The implications of implementing the Directive on Falsified Medicines

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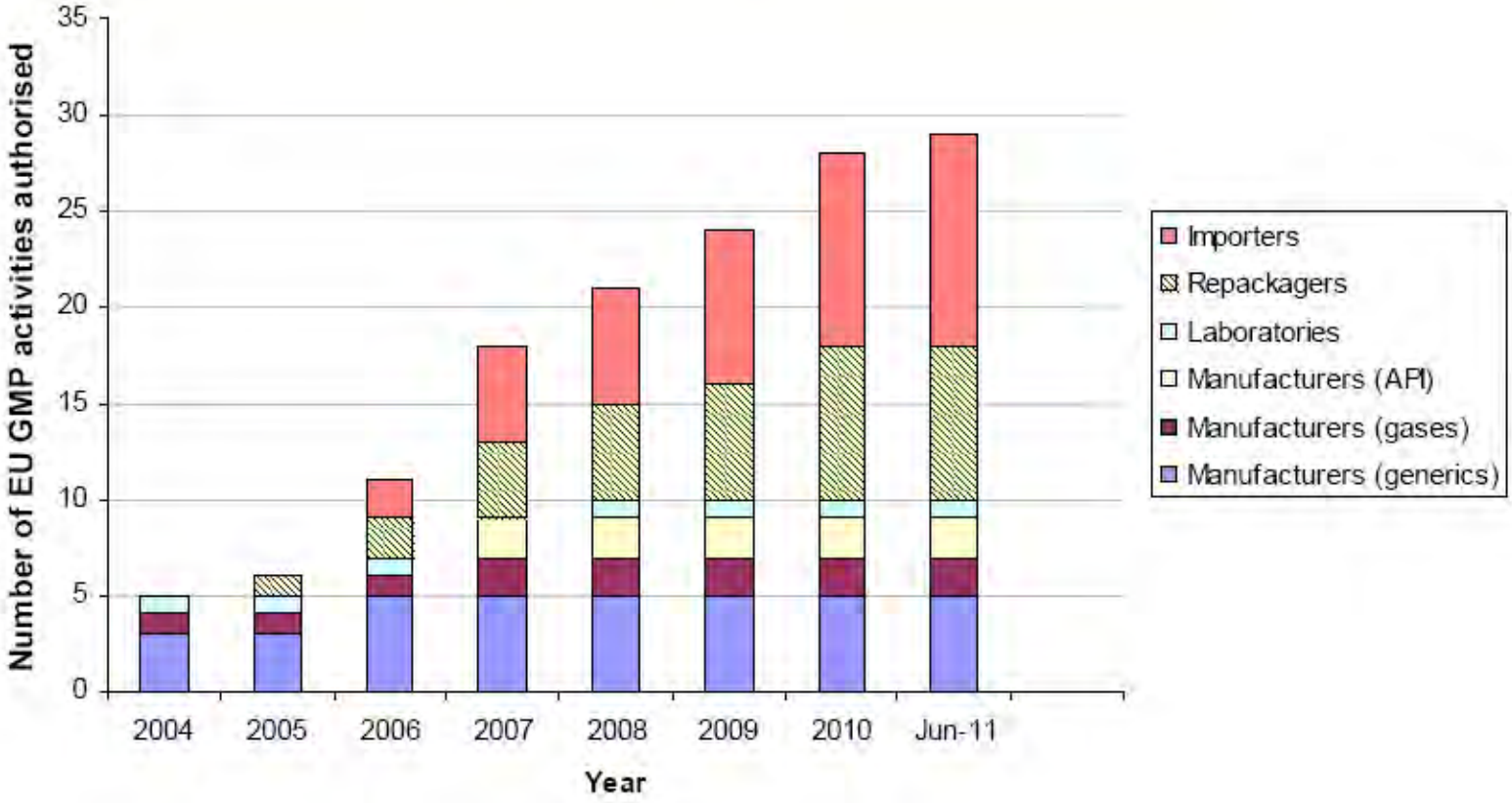
GPIE
EIPG

