

SOCIAL AND ETHICAL FRAMEWORKS AND OBLIGATIONS TO BE MET

Seminar 1: Medicines Shortages – Causation
and Approaches to Improvements

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CONFLICT OF INTEREST

- Within recent months - speakers' honorarium from Amgen (research topic not relevant to this seminar's subject)

DRUG SHORTAGES: ETHICAL AND POLITICAL ISSUES?

(Lipworth, Kerridge 2013)

- Threatening the capacity of states, governments, health care professionals (incl. pharmacists) to fulfill their moral obligations:
 - ✓ provision of benefit
 - ✓ minimizing harm
 - ✓ promoting equity
- Stemming from societal values:
 - ✓ choices about what societies want most from industry, regulators and health care services

ARE DRUG SHORTAGES CHALLENGING THE DELIVERY OF ETHICAL HEALTH CARE?

- Challenges to the delivery of beneficent and non-maleficent health care:
 - ✓ for patients
 - ✓ for institutions and governments
 - ✓ for public health
- Challenges to the delivery of just health care:
 - ✓ the need for guidelines and managerial procedures at health care facility or organization
 - ✓ burden on selected and often disadvantaged groups of patients

ETHICAL PERSPECTIVE ON AETIOLOGY AND PREVENTION OF DRUG SHORTAGES

- Possible industry misconduct
- Systemic issues:
 - ✓ complex processes
 - ✓ reliance on a few generic manufacturers
 - ✓ pressure to lower costs
- Trade-offs between availability of cheap medicines and increased risks related to market behaviour

PRACTICAL RECOMMENDATIONS FOR PREVENTING AND MANAGING DRUG SHORTAGES (ONCOLOGY)

Jagsi et al. 2014

- Organize and plan
- Train and educate
- Research
- Communicate
- Recognize and manage distress
- Advocate

SYSTEMIC MEASURES, LEGISLATIVE AND ORGANISATIONAL FRAMEWORKS AIMED AT PREVENTING OR MITIGATING DRUG SHORTAGES IN 28 EUROPEAN AND WESTERN ASIAN COUNTRIES

Bochenek T, Abilova V, Alkan A et al. Systemic Measures and Legislative and Organizational Frameworks Aimed at Preventing or Mitigating Drug Shortages in 28 European and Western Asian Countries. *Frontiers in Pharmacology*. Volume 8. Article 942. January 2018: 1-24

DRUG SHORTAGES AS A PUBLIC HEALTH PROBLEM – SYSTEMWIDE APPROACH

- Study goal - to characterize, compare and evaluate the current solutions and legislative frameworks which exist within health care systems across a range of European and Western Asian countries, aimed to prevent or mitigate drug shortages.
- Different epidemiologies, geographies, GDPs per capita, levels of spending on health care and approaches to the pricing of medicines.
- Survey results are based on 20 EU/EFTA and 8 non-EU/EFTA countries:

Austria
Belgium
Croatia
Czech Republic
Estonia
France
Greece
Hungary
Ireland
Italy

Latvia
Lithuania
Malta
Norway
Poland
Portugal
Slovakia
Slovenia
Spain
Switzerland

Albania
Azerbaijan
Israel
Kosovo
Montenegro
Republic of Srpska (BIH)
Serbia
Turkey

GENERAL CHARACTERISTICS OF DRUG SHORTAGES PROBLEM: DEFINITIONS

- Formal definitions don't exist in the majority of countries (few exceptions: Be, Fr, It, Sp)
- Definitions focusing on general market availability; stock or supply problems
- Drug shortages sometimes defined indirectly
- Importance of coining commonly understood definitions, facilitating monitoring and international comparisons

PUBLIC HEALTH PERSPECTIVE ON ISSUE OF DEFINITION

- Variety of stakeholders and vested interests
- Agreed terminology should facilitate mutual understanding



- Definitions should embrace severity of harm to patients' health, probably market share too, and should include a public health perspective
- Strategies of coping drug shortages problem should respect differentiated interests and problems of various stakeholders, but most of all – these of patients
- It seems that probably not just one, but a set of definitions of various categories of drug shortages are required (e.g. based on impact and reasons)

