VINZENZ GRUPPE

VINZENZ GRUPPE

Medizin mit Qualität und Seele
www.vinzenzgruppe.at

Falsified Medicines Directive
Did they forget the hospital pharmacy?

A critical appraisal of FMD & dR

22th Congress of the EAHP, March 2017

Dr. Thomas Langebner, MBA
thomas.langebner at vinzenzgruppe.at

Krankenhäuser Barmherzige Schwestern Wien, Linz, Ried • Orthopädisches Spital Speising • St. Josef-Krankenhaus Wien • Krankenhaus Göttlicher Heiland
Herz-Jesu Krankenhaus • Barmherzige Schwestern Pflege • Kurhaus Marienkron • Herz-Kreislauf-Zentrum Bad Ischl

Disclosures

VINZENZ GRUPPE

- nothing to disclose

VINZENZ GRUPPE

3 Questions

- Is the prevalence of falsified medicines in the legal supply chain in Europe 1%?
- Does it take a maximum of 300 milliseconds to verify and decommission (V&D) a medicinal product?
- Is the extra cost per hospital pharmacy max. 750 €/a?

Agenda

- how to buy a falsified medicine
- FMs in the regular supply chain
- without FMD & dR
- impact on hospital pharmacies
- rules & derogations
- a way out of excessive workload
- take home messages

VINZENZ GRUPPE

Agenda

- **how to buy a falsified medicine**
- FMs in the regular supply chain
- without FMD & dR
- impact on hospital pharmacies
- rules & derogations
- a way out of excessive workload
- take home messages

falsified medicines
How to buy a falsified medicine?

In order to buy a falsified medicine I will go to

- a less developed country and buy it out in the street. (up to 100%)
- an internet-based "pharmacy". (around 95%)
- the pharmacy just around the corner. (almost 0%)

VINZENZ GRUPPE

How to buy a falsified medicine 1
the case of less developed countries

Numerous publications on different markets and product groups show a high to very high prevalence of falsified medicines in less developed countries.

[Schweim 2005]

How to buy a falsified medicine 2
internet sales

- > 90% of online “pharmacies” are operating illegally [EAASM 2012]
- >90% of medicinal products purchased via internet were counterfeit or substandard [AGES 2015]

>>> Buying medicines from the internet is like Russian roulette.
You never know what you get until you try.

VINZENZ GRUPPE

Agenda

- how to buy a falsified medicine
- **FMs in the regular supply chain**
- without FMD & dR
- impact on hospital pharmacies
- rules & derogations
- a way out of excessive workload
- take home messages

How to buy a falsified medicine 3a
the regular supply chain

- The proportion of counterfeiting in most developed countries with effective regulatory systems and market control is **less than 1% of market value**. [WHO 2006]
- The responsible expert-group of the WHO estimates that, in industrialised countries, **counterfeit medicines have a market share of up to 1%.** [SEC (2008) 2674]

>> Apparently the only available figure regarding developed countries.
>> No information given on the data this assumption is based on.
>> **Regarding the legal supply chain in developed countries:**
1/100 is obviously too high by several orders of magnitude.

VINZENZ GRUPPE

How to buy a falsified medicine 3b

FMs in the regular supply chain

Published examples of intrusion of legal supply chains are rare, e. g.:

- **The Italian theft case**
  - target markets were countries with insufficient legal supply plus parallel trade
- **The German omeprazole case**
  - German market via a spurious wholesaler
- **The UK retrospective survey**
  - falsified medicines mainly in parallel trade
- **The Canadian retrospective survey**
  - robust GMP inspections – very low incidence rates