Day		Night	
Sunny	High 21°C Precip 0%	Clear	Overnight Low 14°C Precip 0%
Wind:	From NW at 11 km/h	Wind:	From NW at 6 km/h
Humidity:	70%	Humidity:	78%
UV Index:	9 Very High		

Medicines Authority

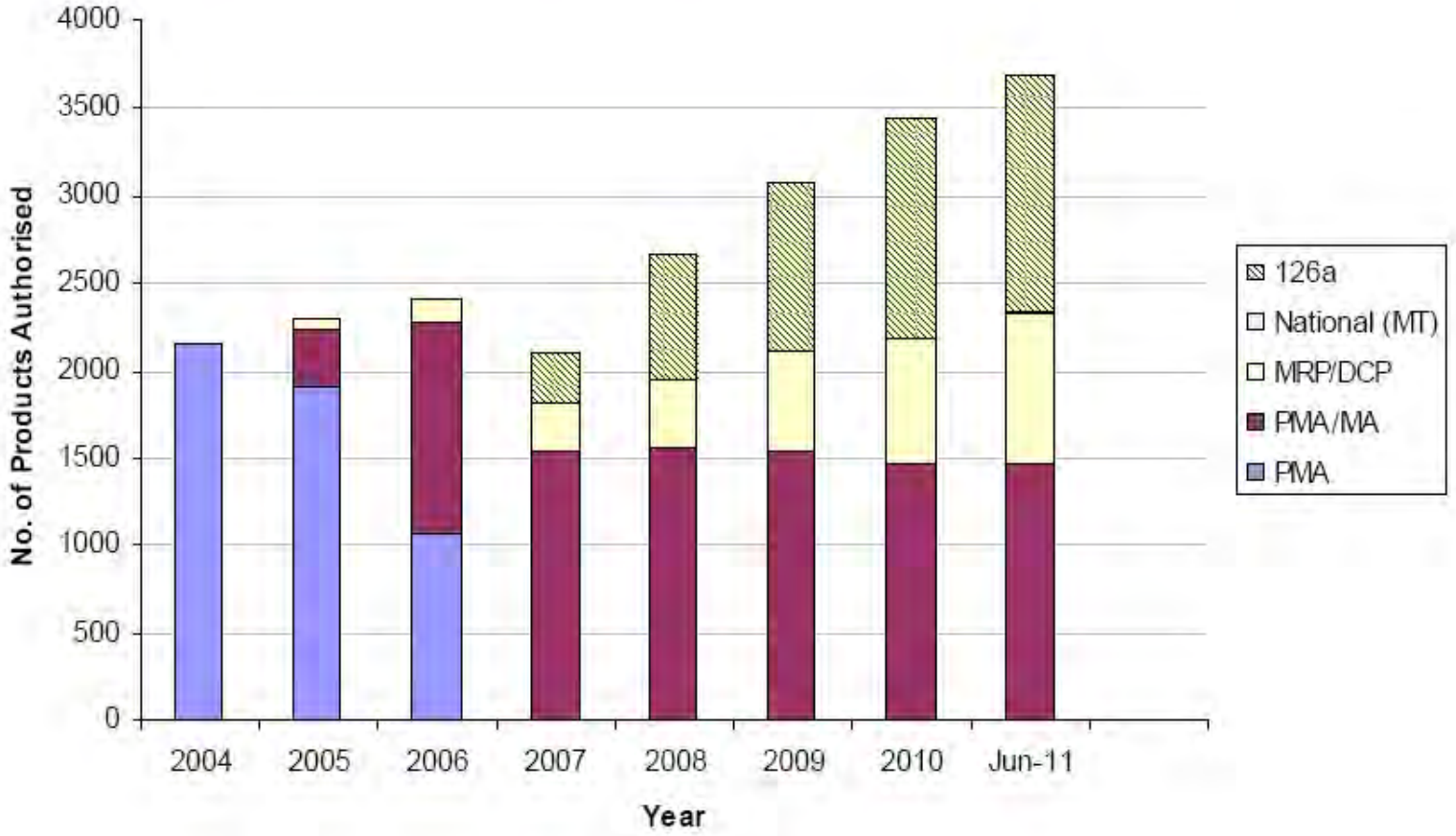
The number of activities authorised in accordance with European Union standards of Good Manufacturing Practice (EU GMP)



Medicines Authority

AWTORITÀ DWAR IL-MEDIĊINI

Number of medicinal products authorised to be placed on the market



Directive on Falsified Medicines

- 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***.