GENERAL CHARACTERISTICS OF DRUG SHORTAGES

PROBLEM: OCCURRENCE AND DYNAMICS

- Have occurred in all studied countries throughout the last decade.
- Generally increasing, „always present”, with starting point difficult to set in time (specific situation of some countries, Al - due to structural issues and systemic reasons; Az, Ko)
- Specific time-frames or starting points.
- Dynamics in past 3 years:
 - increasing (Fr, Gr, It, La, Li, No, Ir, Isr, Slk, Sw, Tu, also Cz)
 - stable (Cr, Ser, Est)
 - formerly increasing but rather decreased recently (Po, Sp)
 - decreasing (Sln)
 - difficult or impossible to assess (Au, Al, Az, RSBiH, Mon)

INFORMATION SYSTEMS AND VIGILANCE

- Reliable statistics, „hard evidence” on drug shortages reported in about half of the studied countries.
- Databases exist in the majority of countries, but sometimes are limited to reimbursed products only, or contain limited amount of information.
- In majority of countries there is at least one additional institution involved in gathering information, usually at the level of the MoH or medicines agency. Information is either shared or gathered independently.

INFORMATION SYSTEMS AND VIGILANCE cont.

- Existence of formal obligations of pharmaceutical companies to notify a certain institution in situations, which could lead to drug shortages - in majority of countries
- Well-recognized assortment in majority of countries, with a few exceptions
- Frequency of shortages usually described as variable, rather not known precisely and unpredictable
- Information available to the public in majority of countries

„BOTTOM-UP” INITIATIVES AND ORGANIZATIONAL FRAMEWORKS

- Different bottom-up initiatives (working groups, informal networks), targeted to tackle the problem of shortages
- Guidelines, codes of conduct, good practices, management plans

„BOTTOM-UP” INITIATIVES AND ORGANIZATIONAL FRAMEWORKS: EXAMPLES

- Quotas in many countries, at different levels
- Working group at hospital pharmacists' association, voluntary reporting of pharmaceutical companies to pharmacists' publisher (Au)
- Informal networks (Cz)
- Standard operating procedures developed at drug registration institution (Es)
- Taskforce or working group (Be, Gr, La)

„BOTTOM-UP” INITIATIVES AND ORGANIZATIONAL FRAMEWORKS: EXAMPLES

- Step-by-step guidance issued for health facilities; pricing and reimbursement-related procedures related to reference products (Hu)
- Set of initiatives (Is, Li, Sp, Slk)
- Hospital pharmacy working group; strong involvement of state medicines agency (No)
- Top-down initiatives (Tu, Az)
- NGO and patient associations (Ma, Se)

VIGILANCE, FLOW OF INFORMATION, INITIATIVES AND FRAMEWORKS: PUBLIC HEALTH PERSPECTIVE

- Up-to-date and reliable information – foundation for appropriate reactions to drug shortages
- Databases and gathering information:
 - public access
 - standard and consistent structure
 - avoidance of multiplication of efforts and waste of public resources
 - ideally, databases not only just in one, national language
- Vicious circle effect of quotas on shortages
- Facilitating role of medicines agencies or other public institutions
- Role of bottom-up initiatives and civil society actions

INFLUENCING TRADE RULES (WITHOUT DIRECT IMPACT ON ARBITRAGE/PARALLEL TRADE)

- Options in pricing and reimbursement policy (Hu) – procedure for selection of another drug with lowest daily treatment cost, in case of shortages occurring among reference products
- Solutions for small markets:
 - Ma: medicinal products could be placed on the market only in one of the official languages of Malta (i.e. Maltese or English); accepting possibility of having joint packs with other larger English – speaking countries, mainly UK and /or Ireland
 - possibility to authorise the placing on the market a medicine in the absence of MA (EU legislation)
 - Al: text translated to Albanian can be provided on packages with use of adhesive labels, in cases when e.g. volume of sale is low, drug is for hospital use

INFLUENCING TRADE RULES (WITHOUT DIRECT IMPACT ON ARBITRAGE/PARALLEL TRADE) - cont.

