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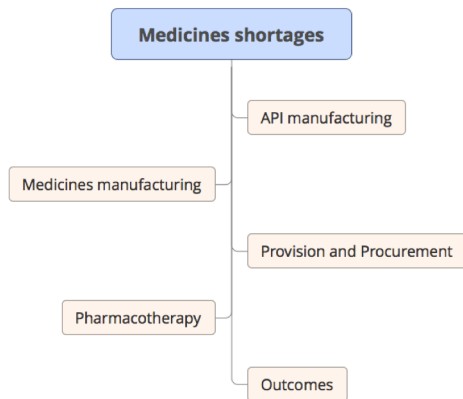


**EAHP ACADEMY SEMINAR**

**19 – 21 October 2018**

**Warsaw, Poland**

**Medicines Shortages –  
Causation and  
Approaches to  
Improvements**



# An international bottom-up approach – analysis of causation of shortages

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# Disclosure of conflicts of interest

- Nothing to declare
- My main interest is the patient's outcome (according to the Hippocratic Oath)
- No research funding from private sources





# Contents

- ▶ Subject of COST Action CA15105 and other attempts
- ▶ Definitions, interpretations, positions, interests
- ▶ Stakeholders and erroneous incentives
- ▶ Vulnerabilities of the supply chain
- ▶ Intermediate results after 2 of 4 years life time of the Action

Subject of COST Action CA15105 and  
other attempts

# A kind reminder: We are not alone in this world



- ▶ Exchange, communicate and find common solutions!
- ▶ Our legislation and acts on medicines impede exchange
  - ▶ Regulation
  - ▶ Prohibitions
  - ▶ Human Research Act

# Matching CA 15105 and \*COST philosophies

- ▶ \* COST is the cooperation in science and technology
- ▶ COST enables **breakthrough scientific and technological developments** leading to new concepts and products...
  - ▶ **Research Question CA15105:**  
**What steps need to be taken to reduce the medicines shortage problem affecting patients and healthcare systems?**
- ▶ ...through **trans-European networking** of nationally funded research activities (leverage)
- ▶ COST Action CA15105 running 2016 – 2020, funded by approximately 500'000€
- ▶ **Bottom-up** principle
  - ▶ as opposed to top-down regulation and legislation
  - ▶ Is this an incentive for pharma industry to join the Action?
- ▶ Key Target Domains
  - ▶ Stakeholders along the supply chain
  - ▶ **Academy Practice Partnership**



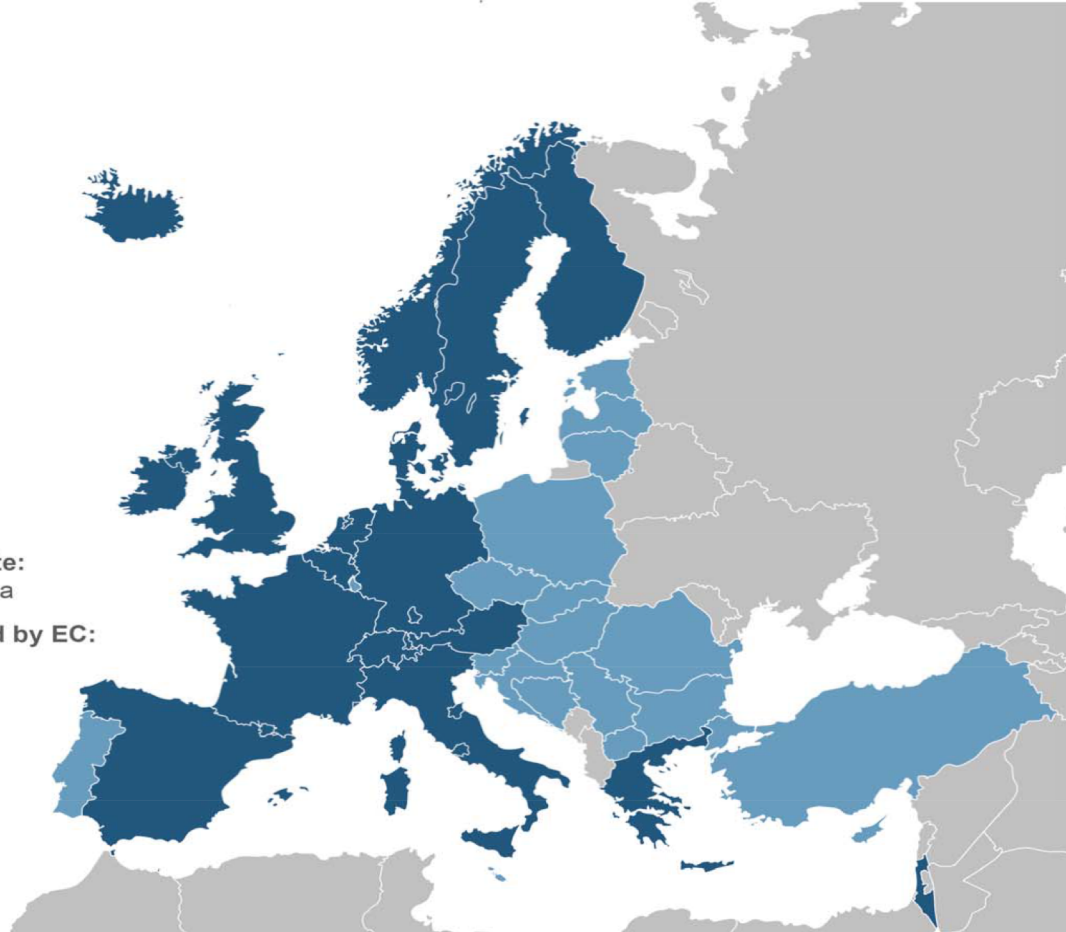
# COST Inclusiveness and Target Countries