What is a falsified medicinal product?

- ***Directive definition:*** Falsified medicinal product: Any medicinal product with a false representation of:
  - its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients
  - its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder
  - its history, including the records and documents relating to the distribution channels used.
- Does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

What is a falsified medicinal product?

- ***WHO definition:***
  - A counterfeit product is one that is deliberately and fraudulently mislabelled with respect to identity and / or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, the wrong ingredients, without active ingredients, with insufficient quantity of active ingredient or with fake packaging.
- Thus infringement of patent rights, or marketing of medicinal products in the absence of a marketing authorisation, whilst illegal, does not constitute counterfeiting

Why a falsified medicines directive?

- Counterfeit medicinal products pose a **direct** risk to health because they may contain insufficient or no active ingredients or excipients, or, worse, because the ingredients that they contain are sub-standard and may contain impurities that are deleterious to human health.
- Counterfeits can kill!!

WHO International Medical Products Anti-Counterfeiting Taskforce (IMPACT)

Commission of the European Communities, COM(2008) 668

Why a falsified medicines directive?

	2005	2006	2007	2008
Number of cases	148	497	2,045	3,207
% of total number of cases	1%	1.33%	4.68%	6.49%
Number of articles	560,598	2,711,410	4,081,056	8,891,056
% of total number of articles	1%	2.11%	5.16%	4.97%

European Commission Taxation and Customs Union

Why a falsified medicines directive?

- In 2010, Centre for Medicines in the Public Interest estimated counterfeit drug sales worldwide at €56 billion this year.
- In 2006, the cost of producing a successful marketable medicinal product was estimated at €980 million.
- In 2000, the ten largest pharmaceutical companies achieved less than 2 "blockbuster" launches per company.
- Losses from counterfeit drug sales compromise the revenue for equivalent to the research and development budget of 57 new successful marketable medicinal products - the "blockbuster" launches of the ten largest pharma companies for 3 years.
- Counterfeits are also an indirect threat to human health by compromising future human health!!

Bulletin of the WHO, 2010; PhRMA, 2009

2011/62/EU: An implementing act

- Directive 2011/62/EU reflects a significant change in European Union comitology, which has been split into:
  - 'Implementing' Acts:
    - Intended purely to execute the basic legislative act
    - Remain subject to comitology committees and the process of the Commission submitting draft measures for discussion and vote;
  - 'Delegated' Acts:
    - Non-legislative acts of general application intended to supplement or amend certain non-essential elements of a basic legal act.
    - No comitology committees (although there is still a need to consult with member states while drafting a delegated act), and legislators' extended powers of veto and revocation.
- Effects:
  - Comitology more transparent and accessible
  - Increased likelihood of challenges to delegated acts by legislators and Parliament
  - Adoption of delegated acts slower
  - More lobbying on delegated acts

The legal supply chain

- The falsified medicines directive targets all players in the legal supply chain.
  - API and excipient manufacturers
  - Finished dosage form manufacturers
  - Partial manufacturers (repackagers and overlabellers)
  - Wholesale distributors
  - Brokers
  - Internet pharmacies

API and excipient manufacturers

- Manufacturer will remain responsible for ensuring EU GMP compliance of the API manufacturers he uses. Applicant for MA must confirm in writing that manufacturer of finished product has verified compliance with EU GMP of API manufacturer through audits. (*Art. 8(3)*)
- Finished product manufacturer must ensure that APIs it uses have been manufactured in line with EU GMP & distributed in line with EU GDP by conducting audits. (*Art. 46 (f)*)
- Same applies for those excipients considered to pose a risk after applying a risk assessment. (*Art. 46 (f)*)