The Italian Theft Case

The transcrime report 2014

VINZENZ GRUPPE

The Italian Theft Case

The transcrime report 2014

- High-price medicines (e. g. Avastin®) were **stolen from Italian hospitals by organized groups**.
- Most of these are … pharmaceuticals fully covered by the Italian National Health System. This may confirm the hypothesis, suggested in 1.4, that stolen products are also **sold on the illegal markets of foreign countries (especially Eastern Europe and Greece) where reimbursement regimes are weaker, or the legal supply is insufficient, or where they can enter the parallel trade and be exported to high-price countries**.
- To be highlighted are also the overlaps between the trafficking of Stolen medicines and the parallel trade (i.e. the legal trade based an price differentials across countries). It cannot be excluded that, because of **loopholes in traceability systems across jurisdictions and the high level of liberalization of the pharmaceutical market,** Stolen medicines re-enter the legal trade through **fictitious wholesale companies** (perhaps set up in foreign countries) **or corrupt brokers**, and are then sold to high-price countries (e.g. Germany, Sweden) or exported back to Italian hospitals or pharmacies.

The German Omeprazole Case

low cost – low risk – high profit

- From 2008-2013 a fraudulent pharmacist and his brother sold 600.000 packages of counterfeit omeprazole- containing generics (at 15 mio. €) to a German **shortline wholesaler** who was entirely "bona fide".
- A mistake found on a package leaflet by a patient which was reported to the pharmaceutical company arose the suspicion of falsification.
- In March 2013 a police raid at 40 locations of wholesalers in Germany finally tracked down the source of the falsified medicines.

[Financial Times 2013, Apotheke adhoc 2013]

>> OTC-omeprazole was added to dR Annex 2 (blacklist).
>> Which non-Rx-medicine is going to be next?

VINZENZ GRUPPE

Open Access Research

BMJ open

Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011)

- **setting**
  - retrospective analysis is drug alerts issued by the Medicines and Healthcare Product Regulatory Agency (MHRA) from 2001-2011
- **results**
  - 280 substandard medicines, 222 recalls (contamination, defective packaging, …)
  - reports of defective medicines increased from 5 (2001) to 50 (2011)
  - **11 cases falsified medicines over an 11-year period**
  - 1/11 was a counterfeit toothpaste!; **9/11 due to parallel trade** (immediate risk to patients unlikely)
- **authors conclusions**
  - Substandard medicines are a significant problem in the UK.
  - increase might be due to improved detection

To cite: Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open* 2013;3:e002924. doi:10.1136/bmjopen-2013-002924

>> NB: Authors do **not** report a 10-fold increase in the number of falsified medicines.

The Canadian retrospective review
low incidences over a 9-year period

VINZENZ GRUPPE

- Almuzaini / Sammons / Choonara (2014):
  Quality of medicines in Canada: a retrospective review of risk communication documents (2005-2013). doi: 10.1136/bmjopen-2014-006088
- **setting**
  - The Health Canada website search for drug recalls and risk communication documents issued between 2005 and 2013.
- **results**
  - There were 653 defective medicines of which 649 were substandard. The number of defective medicines reported by Health Canada increased from 42 in 2005 to 143 in 2013. The two most frequently reported types of defects were stability (205 incidents) and contamination issues (139 incidents).

>> Over a 9-year period 4 out of 653 (0,6%) defective medicines reported were counterfeit. .

VINZENZ GRUPPE

The Canadian retrospective review
robust GMP inspections

VINZENZ GRUPPE

Falsified medicines

Only four incidents of falsified medicines were reported by Health Canada. The detection is extremely low compared with substandard medicine. **Health Canada has robust GMP inspections that cover all drug establishments including manufacturers, distributors and wholesalers.** The reporting system of Health Canada is concerned with falsified medicines detected within the scope of GMP inspections. Some falsified medicines may be intercepted and seized by enforcement bodies on their way to target destinations, but not necessarily intended for the Canadian market. This may explain the low detection rate by Health Canada. [Almuzaini 2014]

Agenda

VINZENZ GRUPPE

- how to buy a falsified medicine
- FMs in the regular supply chain
- **without FMD & dR**
- impact on hospital pharmacies
- rules & derogations
- a way out of excessive workload
- take home messages

VINZENZ GRUPPE

Without FMD & dR
myths of medicines market

- Falsified medicines have **a market share of up to 1%** in industrialised countries.
- Medicines pass through **up to 20 pairs of hand** before reaching the retailer/pharmacist.