- **EU 13:**  
Bulgaria  
Croatia  
Cyprus  
Czech Republic  
Estonia  
Hungary  
Latvia  
Lithuania  
Malta  
Poland  
Romania  
Slovakia  
Slovenia

- EU Candidates:**  
fYR Macedonia  
Republic of Serbia  
Turkey

- EU Potential Candidate:**  
Bosnia and Herzegovina

- EU Countries targeted by EC:**  
Luxembourg  
Portugal



# Basic Research: New knowledge

## Applied Research: Innovation

- ▶ Medicines Shortages Research and COST Action are both new knowledge creating and innovative practical approaches





# ..but an un-coordinated kind of research domain as research remains nationally funded



REPORT  
NOVEMBER 2016

SCM World  
Shaping the Future of Supply Chain

## A VIEW ON DRUG SHORTAGES FROM EIPG

Prof. Claude Farrugia  
Vice-President Communications, EIPG

A Quantitative Analysis of the Causes of Drug Shortages in Jordan: A Supply Chain Perspective  
Essential Medicines in a High Income Country: Essential to Whom?

**DH** Department of Health  
Skepton House  
80 London Road  
London  
SE1 6LH  
Tel: 020 7972 2000  
Direct Line: 020 7972 2833  
E-Mail: [keith.ridge@dh.gov.uk](mailto:keith.ridge@dh.gov.uk)

NHS Hospital Chief Pharmacists in England

14<sup>th</sup> July 2009

Dear colleague

### EXPORTING OF MEDICINES

It has been drawn to my attention that a small number of NHS hospitals are considering entering into agreements to export, or result in the export of, medicines for short term financial gain.

This is wholly unacceptable and should not be done. Such activities in any circumstances threaten the medicines supply chain and therefore patient care. This is contrary to acceptable professional behaviour. However those pharmacists who enter into such agreements at a time of pandemic are acting particularly irresponsibly. Therefore I am asking, through this letter, SHA pharmacy leads, working with the National Pharmaceutical Supplies Group, to let me know if they become aware of such activities in hospital pharmacies.

I recognise that the vast majority of hospital pharmacists would not contemplate threatening patient care in the manner I describe. May I take this opportunity to thank colleagues for their ongoing, significant and central contribution to dealing with the current pandemic and the challenges ahead.

