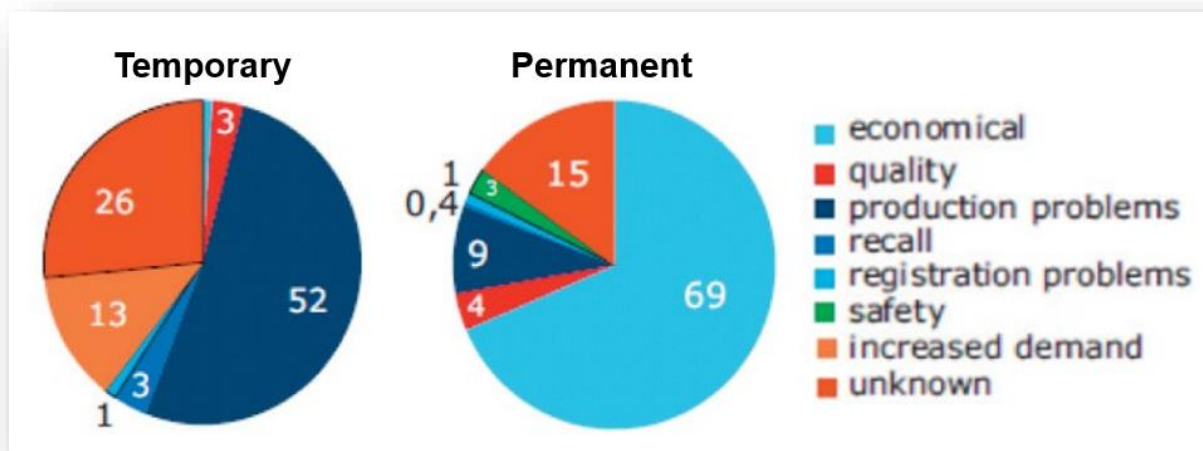
EXAMPLE OF PRICE PRESSURE

ROMANIA: 2000 MEDICINES WITHDRAWN!

- External reference pricing and clawback tax reduce access to medicines
- **European Commission (DG ECFIN):** ‘Joint Report on Health Care and Long-Term Care Systems & Fiscal Sustainability’
“While overspending is recovered via the claw-back tax (...), it has led to **withdrawals of generic medicines from the market**”.

EXAMPLE OF PRICE PRESSURE

THE NETHERLANDS:
69% permanent shortages have an economical
cause



Presentation Marcel van Raaij, Ministry of Health in the Netherlands;
Joint Conference IGBA, Medicines for Europe Lisbon 2017

Thank you.



Lieve Wierinck

Agnès Mathieu



Patient access to medicines: how to prevent shortages

Conference organised by Medicines for Europe

Brussels, 6 December 2017

**Agnès Mathieu
Deputy Head of Unit
European Commission
Unit B4. Medical products:
quality, safety, innovation
DG Health and Food Safety**

Context

- Availability/shortage: important problem with serious consequences for health and sustainability of healthcare
- Driven by manufacturing problems or economic reason
- Affects all products, including cytotoxic, vaccines, blood based medicines

Call from the European Parliament

Report on access to medicines with recommendations on shortages of medicines:

- *formulate a better definition , to assess the impact of parallel trade and supply quotas, to establish and update together with the Member States, the EMA and relevant stakeholders a list of essential medicines, ...to monitor compliance with Article 81 of Directive 2001/83/EC on shortages of supply, to explore mechanisms to address the withdrawal of effective medicines from the market purely for commercial reasons, and to take actions to remedy these shortages;*
- *establish a mechanism whereby medicine shortages across the EU can be reported upon on an annual basis;*

...

Call from the Council

- SK Presidency made "shortages of medicines" a priority for its presidency.
- Working Party on Public Health at Senior level on 15 July 2016 and the informal Health Council on 3-4 October, all Member States agreed that the topic deserves action at EU level.

HMA/EMA Task force on availability

- Theme 1: Marketing of authorised medicinal products
- **Theme 2 - Supply Chain Disruption**

Shortages: Legal Tools (Dir. 2001/83/EC) (I)

Member States' competence

- Article 81 obliges MAH and WD to ensure appropriate and continued supplies so that the needs of patients are covered (within the limits of their responsibilities)
- Article 23a obliges the MAH ceasing production to communicate all data relating to the volume of sales and prescriptions of the medicinal product to the competent authorities so to give advance notice of potential shortages.
- Article 126a enables MS to authorise a medicinal product for which there is no marketing authorisation - for public health reasons and if already authorised in another MS.