Without FMD & dR
FMs - a market share of up to 1%?

The responsible expert-group of the WHO estimates that, in industrialized countries, **counterfeit medicines have a market share of up to 1%.**
[SEC(2008) 2674]

>> This is apparently the only available (and frequently qoted) figure regarding developed countries.
>> There is no information given on the data this assumption is based on.
>> **Regarding the legal supply chain in industrialized countries:**
1/100 is obviously too high by several orders of magnitude.
>> Common experience in a market like Austria would suggest the figure to be in the magnitude of 1/1.000.000 or below.
>> An in-depth analysis of data regarding legal supply chains is still missing.

>> If protection of patients/customers were the primary goal, internet sales of (para-)medicines should be the primary focus of action.

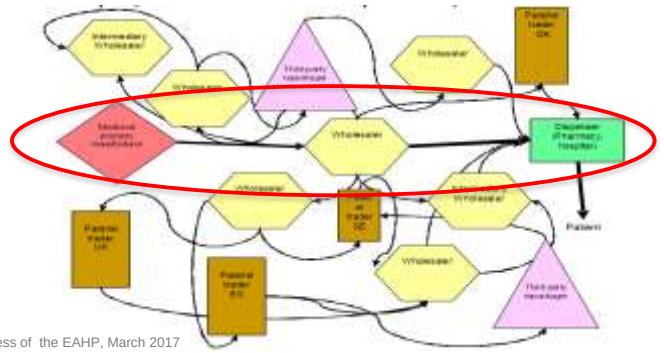
VINZENZ GRUPPE

Without FMD & dR
20 pairs of hand?

VINZENZ GRUPPE

Today's distribution system for medicinal products is highly complex. In the public consultation, manufacturers pointed out that their products may pass through up to **20 pairs of hand** before reaching the retailer/pharmacist. **While this may be an exaggeration**, it is certainly more realistic to describe the distribution chain as follows:

[SEC(2008) 2674]



Parallel Trade
an effective means of cost control?

VINZENZ GRUPPE

Does pharmaceutical parallel trade serve the objectives of cost control?

Panos Kanavos and Stacey Kowal

[Kanavos/Kowal 2008]

>> Parallel trade is **neither associated with direct benefits to patients nor with sustainable financial benefits to payers**.

>> Pricing issues should therefore be addressed directly when negotiating reimbursement.

>> Parallel trade may cause **severe side effects** in both exporting and importing countries.

>> Parallel trade is a major **potential way of entrance** for falsified medicines.

VINZENZ GRUPPE

Without FMD & dR
20 pairs of hand?

Today's distribution system for medicinal products is highly complex. In the public consultation, manufacturers pointed out that their products may pass through up to **20 pairs of hand** before reaching the retailer/pharmacist. **While this may be an exaggeration**, …

[SEC(2008) 2674]

[on wholesalers] Art. 21: Verification of the authenticity of the unique identifier of a medicinal product is not required under Article 20(b) in any of the following situations:
(a) **that medicinal product changes ownership but remains in the physical possession of the same wholesaler**;
(b) … [EU 2016/161]

>> Multiple change of ownership within a network of companies without changes in the physical ownership may be useful to avoid taxes, but does not put medicinal products at an increased risk of falsification.

Without FMD & dR
Why did it work so remarkably well so far?

- reasonably short supply chains
- strict control of market participants
- involvement of well-trained, responsibly acting personnel, e. g. hospital pharmacists

Without FMD & dR

How to combat FMs by conventional means

>> Purchase from reliable sources.

>> Check the whole chain of production and distribution.

>> Stop risky practices if they cannot be adequately controlled.

>> Stop deregulating pharmaceutical markets.

>> FMD & dR cannot replace conventional means of surveillance but will only supplement them.