Yours sincerely

Dr Keith Ridge  
Chief Pharmaceutical Officer

cc: Professor Bill Scott Chief Pharmaceutical Officer for Scotland  
Dr Norman Mearns Chief Pharmaceutical Officer for NI  
Mr Jeremy Savage Acting Chief Pharmaceutical Officer for Wales  
Ian Dalton National Director for NHS Flu Resilience  
Howard Skokos Principal Pharmacist, PASA  
SHA Pharmacy/Prescribing Leads  
National Pharmaceutical Supply Group



The Economist Intelligence Unit  
Healthcare

Addressing medicine shortages in Europe  
Taking a concerted approach to drive action on economic, manufacturing and regulatory factors

A report by The Economist Intelligence Unit

Commissioned by medicines for europe

## Best Practice for Ensuring the Efficient Supply and Distribution of Medicines to Patients



# What's really new as compared to other initiatives?

## -> Integration!

### ▶ **Research Question CA15105:**

**What steps need to be taken to reduce the medicines shortage problem affecting patients and healthcare systems?**

- ▶ Integration of all stakeholders along the entire supply chain (including associations!)
- ▶ Integration of as many countries as possible (actually 27)
- ▶ Grade and skill mix
- ▶ Complementary research activities of participating “schools”
  - ▶ KU Leuven
  - ▶ BFH Bern
  - ▶ University Hospital of Psychiatry PUK Zurich
  - ▶ Politecnico Lisbon / Portalegre
  - ▶ University Cracow
  - ▶ University Tel Aviv
  - ▶ University Dublin
  - ▶ University Istanbul
  - ▶ University Hospital Belgrade
  - ▶ University Hospitals Zagreb
  - ▶ ... and many others

# Action Objectives

## ▶ Capacity-building objectives

- ▶ To stimulate **new research** by early career investigators
- ▶ To expand the **network** and recruit all relevant stakeholders identified
- ▶ To **include** WHO regions, **less research-intensive & NNC**
- ▶ To achieve a year on year increase of as **early career investigators**
- ▶ To provide **training and knowledge transfer** (*STSM, Training Schools*)

## ▶ Research coordination objectives

- ▶ **Prevalence** (*landscape, definition, common understanding*)
- ▶ **Impact** (*directly on patients and healthcare systems, socioeconomic*)
- ▶ **Causes** (*overview of primary causes, processes needing globally priority research*)
- ▶ **Solutions** (*consensus statement on long-term international solutions*)

## ▶ Strategic approach

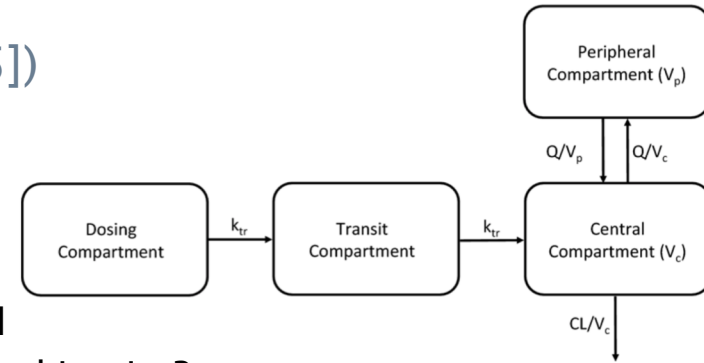
- ▶ To create a research network of all stakeholders within the medicines supply
- ▶ To assemble, synchronise and share the existing and current knowledge
- ▶ To promote stakeholder-government dialogue on the evidence, research findings and potential solutions
- ▶ To create a positive environment for innovative solution identification and implementation

Definitions, interpretations,  
positions, interests

# Definition

(26 different ways of defining [de Weerd 2015])

- ▶ COST Management Committee Meetings
  - ▶ No agreement on a common definition
- ▶ What is obvious in case of medicines shortages
  - ▶ Stock exchange between coupled pools is disturbed
  - ▶ Model as seen for central compartments in Pharmacokinetics?
- ▶ Plan B approach
  - ▶ Define a frame (as a function of registration status, timeframe, indication, reimbursement eligibility, ...)
    - “a medicines shortage is a non-availability of ...registered...  
...reimbursed by insurers...  
...life-saving or essential...  
...non-substitutable medicine of ...  
...the same active ingredient...  
...an active ingredient of the same therapeutic group..  
...an active ingredient indicated for the same pathology...  
...and ... non-substitutable medicinal product...  
...for a period of time between ... days and the time-point of deregistration...”*