Shortages: Legal Tools (Dir. 2001/83/EC) (II)

- Article 63(3) allows, in case of shortages, to waive some of the labelling requirements, thus facilitating the placing on the market of alternative sources.
- Article 5.1 allows the use of unauthorised medicinal products *"to fulfil special needs" and for use by an individual patient under direct responsibility of a doctor.*

Shortages due to parallel trade

- Parallel export: legal form of trade whereby medicinal products are exported to other Member States to benefit from arbitrage
- The Court recognised that in cases where parallel trade would effectively lead to a shortage of medicines on a given national market, national authorities may take action to resolve the situation, by taking **appropriate** and **proportionate** steps that are consistent with the obligations flowing from Article 81 of Directive 2001/83 and with the Treaty (TFEU) rules.

What will be done by the Commission

- EC cannot prevent the withdrawal of a product from the market but an obligation of continuous supply exists if the product is placed on the market
- EC supports the Member States through a project on exchange of best practices
- Close cooperation with the EMA/HMA task force on availability
- Member States have to reply to the enquiry by 5 December 2017 (results available in 2018)
- Databases from the falsified medicines could help in the future
- Generics could diversify the offer of medicines

Thank You

Andreas Schwab

Cristian-Silviu Buşoi

Our panel today

- *Ortwin **SCHULTE**, Head of Health Policy Unit, German Permanent Representation*
 - *Eddy **GILISSEN**, VP Supplier Alliances, IQVIA*
 - *Vlad **VOICULESCU**, Member of Romanian Health Observatory, Romania*
 - *Elfi **DE WEERDT**, PhD medicine shortages, KU Leuven, Belgium*
-

Ortwin Schulte

Eddy Gillissen

IMS Health & Quintiles are now



Medicine shortages and correlation with economic causes

6th December 2017

Eddy Gilissen
VP Supplier Alliances NEMEA

The issue of shortages is still very current

Europe needs a plan to combat cancer drug shortages, says report

PharmaPhorum, 18-May-17

Are low generics prices at risk of causing shortages and sudden spikes?

The Pharma letter, 24-Nov-17

Healthcare Groups Urge Congressional Action on Drug Shortages

Increased Transparency, Improvements to Manufacturing Infrastructure Needed

Newswise, 10-Nov-17

How to cope with medicine shortages in a cut-throat market

Pharmacy News, 23-Nov-17

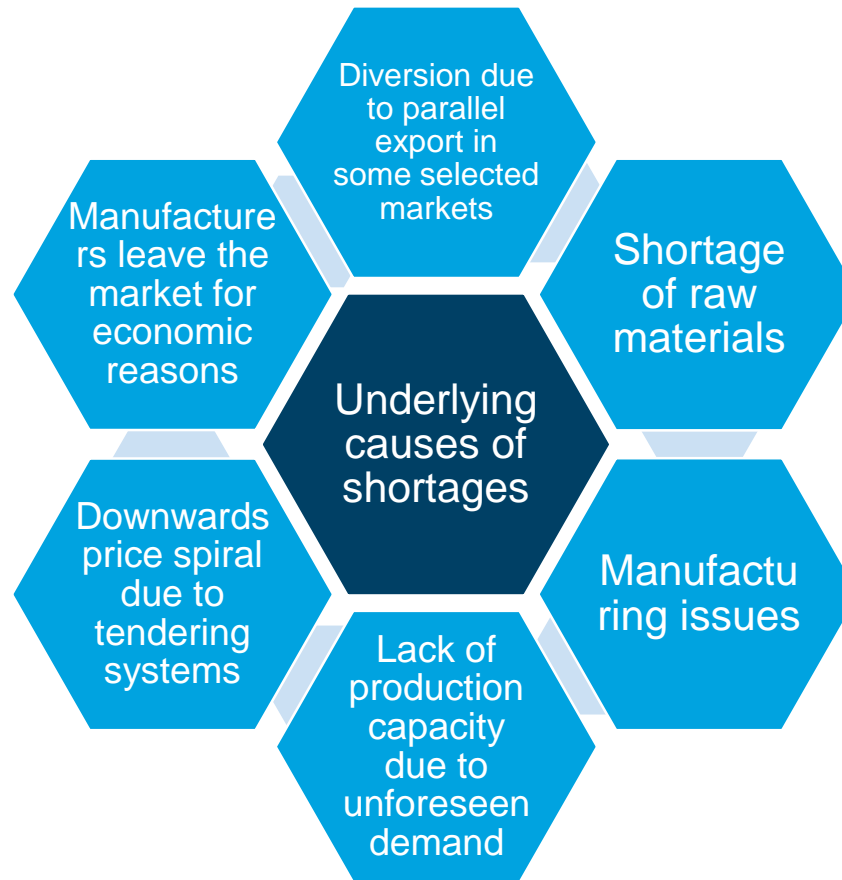
China Focus: China moves to address shortages in life-saving medicines