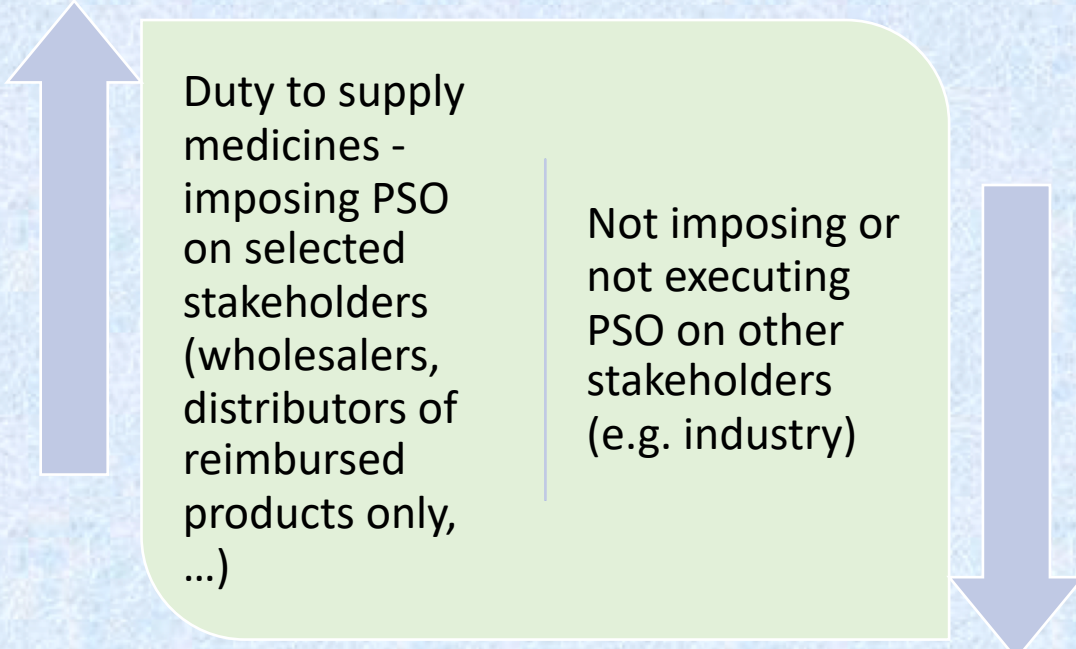
- Differentiated approach to public service obligations (PSO):
 - all registered products (majority of countries)
 - reimbursed drugs only (Cr, It, Slk, Se, also Al)
 - difficulties in enforcing PSO in small countries
- Possibility for physicians to prescribe unregistered medicine, if registered product is not available on market:
 - exists in the majority of countries, including the EU
 - Hu: combined with several obstacles
 - special role in Mo (20% of medicines), Ko (relying on MA issued in the EU MS) – small countries

INFLUENCING MEDICINES TRADE RULES IN RESPONSE TO ARBITRAGE/PARALLEL TRADE

- Limitation of arbitrage/parallel trade in the majority of countries only optional (possible but not implemented so far)
- Top-down approach and changes in legislation to limit parallel export and illegal re-exportation (Po – additionally the role of tracking medications system, Sp, Slk); limitations also in Tu, Fr, Gr

SYSTEMIC OBSTACLES IN FULFILLMENT OF PUBLIC SERVICE OBLIGATIONS

- Duty to supply medicines should be associated with right to be supplied
- Problems with enforcing PSO in small markets
- Initiatives tailored to size of market



Duty to supply medicines - imposing PSO on selected stakeholders (wholesalers, distributors of reimbursed products only, ...)

Not imposing or not executing PSO on other stakeholders (e.g. industry)

RULES OF MEDICINES' TRADE IN ASSOCIATION WITH PROBLEM OF DRUG SHORTAGES

- Intrinsic, insolvable in 100%, conflict of two paradigms
- Problematic can be not only parallel trade but also illegal reversal of trade chain
- Promotion of parallel importing in some countries must contribute to problems with excessive exporting from other countries
- Prevention of shortages increasingly used as justification for increasing prices
- Hopeful message is that the EU MS can live with it, while mitigating problems



Free trade
of goods,
including
medicines

National
pharmaceutical
policies (including
pricing and
reimbursement)



CONCLUSIONS OF THE STUDY

- Drug shortages, although seemingly ever-existing, have constituted an increasingly important public health problem, in the majority of studied countries
- Agreed terminology, reliable and openly accessible national databases on shortages could improve monitoring and prevention of shortages in international dimension
- Some reasons for shortages have intrinsic character and are impossible to eliminate – there is an open question how to deal with them
- Better understanding of drug shortages problem and monitoring it across studied countries should help in shaping strategies for prevention

**DRUG SHORTAGES:
ATTEMPT TO SUMMARIZE SYSTEMIC AND
ORGANIZATIONAL FRAMEWORKS WHICH
COULD COUNTERACT THEM
AND COUNTERWEIGH THEIR IMPACT**

Truong PH, Rothe C, Bochenek T. Drug shortages and their impact on patients and health care systems – how can systemic and organizational frameworks help to prevent or mitigate them? in: Textbook on management of drug shortages, Springer (manuscript in preparation)