# Non-availability or Non-accessibility ? – Do not leave patients alone without adequate medicines!

- ▶ Non-Availability
  - ▶ Supply of a registered medicine is disrupted
- ▶ Non-Accessibility
  - ▶ No provision of medicines to a (part of the) population or to a special patient group
  - ▶ Example Swiss – African collaboration for market admission
    - ▶ funded by Gates Foundation and Swissmedic
    - ▶ A model for Newly Industrialised or Third World countries?
  - ▶ Investigational Medicines
    - ▶ Compassionate use only
    - ▶ Parallel Trial / Early Access Program only
    - ▶ Experimental Therapy (“Heilversuche”, off-label uses, no ethical approval needed if indicated for a single person or a defined group of special patients)
- ▶ Particularity: Orphan drugs supply
  - ▶ In western countries feasible
  - ▶ In Newly Industrialised or Third World Countries hardly feasible
  - ▶ Needs incentives and at least cost coverage

# COST\* Action CA15105: Medicines shortages

We do not need to create more databases. We need solutions!

drugshortage.ch

Newsletter Drugshortage.ch

Meldungen der letzten 7 Tage

12. 10. 2018

Hier die Übersicht über die Meldungen der letzten Tage.

Den vollständigen Überblick über die gemeldeten Lieferengpässe erhalten Sie hier : <http://www.drugshortage.ch/index.php/uebersicht-2/>

Die Sammlung stammt aus freiwilligen Meldungen von Firmen oder von angemeldeten Nutzerinnen und Nutzern dieser Webseite und hat keine Aktualisierung der Meldungen sind die jeweiligen Melderinnen und Melder verantwortlich. Bei Unklarheiten wenden Sie sich bitte an die entsprechende Person.

## Mutationen der letzten 7 Tage

Anzahl offene Lieferengpässe
406

Juli 2017: approximately 270

October 2018: > 400

### Bewertung der Meldungen der Firmen

	Bewertung	Ar
1	Die Firma gibt ihre Daten selber ein und hat sich verpflichtet diese a jour zu halten (Exclusive Access)	in der Regel Firmenmeldung noch über Grossisten verfü
2	Die Firma versendet Updates an die Kunden; die Bewirtschaftung der Meldungen erfolgt durch Drugshortage.ch	in der Regel Firmenmeldung noch über Grossisten verfü

# Stakeholders and erroneous incentives



# Sharing responsibility & commonalities by an interdisciplinary and interassociational approach

- ICT specialists
- government representatives
- healthcare
- professional organisations
- industry federations
- trade associations
- patient organisations

- providers
- wholesalers
- procurement officers
- logistics specialist

- professional associations (provider)
  - medical professionals
  - health professionals
  - patient organisations
  - hospital directors
- health service, policy & politics experts
  - ethicists
  - sociologists
  - economists
  - governmental administration
  - regulatory representatives & inspectors
  - insurers

## PROCESS STEPS RELEVANT FOR MEDICINES SHORTAGES

API  
MANUFACTURING

MEDICINES  
MANUFACTURING

TRADE  
LOGISTICS  
WHOLESALE

PHARMACOTHERAPY

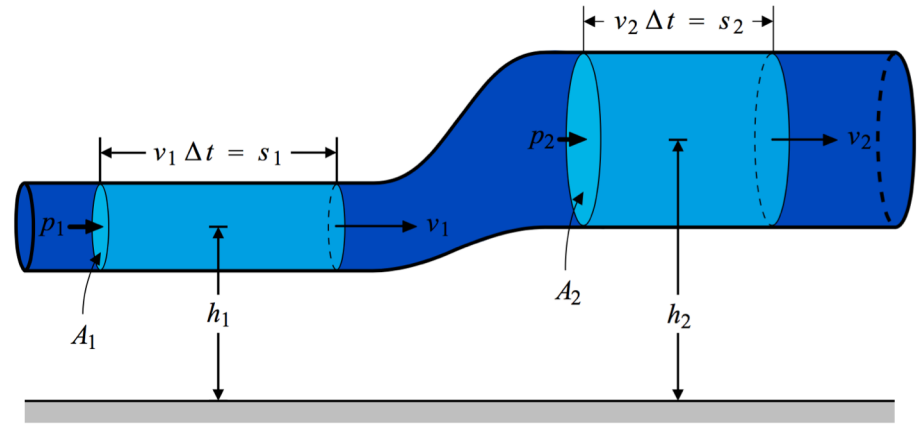
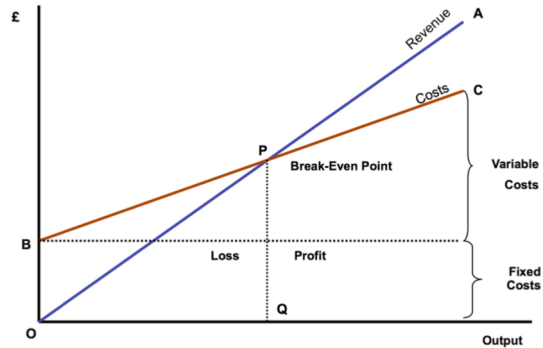
OUTCOMES  
CLINICAL  
FINANCIAL  
QUALITY OF LIFE