Source: Xinhua | 2017-11-22 20:12:02 | Editor: liuxin

Drug shortages: it's time for Europe to act

The Pharmaceutical Journal, 29-Jan-15

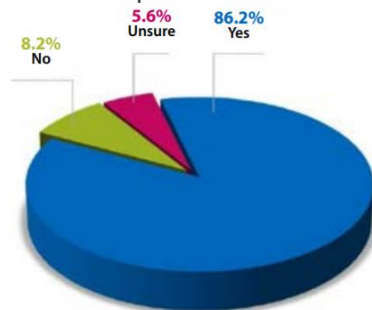
There are different factors which can cause shortages in the market



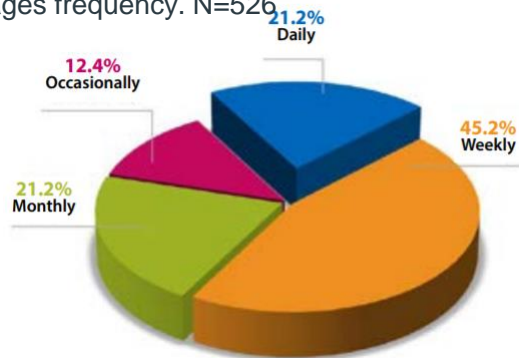
The majority of European hospital pharmacists believe medicine shortages are a problem

Antimicrobials and Oncology are the categories with the highest shortages reported

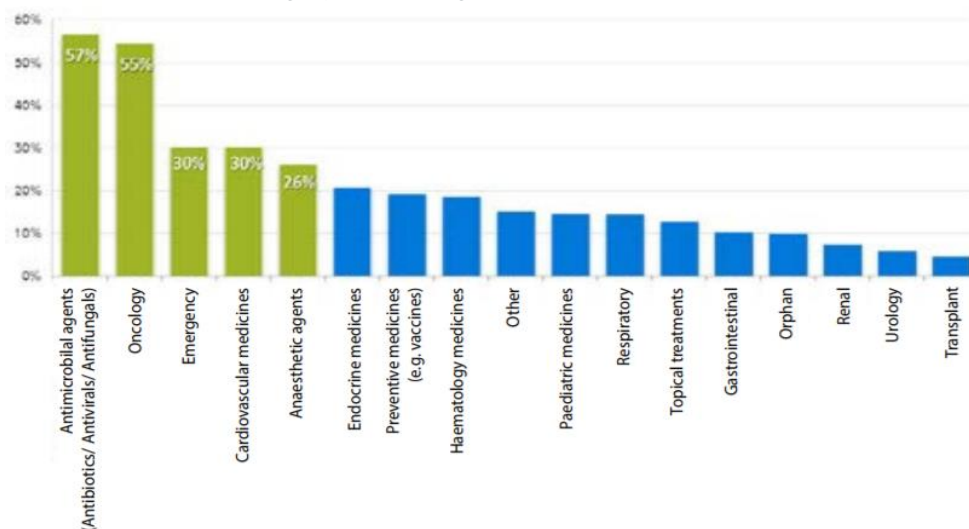
Proportion of hospital pharmacists (%) stating that medicines shortages are a current problem in their country. N=537