Measures aiming to:	Avert DS even from arising	Tackle arising or present DS
Communication	<ul style="list-style-type: none"> • official and uniformly interpreted definition • early warning systems 	<ul style="list-style-type: none"> • informing and counselling patients and care-givers
Organization	<ul style="list-style-type: none"> • development of appropriate environment for medicines manufacturing • multiplicity of suppliers • prescribing and importing medicines licenced in other countries (not a preferred option) • eliminating medicines' stockpiling 	<ul style="list-style-type: none"> • shifting drug inventories between health care facilities • forecasting duration of DS • identifying all patients in need and alternative therapies • trainings for the use of substitute treatments
Legislation	<ul style="list-style-type: none"> • civil penalties and their enforcement on manufacturers failing to notify respective authorities • making use of Public Service Obligations • banning parallel exports temporarily (when public health is threatened) 	<ul style="list-style-type: none"> • creating additional clinical guidelines and policies • criteria to determine patients' allocation to drugs in scarce quantities

Fundamental organizational principles

- Establishing monitoring systems to report DS
- Establishing timely communication systems between pharmacists and prescribers to manage DS
- Predetermining responsible stakeholders and tasks for every phase of the DS
- Standardizing the reporting systems for DS at international level
- Using a mutually agreed definition of DS

DEFINITIONS OF DRUG SHORTAGES PROPOSED BY THE WORLD HEALTH ORGANIZATION (2017)

- On the supply side:
 - ✓ A 'shortage' occurs when the supply of medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas.
- On the demand side:
 - ✓ A 'shortage' will occur when demand exceeds supply at any point in the supply chain and may ultimately create a 'stockout' at the point of appropriate service delivery to the patient if the cause of the shortage cannot be resolved in a timely manner relative to the clinical needs of the patient.

DRUG SHORTAGES VS. FUNCTIONS OF A HEALTH CARE SYSTEM

- Providing health care services
- Investments to accumulate resources (human resources and fixed capital goods)
- Financing – gathering and distribution of financial resources
- Careful and responsible management; stewardship

**WHICH FUNCTIONS OF A HEALTH CARE SYSTEM
SHOULD BE TACKLED,
WHEN ACTIONS ARE TAKEN TO PREVENT OR
MITIGATE DRUG SHORTAGES?**



DRUG SHORTAGES IN EUROPE

DRUG SHORTAGES IN EUROPE

- Study of European Association of Hospital Pharmacists (EAHP) from 2013
- 99% of pharmacists experienced this problem in last year
- 63% of pharmacists experience it weakly and sometimes every day; 27% - at least monthly
- 77% of pharmacists claim that problem increased in last year
- 57% of events pertain to generic medicines (the rest to originators)
- Oncologic drugs mentioned by 71% of respondents; emergency medicine drugs – 44%; cardiovascular drugs - 35%; hematologic drugs - 22%

DRUG SHORTAGES IN EUROPE (cont.)

- Role of economic crisis:
 - debt to industry and delayed payments
 - switching to cash-only transactions and cutting expenses
- Reduction of prices and expenditures, other tools of pharmaceutical pricing and reimbursement policies, e.g.:
 - Spain: - EUR 2.2 bln 2012/2008
 - Greece: - EUR 1.65 bln EUR 2012/2008 (public expenditure on drugs)
 - Poland: - EUR 650 mln 2013/2012 (Rx sales)
 - France, Germany, Italy, Spain, UK: prolonging payment terms to wholesalers in 2012 equalled to a 44-day credit = EUR 10.4 bln
- Role of international reference pricing - e.g. cutting prices by 10% in Greece results to the industry in following costs:
 - EUR 300 mln in Greece
 - EUR 800 mln in Europe
 - EUR 2.2 bln globally

DRUG SHORTAGES IN EUROPE (cont.)