- active ingredient manufacturers
  - managers
  - directors of industrial associations
  - chemists
- business managers
- economists

- manufacturing pharma enterprises
  - managers multinational enterprises
  - manufacturing SME
  - directors of industrial associations
  - chemists, industrial pharmacists
- business managers
- economists

- prescribers and providers
  - physicians
  - pharmacists
  - therapists

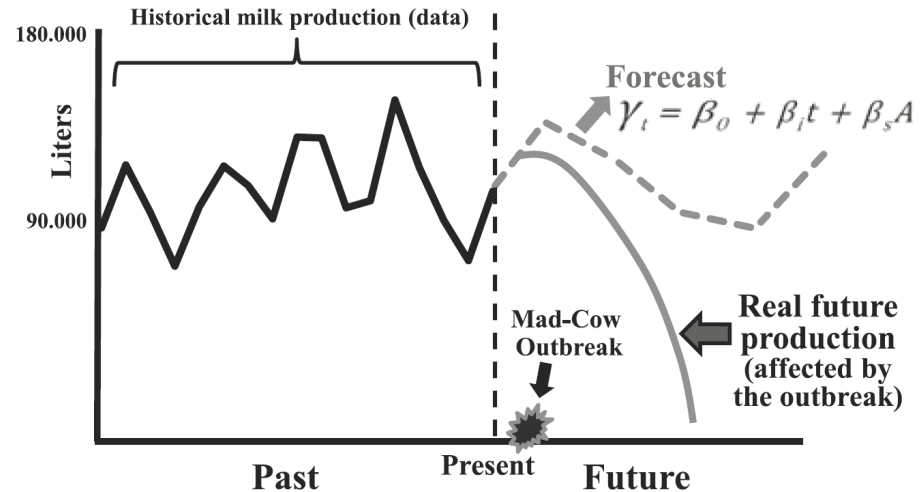
# Erroneous incentives



- ▶ Free trade warranted by the constitution
  - ▶ ... but support of macro-economy only
  - ▶ ... but capital bound in stocks is kept lean
- ▶ High regulation of procedures, low delegation of leadership for troubleshooting
  - ▶ ... but no shared responsibility
  - ▶ ... but intervention option of authorities only in case of epidemics or pandemics
- ▶ Mergers to maximise gain while production expenditures decrease
  - ▶ ... but risk of chain disruption increases
- ▶ Focus on steadily increasing macro-economy
  - ▶ ... but creates problems on a micro-economy level
  - ▶ ... but favours competition original - generic
- ▶ National supply (contracting with manufacturers)
  - ▶ ... but applicable for medicines considered life-saving only