Shortages frequency. N=526






Category of shortages reported overall. N=418



Lack of competition can make markets more susceptible to shortages and have a negative impact on prices

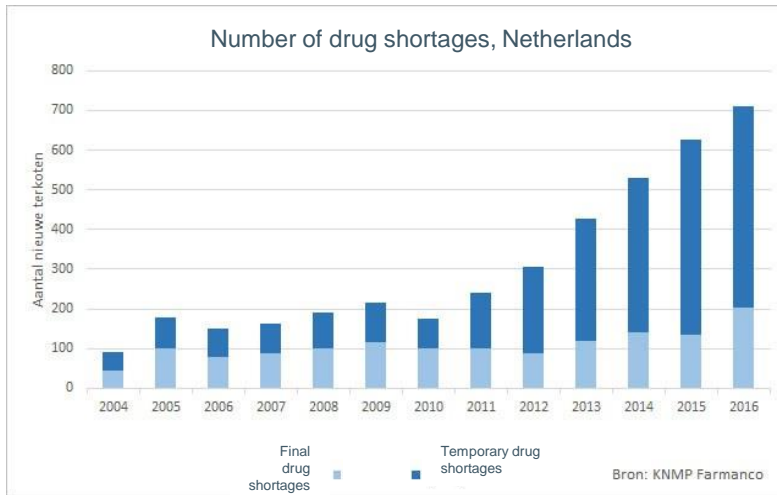
Case study:

- Amoxicillin
- ATC4: J1C1
(BRD.SPECT.PENICILL.ORAL)
- NFC123: DGJ (DRY SYRUP/DROP)

		QTR_09_2012			QTR_09_2016		
Country	Manufacturer	Sales mnf (LC_EUR)	Standard Units	Price (per SU)	Sales mnf (LC_EUR)	Standard Units	Price (per SU)
 Denmark	MEDA AS	107370	342605	0.31	161384	257380	0.63
 Sweden	MEDA	70674	143528	0.49	61706	117582	0.52
	MYLAN	391	1650	0.24	0	0	0
	SANDOZ GMBH	5051	8192	0.62	15141	26536	0.57
 Spain	ARISTO PHARMA IBER	6750	110208	0.06	104778	1708088	0.06
	BOHM	0	0	0	0	0	0
	GSK	31237	509948	0.06	2837	45584	0.06
	NORMON	329368	5021724	0.07	323837	5180476	0.06
	SANDOZ FARMACEUTIC	108301	1768176	0.06	118060	1927512	0.06
	QUIMIFAR	4067	62544	0.07	1962	17448	0.11
	REIG JOFRE	57962	876144	0.07	93280	1447736	0.06
	MUNDOGEN FARMA	21830	356400	0.06	8850	144504	0.06
	VIR	67	420	0.16	0	0	0

- In Denmark and Sweden, there are only a few manufacturers which produce this form of Amoxicillin, which makes these markets more susceptible to shortages.
- With only a few providers left in Denmark and Sweden, a monopoly situation has been established, and prices have risen because of lack of competition.
- In Spain, there are several more manufacturers of this molecule in the market, and as a result, the price of the product has remained low.

Manufacturers may leave the market for economic reasons



- **Temporary drug shortages** often arise due to production problems or due to increased demand.
- **Final drug shortages** are when pharmaceuticals are completely withdrawn from the market

- Drug shortages are becoming more common in the Netherlands. In 2016, 710 medicines were not available. In 2015, these were more than 625 medicines.
- **Every month pharmacists have to look for alternative medication for 580,000 prescriptions due to shortages;** this doesn't mean that the molecule could not be available, but the "preferential" product isn't. In many cases, due to low market attractiveness resulting from the tendering system, alternative providers haven't stayed in the market.
- **In 70% of cases, pharmaceuticals are completely withdrawn from the market for economic reasons.** Simple, relatively cheap medicines regularly disappear from the Dutch market because drug prices are so low here. Combined with the low population and low drug consumption, the low prices can make the Netherlands a relatively unattractive market.