- Development of drug bidding, also in ambulatory care and even on monthly basis
- Role of parallel trade:
 - Various forms of promoting it e.g. in Denmark, Germany, the Netherlands, Norway, Sweden, the UK
 - Formal requirement from German pharmacies to have at least minimum 5% of drug supplies from parallel trade – this results in necessity to import medicines of value of EUR 1.35 bln (there are estimates that in reality it is even c.a. 12% = EUR 3.0 bln)
 - Influence on countries being source of import, e.g. Poland
- Rationing (quotas) in reaction to parallel trade
- Decreased number of production sites (also in the USA), moving production to other continents – effects of globalisation
- Influence of Falsified Medicines Directive of 2011: requirement of obtaining API certificates also from outside of the EU since 2013
- Birgli's Report (2013)

**EXPORT BAN ON MEDICINES ENDANGERED BY
LACK OF AVAILABILITY
TO PATIENTS IN POLAND**

PROCEDURE OF IMPOSING AN EXPORT BAN

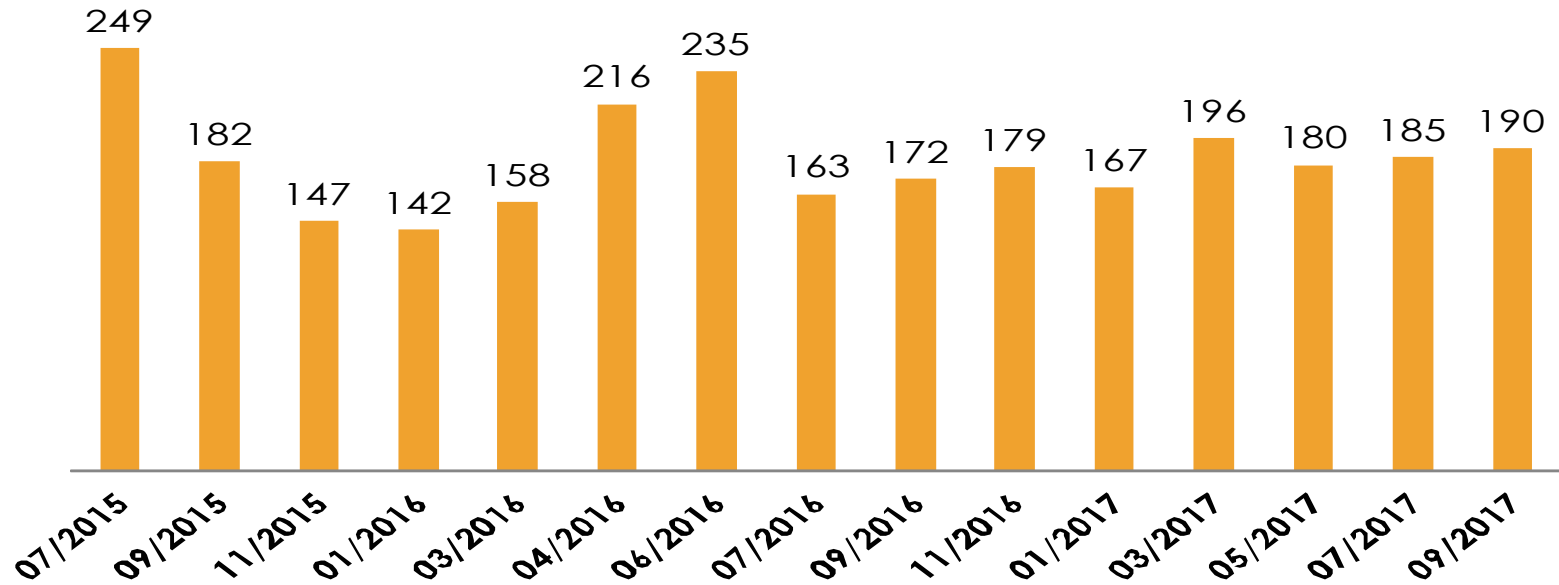
- Pharmacies (community and hospital) are obliged to report, if they cannot secure availability of a Rx medicine or a product from reimbursement lists, within 24 h to the Provincial Pharmaceutical Inspectorate (PPI)
- PPI assesses the level of threat within 3 days, if more than 5% of community pharmacies report the same threat within 3 consecutive days, and in case of any report from a hospital pharmacy
- PPI reports the above to the Chief Pharmaceutical Inspectorate (CPI), who assesses availability in trade on the national level
- CPI may ask the MoH to impose export ban on a particular product and the MoH announces a list of such medicines, at least every 2 months