API and excipient manufacturers

- Competent Authorities of Member States must ensure that manufacturers, importers & distributors of APIs on their territory comply with EU GMP & EU GDP for APIs. (*Art. 46b*)
- APIs can be imported only if manufactured in accordance with EU GMP and the competent authority of the exporting country submits a written confirmation that exporting country has standards, inspections and enforcement similar to that of the EU (unless on approved list of countries issued by Commission) and that in case of any non-compliance it immediately notifies the Union. (*Art. 46b* & *111b*)

API and excipient manufacturers

- Manufacturers, importers & distributors of APIs established in the Union must register themselves with the Competent Authority 60 days prior to commencement of their activity. If not informed that they will be inspected, can start their activity, but can always be inspected at any time. Those already in operation have to submit their registration by 2nd March 2013. (*Art. 52a*)
- All this data will be entered into the EudraGMP and (future) EudraGDP). EU GMP & EU GDP guidelines for APIs will be set up by the Commission together with guidelines for risk assessment to be used to identify excipients requiring assurance with GMP. (*Art. 47*)

Current state of play: API manufacturers

Article in Directive 2001/83/EC	Measure	Topic
47	Delegated Act	GMP for APIs
47	Guidelines	GDP for APIs
47	Guidelines	Risk assessment for verification of appropriate GMP for excipients
52b	Delegated Act	Criteria to be considered and verifications to be made when assessing the potential falsified character of medicinal products introduced into the EU but not intended to be placed on the market
111b	Implementing Act	Requirements for the assessment of a third country in terms of API manufacturing
111b	Autonomous decisions	Inclusion of a third country on a list

Current state of play: API manufacturers

- Implementing Act On The Requirements For The Assessment Of The Regulatory Framework Applicable To The Manufacturing Of Active Substances Of Medicinal Products For Human Use (Consultation Document issued Dec 2011; responses Mar 2012)
  - Equivalence assessment of the rules for GMP
  - Equivalence assessment of the regularity of inspections to verify compliance with GMP and the effectiveness of enforcement of GMP
  - Regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances
  - Other issues: Form of assessment, interface with existing mechanisms, regular verification, date of application

EIPG position: API manufacturers

- EIPG key positions:
  - The regulatory GMP compliance inspection is essential but is often not undertaken due to limited resources.
  - The EDQM is very effective, since they inspect the API manufacturing site, monitor all variations in the manufacturing process, and provide a 3-year certificate of suitability. However, this is limited to drug substances in the European Pharmacopoeia.
  - Problems with APIs not present in any pharmacopoeia and supplied from third countries, since regulatory authorities do not have resources to adequately monitor GMP compliance.
  - Regulatory agencies should ensure that at time of submission of marketing authorisation, all details of CTD Module 3S (Drug Substance) are supplied as well as means by which GMP will be monitored.
  - Rapid alert system should link with WHO and FDA to obtain early warning of problems.
  - Lack of resources in EMA and other agencies is a problem.

Current state of play: API manufacturers

- Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use (Concept Paper issued Jan 2012; responses Mar 2012)
  - Extension of the Directive on GMP for medicinal products (2003/94/EC) to active substances
  - Adaptation of regulatory requirements of Directive 2003/94/EC to active substances
    - Provisions that would not apply: marketing authorisations, qualified persons, manufacturing authorisations? (?)
    - Provisions that would need to be amended: definitions of active substance and manufacturer to be added
    - Other provisions to be added: issue re starting materials of active substances.
  - Dates of transposition and application

EIPG position: API manufacturers

- EIPG key positions:
  - Agree with the extension of the Directive of GMP for medicinal products to active substances.
  - Agree that certain provisions in 2003/94/EC would not apply to active substances
  - However, believe that the concept of a Qualified Person and a marketing authorisation should be introduced for APIs to make GMP guidelines for medicinal products (EudraLex-Vol. 4 Part I) and APIs (EudraLex-Vol. 4 Part II) identical in terms of quality responsibility and management, while maintaining specific differences in terms of manufacturing process.