# Vulnerabilities of the supply chain

# Shortages foresight: „gouverner c'est prévoir“ – What did we miss? Variables?



# Some cases – a kind reminder

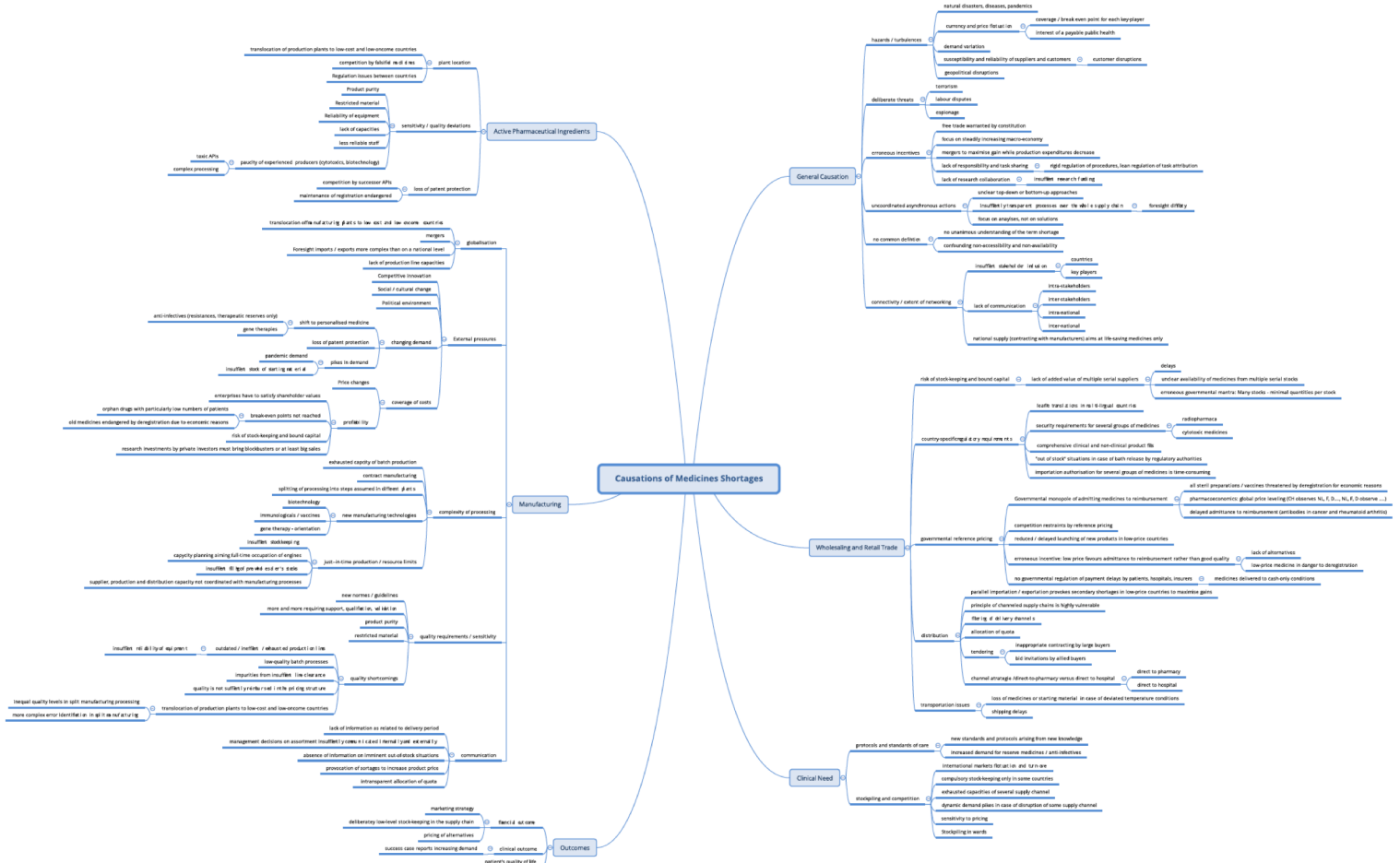
- ▶ Quality or availability problems related to active ingredients (APIs), to production processes, or equipment
  - ▶ heparin contamination
  - ▶ valsartan
  - ▶ piperacillin - tazobactam
- ▶ Restrictions imposed by authorities followed by high cost and low profit situations resulting in discontinuation decisions taken by producers
  - ▶ all sterile preparations / vaccines
  - ▶ antibodies in cancer and rheumatoid arthritis
  - ▶ pharmaco-economics: Global price levelling (CH observes NL, F, D..., NL, F, D observe ...)
- ▶ Risk and safety / gain perspectives
  - ▶ anti-infectives (resistances, therapeutic reserves only)
  - ▶ gene therapies (low number of cases)
- ▶ Increased demand following anticipating bird and swine flu pandemic scenarios and overstocking caused by panic buying
  - ▶ oseltamivir
- ▶ Inappropriate contracting by large buyers leading to the loss of small suppliers
  - ▶ parallel importing / exporting to maximise gains
  - ▶ tendering