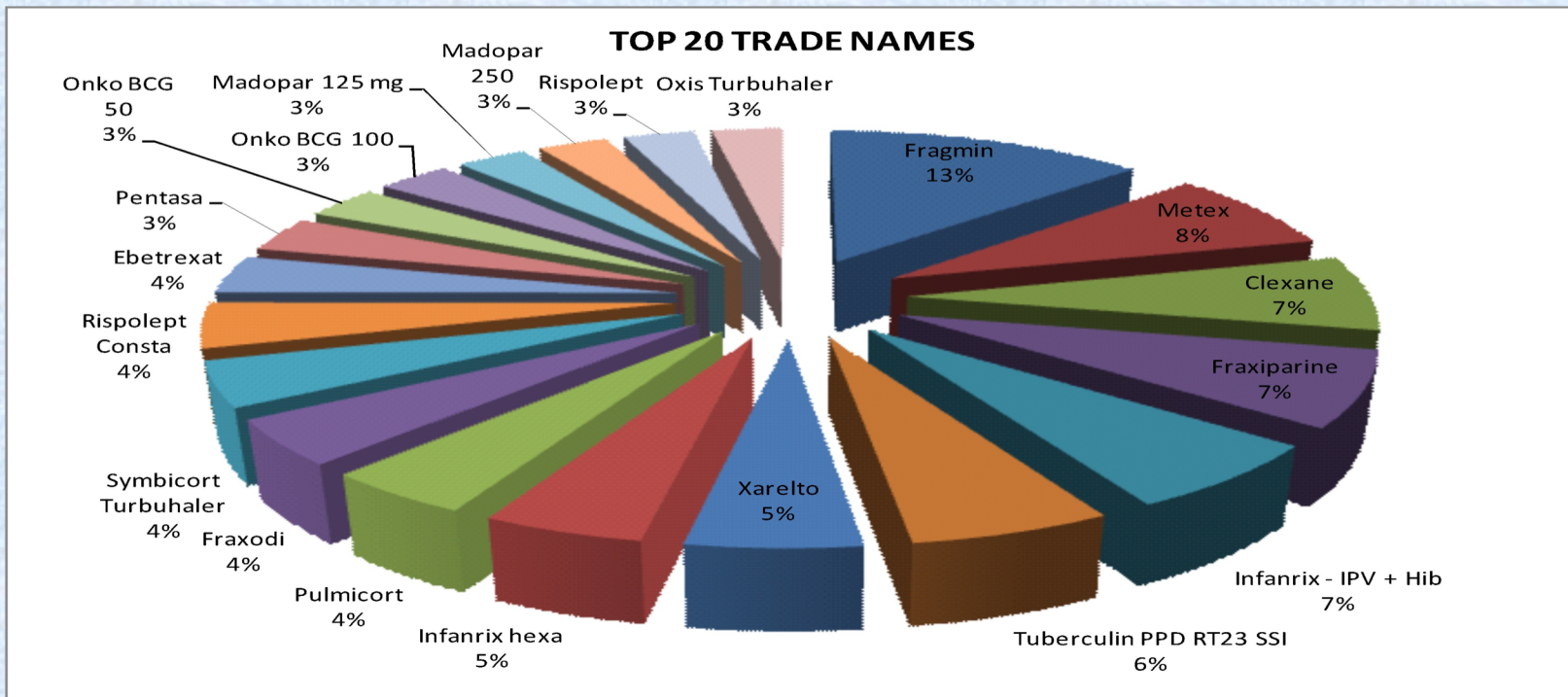
PROCEDURE OF IMPOSING AN EXPORT BAN

cont.