Repackagers and overlabellers

- Must hold a manufacturing authorisation
- Are fully liable if they have falsified medicines in their possession
- Cannot remove or cover safety features unless they have :
  - Verified authenticity of the products that they receive and that they have not been tampered with
  - Replace with equivalent safety features providing equivalent protection
  - Immediate packaging cannot be opened
  - All operations always carried under EU GMP

(*Art. 47a*)

Wholesale distributors

- Must inform MAH & CA when they intended to place a product on the market. (*Art. 76*)
- Authorisations should be entered into a Union database (EudraGDP) (*Art. 77*)
- Holders of Wholesale Distributors Authorisations must:
  - Verify and check safety features that the products that they receive have not been tampered with and this in line with the modalities set out by the Commission through delegated acts
  - Batch number must be included in transaction records kept
  - Quality System must list responsibilities, include all processes and have a risk assessment approach
  - Inform CA & MAH if they suspect any falsified medicines in products offered to them
  - Verify that their suppliers conform with principles & guidelines of GDP and manufacturers and importers hold an MIA

(*Art. 80*)

Current state of play: Wholesale distributors

- Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use (Consultation Document issued Jul 2011; responses Dec 2011)
  - A considerable improvement over previous guidelines (30 pages vs 4 pages in 94/C 63/03)
  - A degree in pharmacy desirable for the Responsible Person
  - Medicinal products should not be transferred to saleable stock before assurance has been obtained that they are authorised and released for the market in question.
  - Will come into effect 6 months after publication.
  - As yet no guidance no how to verify and check safety features.

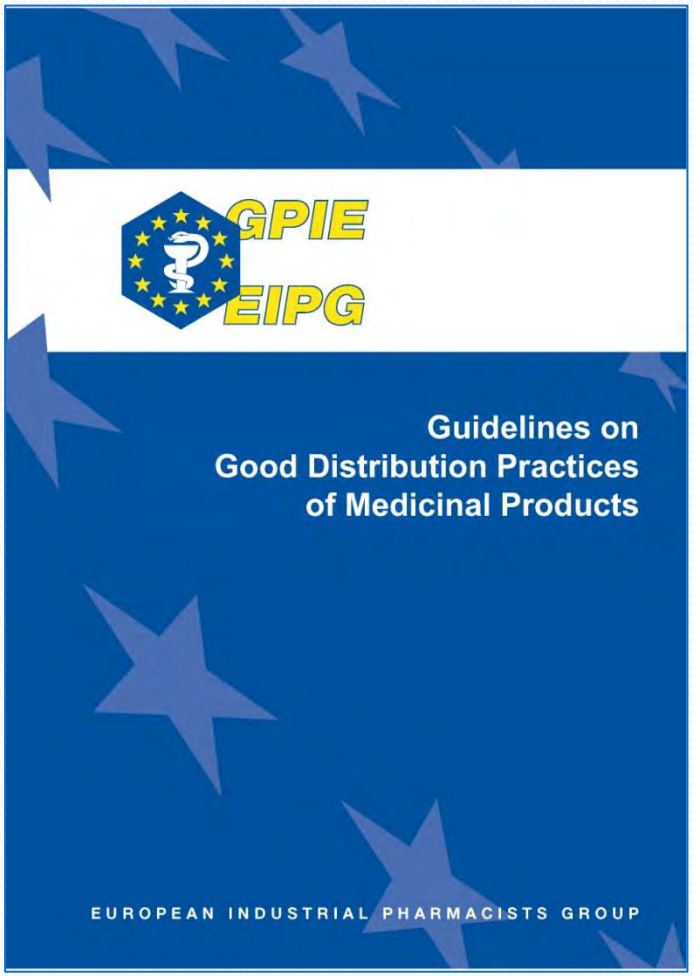
EIPG position: Wholesale Distribution

- EIPG key positions:
  - Agree with recommendation that Responsible Person should be a pharmacist
  - However, EIPG feels that the guidelines are overly restrictive on RP's (e.g. the RP has to be permanently available, should carry out activities personally, should delegate duties when absent) presumably to compensate for Member States where RP does not have to be a pharmacist.
  - Guidelines need to make allowance for the creation of a record of all GDP-relevant changes and deletions (audit trail), particularly in view of new information technology challenges with the introduction of verification of the security feature.