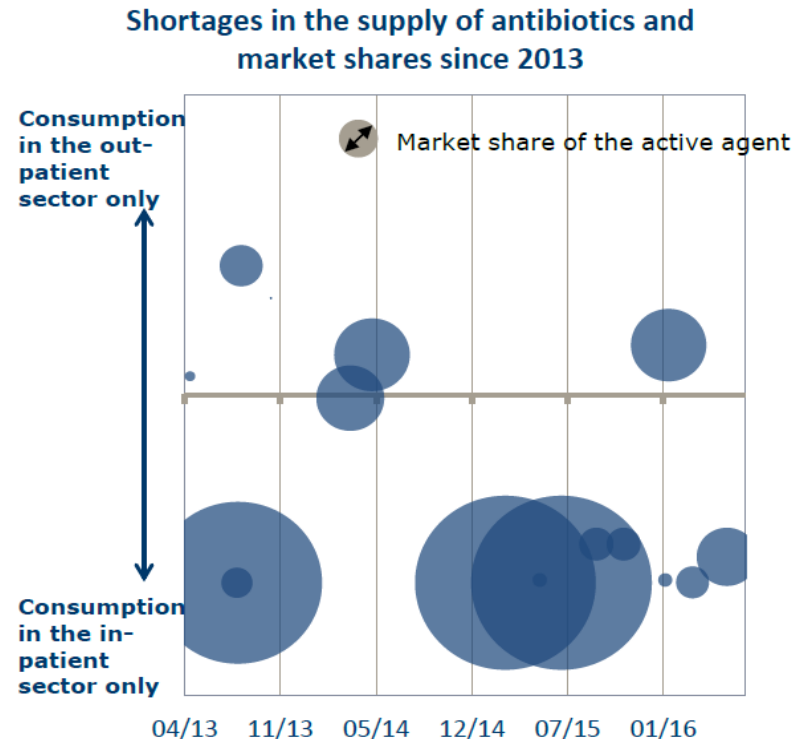
Significant price drops carry a high risk potential for shortages



Reported shortages in the supply of **antibiotic** agents is particularly common in the in-patient (hospital) sector in Germany.

In the in-patient sector, an increasing number in suppliers or less market concentration reduces the risk of shortages in supply.

However, **dramatically decreasing prices despite higher requirements for production** (high percentage of parenteral solutions) carry a high risk potential.



The dependence on imports of intermediates and APIs leads to supply shortages of (generic) antibiotics in Germany



Causes for Supply shortages of Antibiotic intermediates and API's in Germany:

Increasing concentration of foreign producers of inter-mediate and APIs, especially in China and India

- **Only few suppliers are available** due to a high market concentration.
- **Growing quality requirements** for local production plants, which cannot be fulfilled by all manufacturers
- **Expensive "multiple sourcing"** not feasible for German antibiotics producers due to cost pressure, thus lack of alternative suppliers in case of supply shortages

Production deficiencies of foreign manufacturers

- **Operational problems in the production process** of intermediates and APIs, which may lead to delays in the supply
- **Quality deficiencies** of imported intermediates and APIs, thus uselessness of delivered products

API = Active Pharmaceutical Ingredient

Lack of production capacity can result from unforeseen demand or production or quality problems

Flu Vaccines



- In 2013, in US Roche had a temporary shortage of the liquid version of Flu vaccine, Tamiflu, given to children, because of over demand and supply issue
- In the same year in the US, Sanofi SA, the largest flu vaccine provider in the United States, said on Thursday it had sold out of four of the six different dosages of Fluzone seasonal flu vaccine due to unanticipated demand.

Heparins



- In 2008, major recalls of heparin were announced by the FDA due to contamination of the raw heparin stock imported from China.
- This contaminated heparin caused the death of 81 people and 785 reports of serious injuries.
- This changed the regulation and the enforcement actions against API manufacturers.

Conclusions

- There are a few main underlying causes of shortages in Europe, grouped into economic, business and supply chain.
- Shortages can be split into short-term and long-term shortages:
 - › Short-term, usually local shortages, which can arise because **distribution problems**.
 - › More serious long-term shortages at a national level may also result from important **price drops** and high differences in pricing between countries.
- When prices drop so low that the **number of providers becomes very limited**, this has implications on the **sustainability of our healthcare system** and the provision of pharmaceuticals. This is not only an issue for the pharmaceutical manufacturers, but also for the wholesalers and the pharmacists who have to be available to provide medicines for the patients.
- **Dependence** on non-EU imports can increase risk of supply issues
- The **impact on patients** is difficult to quantify, but existing. An equal effective alternative should be available, what is not always the case today. A drastic change in their treatment pattern could lead to side effects and errors and a **reduction of adherence and compliance** levels. In cases where there is no alternative available, or the alternative is ineffective, the disease can resume.