Agenda

- how to buy a falsified medicine
- FMs in the regular supply chain
- without FMD & dR
- **impact on hospital pharmacies**
- rules & derogations
- a way out of excessive workload
- take home messages

VINZENZ GRUPPE

FMD & dR
impact on hospital pharmacies

- The ECORYS impact assessment
- facts & figures to estimate the impact more realistically

The ECORYS Impact Assessment 2
fishing in troubled waters

Table 3.3 Investment costs for pharmacies (annualised)

	Total costs for sector (in million euros)	Costs per pharmacy (in euros)
Hospital pharmacies		
Modify pharmacy software	.	>100
Buy scanning equipment (2D)	1–3	140–500
Scanning time	PM(+)	PM(+)
Connect to repository system	0	0
Staff training & support	.	150
Total costs	**2–4+PM(+)**	**290–750+PM(+)**

- snap-Custos adaptation + implementation approx. 10.000 €
- e.g. Unitech rugged scanner approx. 500 €, BHS Linz: 5 required

[SWD(2015) 0189]

VINZENZ GRUPPE

Facts & Figures
e. g. Austria

- **community pharmacy**
  - 1.340 community pharmacies (CP)
  - prescription medicines: 141,5 million pkg/year (average per community pharmacy: 106.000 pkg/year)
  - (OTC products: 47 million pkg/year)
  - purchased mainly via wholesalers
  - POS system established in every pharmacy
  - >> V&D-scanning of single package does not require additional process steps.
- **hospital pharmacy**
  - 42 hospital pharmacies (HP)
  - prescription medicines: 19,3 million pkg/year (average per hospital pharmacy: 460.000 pkg/year)
  - 93% of pkg purchased directly from manufacturer/market authorization holder/pre-wholesaler (MMP)
  - Scanning of single items at receipt or dispensation is not regularly implemented.
  - Dispensing of medicinal products in tertiary packaging is very common.
  - V&D-scanning of single pkg requires time consuming extra steps (incl. opening/destruction of tertiary packaging or unpacking of pallets).

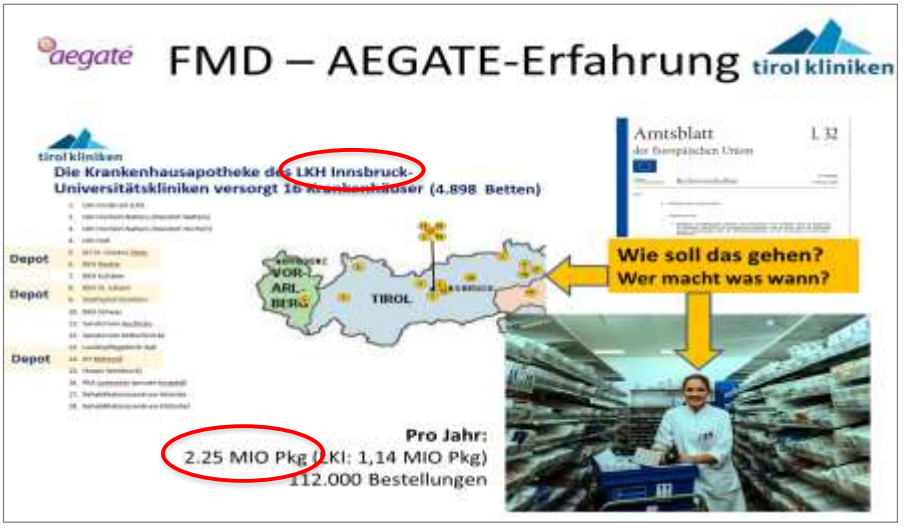
[fig: IMS Austria, pers. comm.]