Wholesale Distributors: EIPG Guide to GDP

- An amalgamation of:
  - Guidelines on Good Distribution Practice of Medicinal Products for Human Use (Text with EEA Relevance) (94/C 63/03)
  - WHO guide to good storage practices for pharmaceuticals.
  - WHO guide to good distribution practices for pharmaceuticals
  - Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use. In: The Rules Governing Medicinal Products in the European Union, Volume 4.
  - UK Guidance on Wholesale Distribution Practice. In: Rules & Guidance for Pharmaceutical Manufacturers & Distributors, Medicines and Healthcare products Regulatory Agency (MHRA), 2007.

Wholesale Distributors: EIPG Guide to GDP



GUIDELINES ON GOOD DISTRIBUTION PRACTICES OF MEDICINAL PRODUCTS
European Industrial Pharmacists Group

Contents

The European Industrial Pharmacists Group (GPIE/EIPG) is the European Association representing the national professional organisations of pharmacists employed in the pharmaceutical and allied industries of the member states of the European Union.
Further information can be found on their website http://www.eipg.eu

Safety features

- Medicinal products to bear safety features enabling whole distributors and persons authorised or entitled to supply medicinal products to the public to verify the authenticity of the medicinal product and identify individual packs, as well as a device allowing verification of whether the outer packaging has been tampered with. (*Art. 54(o)*)
- Qualified Person has to ensure that the safety features have been affixed on the packaging. (*Art. 51(1)*)

Safety features

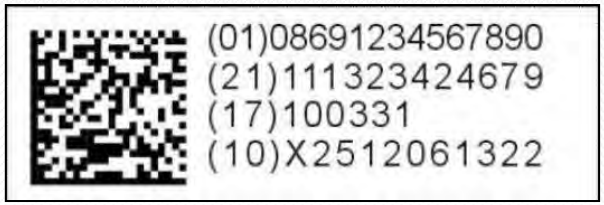
- Medicinal products subject to prescription shall bear the safety features unless excluded by exception by the Commission ('white' list) (*Art. 54a*)
- Medicinal products not subject to prescription shall not bear the safety features unless included by exception by the Commission ('black' list) (*Art. 54a*)
- Wholesale distributors must verify that the medicinal products received are not falsified by checking the safety features on the outer packaging. (*Art. 80(ca)*)

Current state of play: Safety features

- Delegated Act on the Detailed Rules for a Unique Identifier for Medicinal Products for Human Use, and its Verification (Concept Paper issued Nov 2011; responses Apr 2012)
  - Characteristics and technical specifications of the unique identifier – leaving the choice of the specifications to the individual manufacturer or harmonisation through regulation?
  - Regulation of the composition of the serialisation number: manufacturer product code, unique identification number, national reimbursement number, expiry date, batch number?
  - Regulation of the technical characteristics of the carrier: linear barcode, 2D-barcode or RFID?