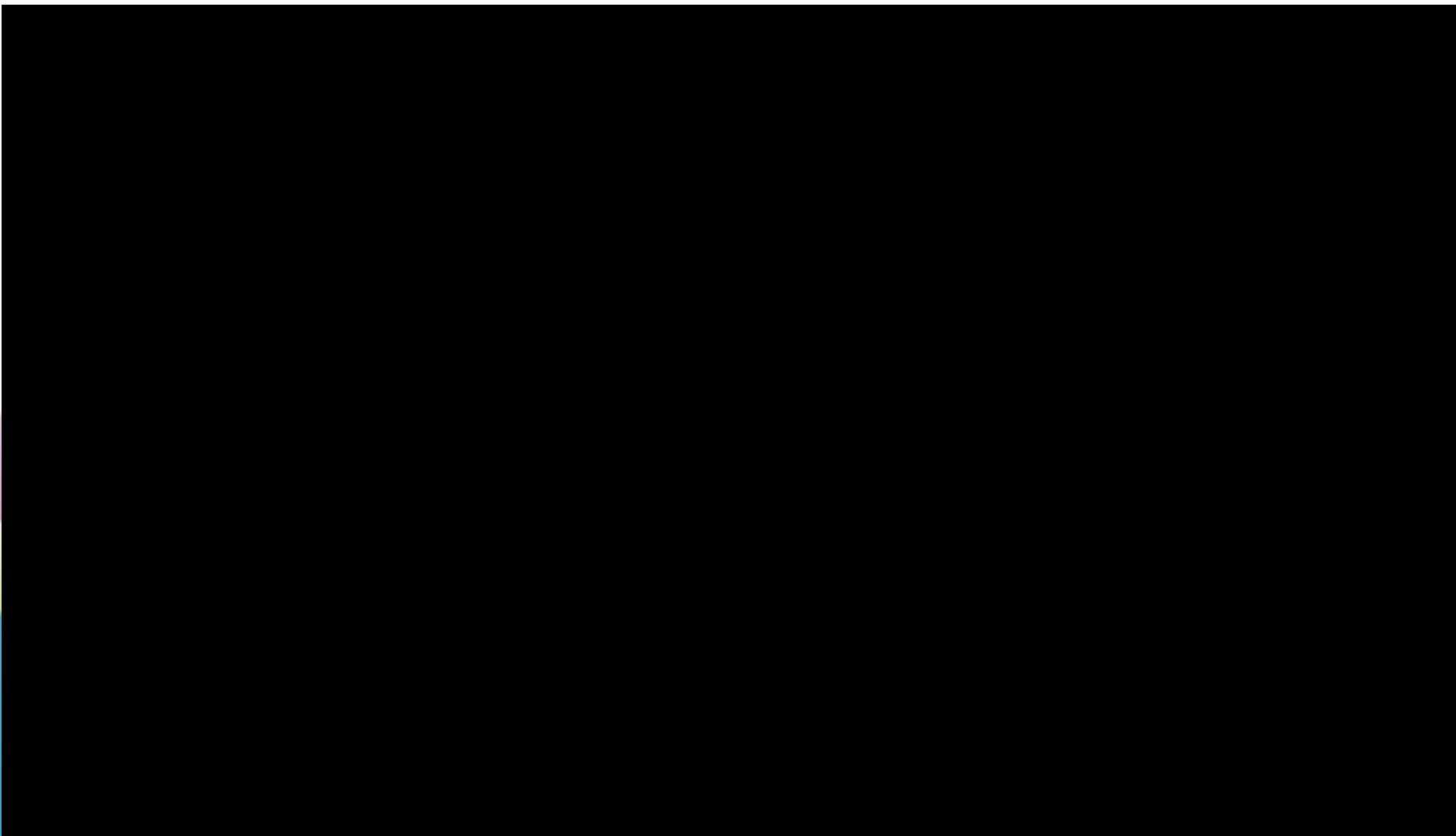
IMS Health & Quintiles are now



**Looking forward to
the solutions!**

eddy.gilissen@iqvia.com

Vlad Voiculescu



[https://www.youtube.com/watch?v=Ht
rmVQMUXnw](https://www.youtube.com/watch?v=Ht
rmVQMUXnw)