Facts & Figures
extra workload - our own data

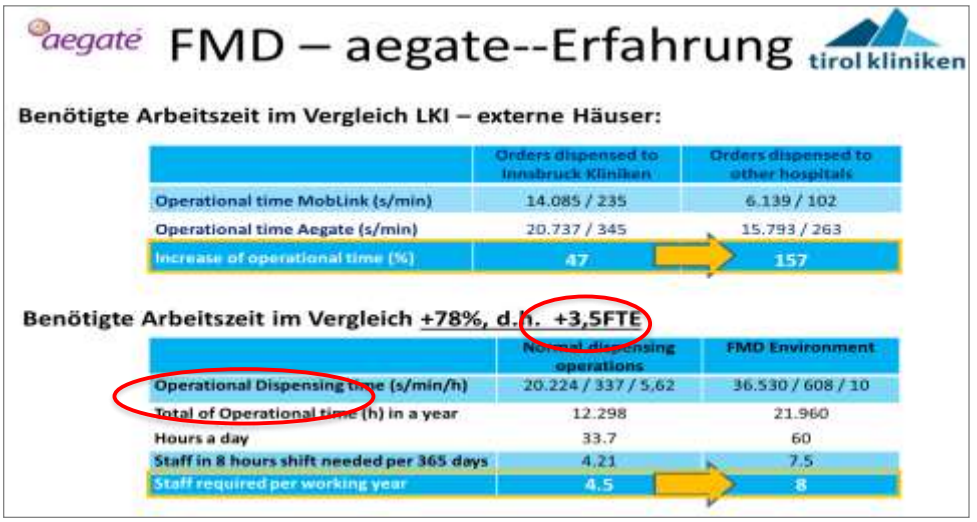
- Krankenhaus der Barmherzigen Schwestern Linz (BHS-L)
  - general teaching hospital,
  - 650 beds
- **retrospective evaluation**: number of **goods-in (Rx-medicines)**
  - approx. 7.000 pkg/week
- **real-life test**: time required for V&D of goods-in (Rx-medicines)
  - extra time: approx. 10 sec/pkg (incl. unpacking, scanning, …)
  - extra time: approx. 20 h/week (0,5 FTE)
  - **>> extra personnel costs**
  - Austria: pharmaceutical technicians 1 FTE = 44 T€/a
  - BHS-L: 22 T€ /a
  - LKH Innsbruck: 2,25 Mio pkg/a = 6 T h/a = 3 FTE/a = 132 T€/a
  - all Austria: 19,3 Mio pkg/a = 54 T h/a = 26 FTE = 1,2 Mio €/a
- "relatively low compared to the total budgets of hospitals"
  - but it is not yet in the budgets (personnel, finances)
  - Of what value is that faulty impact assessment ECORYS gave? (750 €/a /hospital)

VINZENZ GRUPPE

Facts & Figures
The Innsbruck-Experience 1



Facts & Figures
The Innsbruck-Experience 2



Facts & Figures
robotic dispensing as an alternative?

- investment costs approx. 300.000 - 500.000 €
- + annual costs of maintenance etc.

[http://bd.com/spotlight/rowa.aspx#]

Agenda

- how to buy a falsified medicine
- FMs in the regular supply chain
- without FMD & dR
- impact on hospital pharmacies
- **rules & derogations**
- a way out of excessive workload
- take home messages

rules & derogations
a matter of appropriateness

- derogations for wholesalers
  - verification of UIs only in certain cases
- derogations for healthcare institutions
  - V&D at any time
  - V&D by certain wholesalers
- “in order to avoid an excessive impact”

a risk-based approach
derogations for wholesalers

- **No verification of UI required if**
  - the medicinal product is received directly from industry since it is “not at higher risk of being falsified”
  - change of ownership without change of physical possession
  - transfer between two warehouses belonging to the same wholesaler
- **>> There is no such risk-based approach regarding hospital pharmacies.**

in order to avoid an excessive impact derogations for hospital pharmacies

- **derogations regarding hospital pharmacies:**
  - V&D **at any time**
  - V&D **by a wholesaler** belonging to the same legal entity as the healthcare institution

>> The derogation according to Art. 26 par. 3 is only applicable to a few, very specific settings in EU-countries (e. g. DK, Amgros)

>> The derogations regarding hospital pharmacies at present are not suitable to avoid an excessive impact on the daily operations of healthcare institutions in most EU-countries.