# Vulnerabilities of the Supply Chain grouped by behaviour causes

(a kind of „risk“ assessment, Reference: Pettit, Croxton, Fiksel 2013 )

- ▶ **Turbulence (external factors beyond our control)**
  - ▶ Natural disasters, diseases, pandemics
  - ▶ Geopolitical disruptions
  - ▶ Demand variation
  - ▶ Currency and price fluctuation
- ▶ **Deliberate Threats**
  - ▶ Terrorism
  - ▶ Labour disputes
  - ▶ Espionage
- ▶ **External pressures**
  - ▶ Competitive innovation
  - ▶ Social / cultural change
  - ▶ Political environment
  - ▶ Price changes
- ▶ **Resource limits**
  - ▶ Supplier, production and distribution capacity
- ▶ **Sensitivity**
  - ▶ Product purity
  - ▶ Restricted material
  - ▶ Reliability of equipment
- ▶ **Connectivity (interdependence and reliance on outside entities)**
  - ▶ Scale of network
  - ▶ Reliance upon information
  - ▶ Import and export channels
- ▶ **Susceptibility and reliability of suppliers and customers / Customer disruptions**

# Causations - Mindmap (6 groups)





# Multiple shortcomings with Sandoz-generics

- ▶ Stock-outs
  - ▶ in 2014: 98 products (16% of the assortment)
  - ▶ in 2017: 50 products ( 8% of the assortment)
  - ▶ in 2018: 90 products (15% of the assortment)
- ▶ Reasons for the sharp rise of unavailable Sandoz products (mainly CNS)
  - ▶ Strike in India from July to December 2016 (Kalwe, India)
  - ▶ All Sandoz-psychopharmaceuticals (e.g. Mirtazapine) but risperidone produced in Kalwe
  - ▶ 2<sup>nd</sup> production site (Bangladesh, Tongi, Gazipur) was hit by heavy monsoon rain and floods in 2018 (GSK closes Bangladesh unit)
  - ▶ Risperidone: Blister material with defect – not available until change is approved by Swissmedic
  - ▶ Ibandronate: new analytical method in review process at Swissmedic since 6 months – no stocks to cover this length of time -> bad priority planning in production
  - ▶ Tamper evident seal: Needs packages in EU to be renewed until spring 2019
  - ▶ No problems with Citalopram and Fluoxetine
- ▶ Sandoz should have known and planned better – bad anticipation!
- ▶ Negotiations for increasing safety stocks at Sandoz

# Should we & Sandoz have known? FDA Warning Letter

- ▶ <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm474013.htm>
- ▶ CC even to CEO Joe Jimenez
- ▶ Decisions in such a situation?

The screenshot shows the FDA website interface. At the top, the FDA logo and 'U.S. FOOD & DRUG ADMINISTRATION' are visible. A search bar and navigation tabs for various product categories are present. The main content area is titled 'Inspections, Compliance, Enforcement, and Criminal Investigations' and includes a breadcrumb trail: 'Home > Inspections, Compliance, Enforcement, and Criminal Investigations > Compliance Actions and Activities > Warning Letters > 2015'. A blue button labeled '2015' is highlighted. The specific document is titled 'Sandoz Private Limited 10/22/15'. Below the title are social media sharing options: 'SHARE', 'TWEET', 'LINKEDIN', 'PIN IT', 'EMAIL', and 'PRINT'. The 'Department of Health and Human Services' logo and address are shown on the right. The document is identified as a 'Warning Letter' with ID 'WL: 320-16-01', dated 'October 22, 2015'. The recipient is 'Mr. Richard Francis, Division Head, Sandoz International GmbH, Industriestrasse 25, 83607 Holzkirchen, Germany'. The letter text begins with 'Dear Mr. Francis: The U.S. Food and Drug Administration (FDA) inspected the following two pharmaceutical manufacturing facilities:' followed by two bulleted items: 'A. August 25-29, 2014: Sandoz Private Limited, MIDC Plot Nos. 8-A/2 & 8-B, TTC Industrial Area, Kalwe Block, Village Dinghe, Navi Mumbai 400 708, Maharashtra, India (Kalwe facility)' and 'B. August 12-28, 2014: Sandoz Private Limited, Plot Nos. D31 & D32, MIDC, TTC Industrial Area, Turbhe, Thane-Belapur Road, Navi Mumbai 400 705 Maharashtra, India (Turbhe facility)'. The letter concludes with: 'At both sites, we identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211.'