Vlad Voiculescu

Elfi De Weerdt



Causes of drug shortages

Medicines for Europe – 6/12/2017

Elfi De Weerd
PhD-researcher

Supervisor: prof. Isabelle Huys
Co-supervisors: prof. Steven Simoens
prof. Minne Casteels





SCOPE AND CAUSES

Chapter 1: Definition of drug shortages

Chapter 2: Influence of legal framework on drug shortages

Chapter 3: In-depth database analyses on reported drug shortages in EU



IMPACT

Economic impact of drug shortages

Chapter 4: in hospital pharmacies

Chapter 5: in community pharmacies

Chapter 6: Clinical and economic impact of drug shortages on patients



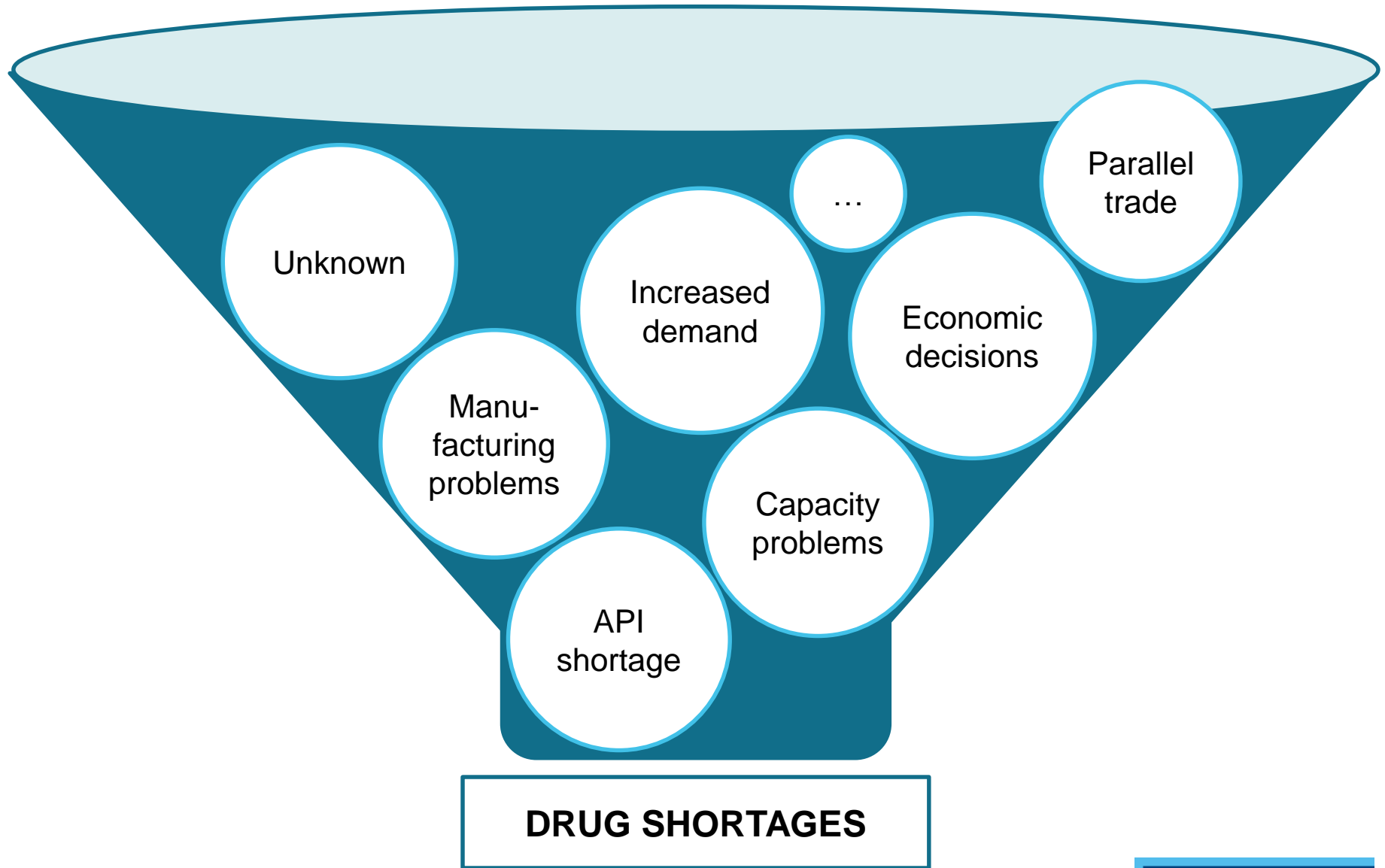
MEASURES

Chapter 7: Measures to prevent drug shortages across EU

Chapter 8: Measures to manage drug shortages across EU

Chapter 9: Recommendations towards preventing and mitigating drug shortages

Causes of drug shortages described in literature



Review on legal framework causing drug shortages

Aim

- Causes of drug shortages in legal pharmaceutical framework?

Methodology

- Review of European legislations
- Review of national legislations
- Review in published literature

Causes in the legal pharmaceutical framework

Patented drugs

- Price settings
 - External reference pricing
- Reimbursement procedures

Generic drugs

- Price settings
 - Tendering
 - ↓ Manufacturers → vulnerable market for drug shortages
 - Price capping
 - ↓ Price → no incentive for manufacturers
 - Internal reference pricing

Causes in the legal pharmaceutical framework

Parallel trade

- Key concept = free movement of goods
- Quota
 - Back-up system

Manufacturing and quality requirements

- GMP Directive
 - Audits
 - Safety, effective and quality
 - Active pharmaceutical ingredient + drug manufacturers
- Falsified Medicines Directive
 - Import of API
- Quality requirements
 - Labelling, leaflet

Causes in the legal pharmaceutical framework

Withdrawal of market authorization

- Pharmaceutical company
 - Business decisions
 - Portfolios adjusted: looking for higher margin options
 - No incentive for sustainable production
 - Change of drug status
 - Prescription → OTC
- Competent authorities
 - Ultimate measure