Commission Delegated Regulation (EU) 2016/161

V&D at any time

- **>>> the right time – different approaches**
  - goods-in (hospital pharmacy)
  - goods-out (hospital pharmacy)
  - …
  - dispensing to patient (ward level)
    - e. g. Naughton B, et al.
      BMJ Open 2016;6:e013837. doi:10.1136/bmjopen-2016-013837

VINZENZ GRUPPE

Open Access Research

BMJ Open **Effectiveness of medicines authentication technology to detect counterfeit, recalled and expired medicines: a two-stage quantitative secondary care study**

VINZENZ GRUPPE

- **setting**
  - scanning at ward level by technicians or hospital pharmacists
  - > 4.000 packages with UIs
  - 4% experimental contamination rate (“expired”, “recalled”, “counterfeit”)
- **results**
  - operational detection rate was 81% or 87%
- **authors conclusions**
  - a “technically perfect system”
  - improvement of operational detection rate by incentives (“payment by authentication”).

To cite: Naughton B, Roberts I, Dopson S, *et al*. Effectiveness of medicines authentication technology to detect counterfeit, recalled and expired medicines: a two-stage quantitative secondary care study. *BMJ Open* 2016;6:e013837. doi:10.1136/bmjopen-2016-013837

>>> remarks

- 4% is obviously not a realistic contamination rate.
- **Dispensing to patients at ward level is apparently not the right point of time for V&D.**

Agenda

VINZENZ GRUPPE

- how to buy a falsified medicine
- FMs in the regular supply chain
- without FMD & dR
- impact on hospital pharmacies
- rules & derogations
- **a way out of excessive workload**
- take home messages

A risk-based approach
to avoid an excessive impact

>> For medicinal products purchased directly from industry (manufacturer/market authorization holder/pre-wholesaler MMP) the risk of falsification is negligible.

>> Therefore it would be fully justified to exempt healthcare institutions from performing V&D of such medicinal products.

>> This would effectively reduce the extra workload (by >90%).

Aggregated Codes
to avoid an excessive impact

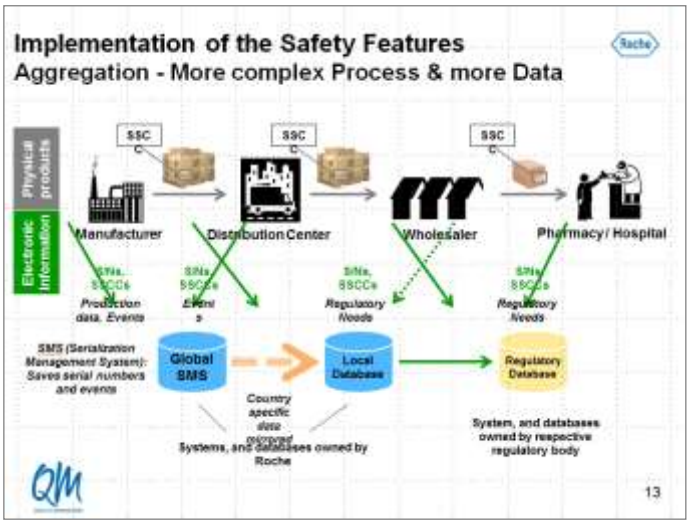
>> Regarding wholesalers the commission states that verification **would be equally effective** whether performed by scanning **individual unique identifiers or an aggregated code** allowing the simultaneous verification of multiple unique identifiers.

>> This is of course also true regarding V&D by hospital pharmacies.

>> Aggregated codes would really help to avoid excessive workload in each European hospital pharmacy.

Aggregated Codes
Aggregation – The Roche approach

Aggregated Codes
Aggregation – The Roche approach



Aggregation is technically feasible but more complex than simple serialization.

>> Mandatory aggregation is required to obtain a uniform solution and to avoid an excessive impact on hospital pharmacy.