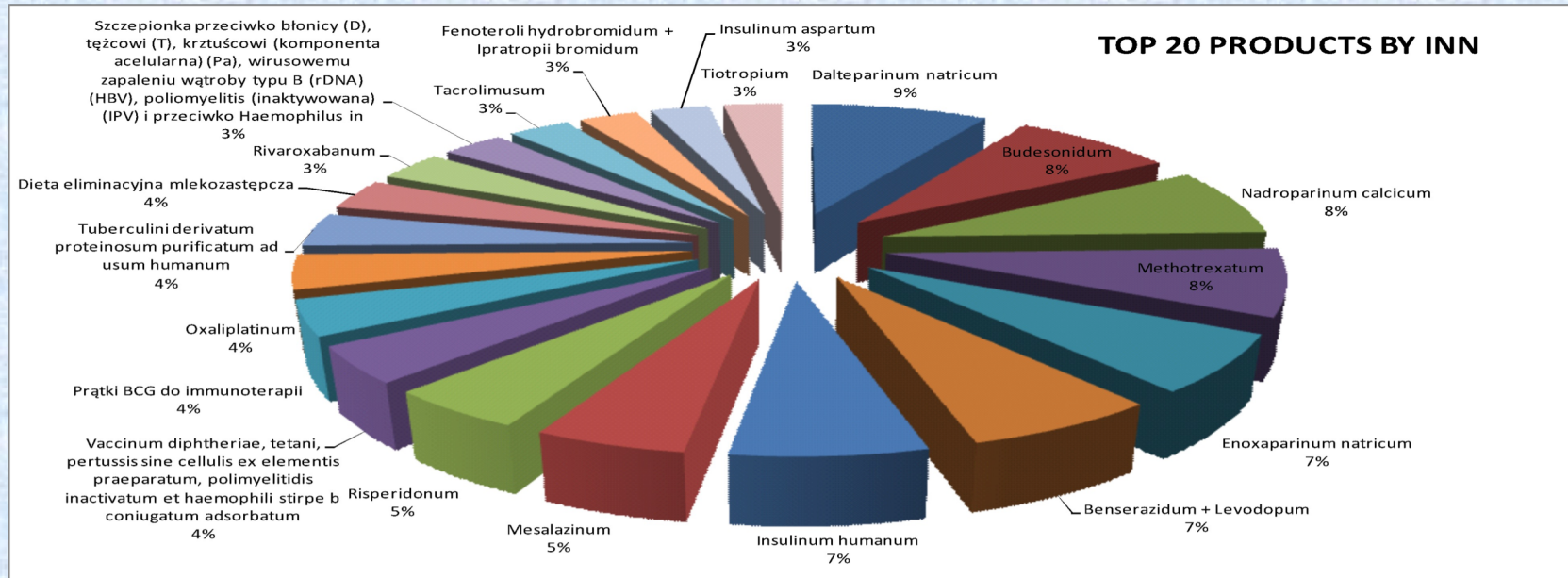
- CPI may ask the MoH to impose export ban on a particular product and the MoH announces a list of such medicines, at least every 2 months
- Wholesaler must ask the CPI for permission on export of such product
- CPI may object it within 30 days, considering the existing threat to availability or product's significance to public health
- After objection, request may be repeated after 30 days again

DYNAMICS - EAN IN SUBSEQUENT LISTS (MEDICINES)





195 trade names in the whole analyzed period



137 international non-proprietary names or their combinations in the whole analyzed period

ASSESSMENT OF EFFECTS

- Products – medicines, but also some medical devices and food products for special dietary use
- 2,818 products between July 2015 and September 2017
- 124 ATC codes
- How to measure effectiveness, considering the available data?
- Indirect measurement – the recent initiatives and other governmental plans for action, regarding reaction to the reversed chain of trade

DRUG SHORTAGES – DETERMINANTS AND SOLUTIONS: SURVEY ON SITUATION IN CHINA (SHAANXI PROVINCE)

Yang C, Wu L, Cai W, Zhu W, Shen Q, Li Z, et al. (2016) Current Situation, Determinants, and Solutions to Drug Shortages in Shaanxi Province, China: A Qualitative Study. PLoS ONE 12(6): e0178429.

SHORTAGES IN CHINA

- Study aiming to analyze, characterize and assess the drug shortages in Shaanxi Province, western China
- Shaanxi Province – 15th for GDP per capita among all 31 provinces; c.a. 38 mln citizens; broadly representative
- 30 interviews; hospital staff, pharma industry, wholesalers, local authorities
- Current situation:
 - Assortment
 - Information systems
 - Coping strategies

CAUSES

Causes of drug shortages	Representative drugs
1) Too low prices	Dexamethasone; Thiamazole; Deslanoside; Adrenaline; Alprazolam.
2) Too low market demands	Pralidoxime Chloride; Pralidoxime Iodide; Snake venom antiserum; Ketamine.
3) GMP issues	Doxorubicin; Cefuroxime; Hyaluronic acid sodium eye drops.
4) Materials issues	Human serum albumin; Human gamma globulin; Clotrimazole.
5) Approval problems of imported drugs	Mupirocin ointment; Linezolid Injection; Piperacillin; Paroxetine Hydrochloride.

SOLUTIONS

Ranking	Solutions
1	Let the market decide the drug price and modify the public bidding mechanism.
2	Establish an information platform for medicines in short supply.
3	Establish a reserve system for medicines in short supply.
4	Enhance the communication among the three parties (manufacturers, wholesalers, and hospitals) in the supply chain.
5	Improve hospital inventory management.