Conclusions

- Pricing procedures and quality requirements seem to strengthen each other in causing drug shortages
 - Price regulated by authorities, not by company
 - Quality is mandatory by law
 - Companies want to deliver high quality drugs

Manufacturers will leave markets when profit-margins for generic drugs decrease.

**→ Need for balance between
quality requirements and prices of drugs**

COST Action: medicine shortages*

- European framework supporting trans-national cooperation among researchers, engineers and scholars across Europe
- COST does not fund research itself, but provides support for networking activities carried out within COST Action
- Involvement of:
 - National health authorities, universities, EAHP, EURORDIS, medical doctors, *etc.*
- *Prof. Huys is lead of work package 1: landscape of drug shortages*

Q&A

‘Patient access to medicines: how to prevent medicine shortages?’

Marc-Alexander Mahl
Brussels, 06 December 2017

CREATING AND MAINTAINING A MULTI-SOURCE MARKET



**MORE
MANUFACTURERS
= LESS
SHORTAGES**



- Improve regulatory efficiency to reduce administrative and cost burden of keeping products in the market



- Ensure market predictability



- Address negative impact of parallel trade



- Manage available market stock information

MITIGATE SHORTAGES



- Specific regulatory measures to mitigate imminent medicine shortages

TACKLING SHORTAGE IN THE OFF-PATENT SECTOR

- Multi-source markets with healthy competition **can prevent medicines shortages**
- Shortages risk increases when market relies **on small number of manufacturers**
- Price cuts/pricing mechanism such as tendering and increasing regulatory costs reduce incentives **for introducing or maintaining generic product in the market**
- **Parallel trade is not the main cause of generic medicines shortages**
- Penalties increase the risk for MAH, reducing incentives to **maintain products in the market**
- Aligned communication between authorities and MAH can help to **prevent shortages**
- **Continuous dialogue between MAH and NCA** to validate solutions is required



Thank you!



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