VINZENZ GRUPPE

3 Questions

- Is the prevalence of falsified medicines in the legal supply chain in Europe 1%?
  - No. The prevalence of falsified medicines in the legal supply chain in Europe is several orders of magnitude lower (below 1/1.000.000).
- Does it take a maximum of 300 milliseconds to verify and decommission (V&D) a medicinal product?
  - No. The total process time for one V&D-step is several seconds (approx. 3-10 sec) summing up to a total of 20-140 hours/week of extra workload.
- Is the extra cost per hospital pharmacy max. 750 €/a?
  - No. The extra cost is significantly higher (e. g. est. 25-30.000 €/a for a 650-bed-hospital)

VINZENZ GRUPPE

Agenda

- how to buy a falsified medicine
- FMs in the regular supply chain
- without FMD & dR
- impact on hospital pharmacies
- rules & derogations
- a way out of excessive workload
- **take home messages**

VINZENZ GRUPPE

Take home messages

VINZENZ GRUPPE

- The impact of FMD&dR on hospitals and hospital pharmacies has **neither been adequately assessed nor been adequately communicated** to hospital owners.
- The implementation of FMD&dR in hospitals causes **significant extra workload and significant extra costs.**
- There should be an open and fair discussion with hospital pharmacists and hospital owners **how to modify the dR to avoid an excessive impact on hospitals effectively**.

VINZENZ GRUPPE

Medizin mit Qualität und Seele
www.vinzenzgruppe.at

Thank you for your attention.

VINZENZ GRUPPE

Regulation & impacts assessments

- **DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL** of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
- **COMMISSION DELEGATED REGULATION (EU) 2016/161** of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf
- Commission Staff Working Document. **Impact Assessment. SEC(2008) 2674**. Brussels 10.12.2008. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52008SC2674&from=EN
- Commission Staff Working Document**. Impact Assessment. SWD(2015) 188.** Brussels, 2.10.2015. http://ec.europa.eu/transparency/regdoc/rep/10102/2015/EN/SWD-2015-189-F1-EN-MAIN-PART-1.PDF

VINZENZ GRUPPE

Sources cited

- **Aegate**: Hospital Authentication. Issue #2/ 2016. https://aegate.com/wp-content/uploads/2016/09/Aegate_issue_2.pdf
- **Almuzaini T**, Sammons H, Choonara I: Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open*. **2013**;3(7):e002924. doi:10.1136/bmjopen-2013-002924.
- **Almuzaini T**, Sammons H, Choonara I. Quality of medicines in Canada: a retrospective review of risk communication documents (2005–2013). *BMJ Open*. **2014**;4(10):e006088. doi:10.1136/bmjopen-2014-006088.
- N. N: Omeprazol – 600.000 gefälschte Packungen. **Apotheke Adhoc**. 23. March 2014. http://www.apotheke-adhoc.de/nachrichten/markt/nachricht-detail-markt/arzneimittelkriminalitaet-anklage-im-faelschungsskandal-omeprazol/?L=&cHash=12b23747879b830bb9b57028a9d43f27
- **Dahl J**: Stopping the spread of counterfeit drugs and illegal Internet pharmacies. (blog dated with 10. June 2014) http://thehill.com/blogs/congress-blog/healthcare/219714-stopping-the-spread-of-counterfeit-drugs-and-illegal-internet
- European Alliance for Access to Safe Medicines (**EAASM**): Couterfeiting the counterfeiter. Leigh-on-Sea 2012. http://www.eaasm.eu/counterfeiting-the-counterfeiter-report.download
- European Medicines Verification Organisation (**EMVO**): EMVO FMD Workshop. Brussels 13. December 2016. https://www.emvo-medicines.eu/wp-content/uploads/2016/09/State-of-Play---EMVS-and-connected-Systems.pdf
- **Hogson** G: Falsified medicines directive: A great opportunity for improving patient safety. National Health Executive (NHE) 4. July 2016. http://www.nationalhealthexecutive.com/Comment/falsified-medicines-directive-a-great-opportunity-for-improving-patient-safety
- N. N: Teva discovers sophisticated fakes. **Financial Times** 28. April 2013. https://www.ft.com/content/bd988804-afed-11e2-8d07-00144feabdc0
- **Kanavos** P / Kowal S: Does pharmaceutical parallel trade serve the objectives of cost control? Eurohealth 14 (2008), 22-26. http://www.lse.ac.uk/LSEHealthAndSocialCare/pdf/eurohealth/VOL14N2/Kanavos%20and%20Kowal.pdf