DRUG SHORTAGES SEEN FROM DIFFERENT STAKEHOLDERS' PERSPECTIVES: SURVEY ON SITUATION IN FIJI

Walker J, Char BB, Vera N, Pillai AS, Lim JS, Bero L, et al. (2017) Medicine shortages in Fiji: A qualitative exploration of stakeholders' views. PLoS ONE 12(6): e0178429.
<https://doi.org/10.1371/journal.pone.0178429>

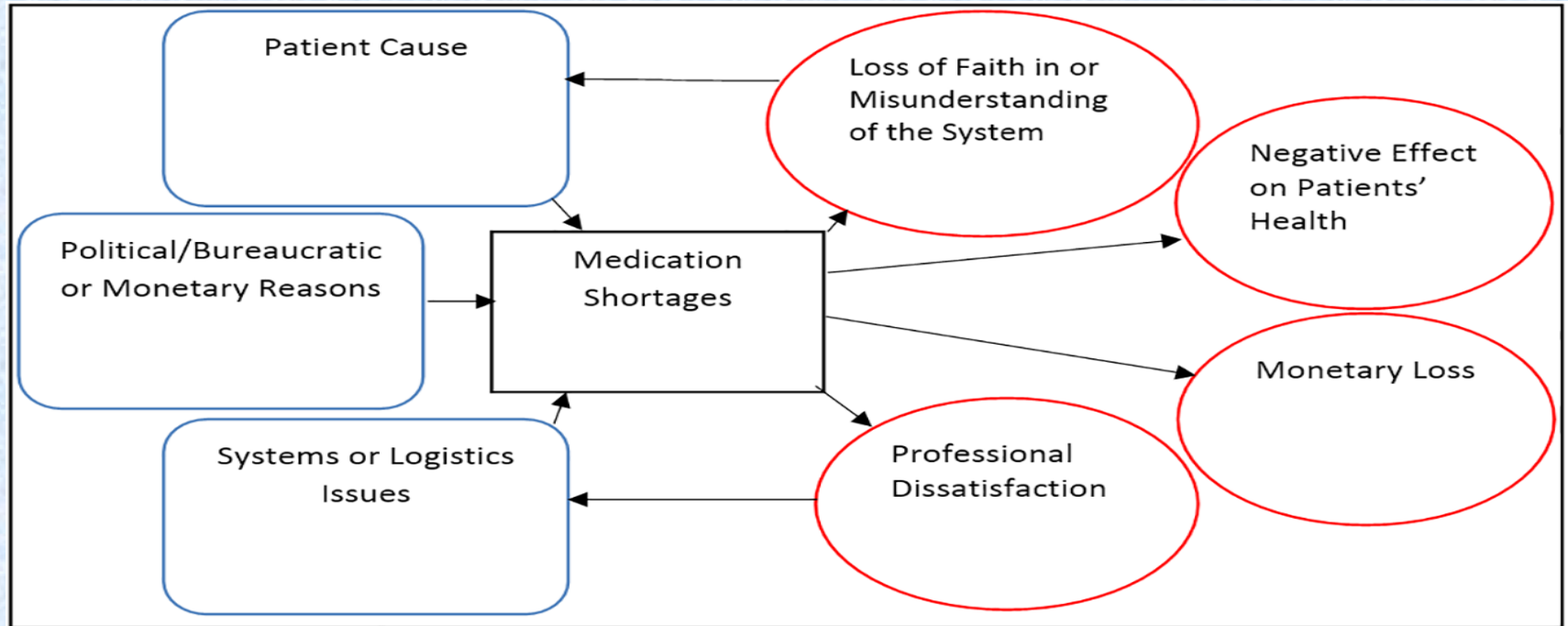
SHORTAGES IN FIJI (1.)

- Island nation in the South Pacific; 0.85 mln citizens
- Developing, health-conscious state, focused on public health but with many problems, incl. access to medicines
- 37 interviews; 48 interviewees (pharmacists, physicians, nurses, bureaucrats/policy-makers)
- Three major themes extracted:
 - Causes
 - Impacts
 - Solutions

SHORTAGES IN FIJI (2.)

- Causes:
 - Political/Bureaucratic or monetary reasons
 - Systems issues or logistics
 - Patient causes
- Impacts:
 - Negative effect on patients' health
 - Professional dissatisfaction
 - Monetary loss
 - Loss of faith in or misunderstanding of the system
- Solutions:
 - Current work-arounds
 - Improvement in operations
 - Change in policy and/or government intervention
 - Education and training

COMPLEX PICTURE OF CAUSES AND IMPACTS – INFLUENCE DIAGRAM



Thank you for your attention!

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