# Harmonisation and globalisation at what price? To produce in Asia seems to be high risk!

Nau.ch

novartis

## Novartis streicht in der Schweiz über 2000 Stellen

Der Schweizer Pharmakonzern Novartis streicht über 2000 Jobs. Betroffen sind die Standorte Basel, Schweizerhalle, Stein und Locarno.



Der Hauptsitz des Pharmakonzerns Novartis in Basel. - Keystone

## Sandoz to Shutter India API Plant

Source: Hindu Business Line  
Jul 17, 2015

[Print](#) [Email](#) [Tweet](#) [Share](#) [G+](#) [Share](#)

Novartis' Sandoz will discontinue operations at its Maharashtra, India site by December 2016, as part of global plans to optimize manufacturing.

The site, located in west-central India, employs 170 people and manufactures antibiotics and APIs.

Sandoz will continue to serve the India market, but will instead focus its manufacturing at its two other, larger sites in India.

Read the [Hindu Business Line release](#)

## Aurobindo Pharma acquires dermatology business from Sandoz in a \$900 million cash deal

By DIVYA RAJAGOPAL, ET Bureau | Updated: Sep 06, 2016, 10:00 AM IST

## Sandoz announces exclusive global collaboration with Biocon on next-generation biosimilars

Jan 18, 2018

## Sandoz(Novartis) kalwe plant strike

 Nilesch Kamble  
@NileschK1234210 · July 19, 2017

Sandoz kalwe plant (Mumbai) employees strike was started on 18th July 2017 at 7am

1 Likes















[Like](#)



Intermediate results after 2 of 4  
years life time of the Action

# COST Action CA15105 - Objectives met after 2 years

- <https://e-services.cost.eu/action/objectives/overview/CA15105>

Type	Objective
Challenge 	to denominate the steps needed to be taken to reduce the medicines shortage problem affecting patients and healthcare systems
Research Coordination 	Prevalence: By the end of year 1: the research network will agree a set of definitions on the topic of medicine shortages. By the end of year 2: the research network will form a common understanding on the prevalence of medicine shortages in the countries represented.
Research Coordination 	Impact: By the end of year 2: the research network will have assessed the direct impact shortages have on patients and healthcare systems. By the end of year 4: the research network will review the socioeconomic impact on healthcare systems.
Research Coordination 	Causes: By the end of year 2: the research network will provide policy makers, regulatory agencies and other stakeholders including the pharmaceutical industry an overview of the primary causes of shortages By the end of year 2: the research network will identify processes requiring priority research from a global perspective.
Research Coordination 	Solutions: By the end of year 4: the research network will develop a consensus statement identifying long-term international solutions.
Capacity Building 1 	By the end of year one: the establishment of the COST Action will have stimulated new research in the area of medicines shortages by early career investigators.
Capacity Building 2 	By the end of year one: the COST Action will have recruited all relevant stakeholders identified in the expansion strategy.   
Capacity Building 3 	By the end of year one: the COST Action will contain participants from each WHO region.
Capacity Building 4 	By the end of year two: the COST Action will have expanded through wide inclusion of less research intensive countries and near neighbour countries.
Capacity Building 5 	By the end of year four: the COST Action will have achieved a year on year increase of as early career investigators as participants.
Capacity Building 6 	By the end of year four: the COST Action will have provided training and knowledge transfer activities via Short-Term Scientific Missions and Training Schools in less research-intensive countries.

# Summary

# Critical elements seem to be (lacking) governmental forsight and/or shared responsibility



- ▶ To tackle together what individuals did not succeed
- ▶ To collaborate and create synergies and added values
- ▶ To dedicate our actions to humanitarian goals (Hippocratic Oath, patient-centered approaches and promises)
- ▶ As revealed in the Swiss shortages project there is currently no sensibility and will to share responsibilities
  - ▶ Authorities only act if there is a legal or constitutional task
  - ▶ Major stakeholders are satisfied with the macroeconomic success of the partnership of public health and industry and / or (pre-)wholesalers



That's all folks – questions or coffee break?