Current state of play: Safety features

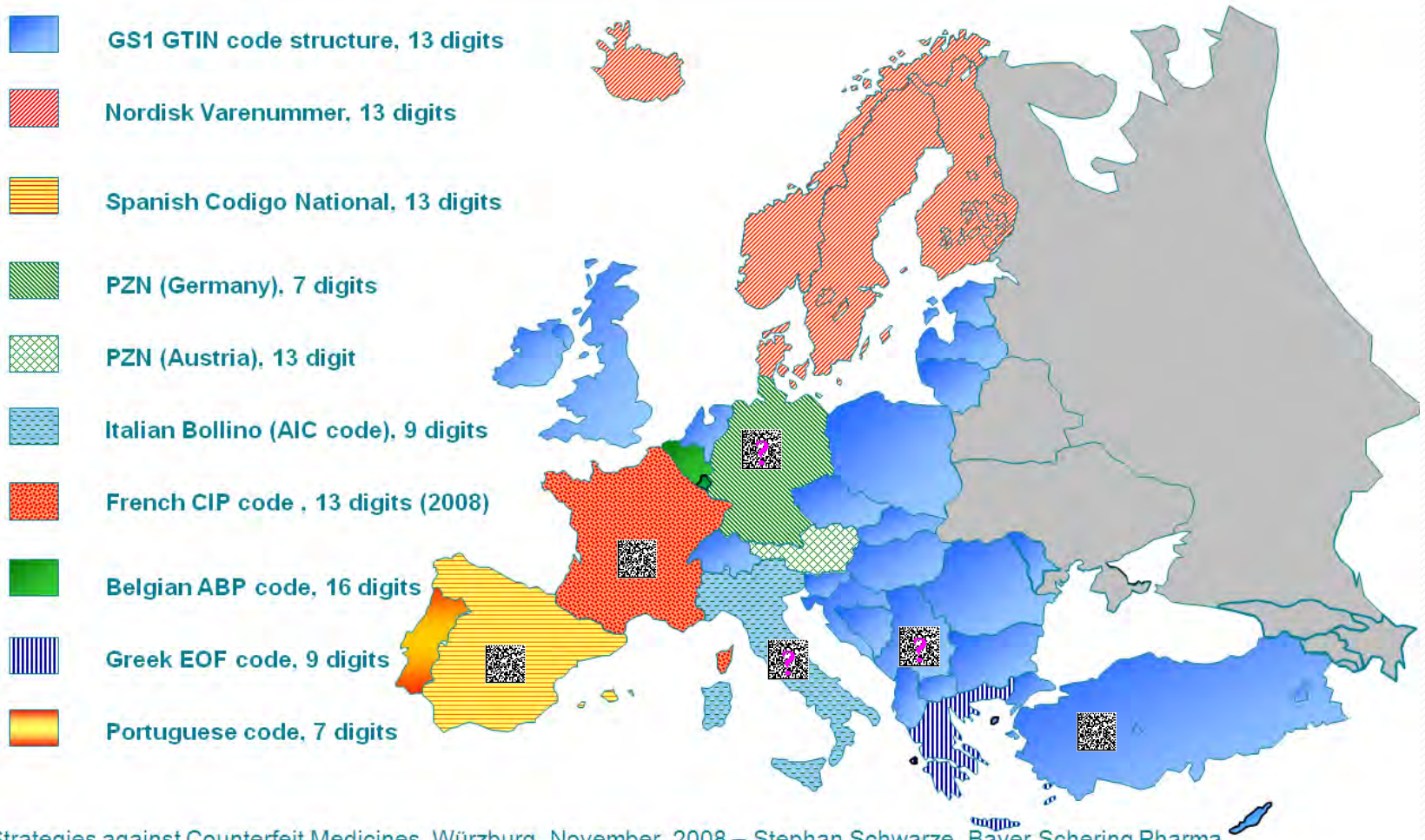
Manufacturer Product code (which includes the prefix of the country)	Unique Identification number of the pack	National reimbursement number	Expiry date	Batch number
XXXXXXXXXXXXXX	XXXXXXXXX	XXXXXXXX	XXXXXX	XXXXX



Application Identifier (AI)	Manufacturer Product Code / Barcode Number (GTIN™)
01	08691234567890
Application Identifier (AI)	**Serial Number**
21	111323424679
Application Identifier (AI)	**Expiry Date**
17	100331
Application Identifier (AI)	**Batch number**
10	X2512061322

Current state of play: Safety features

The coding situation in Europe today: Overview of National Codification Systems



Current state of play: Safety features

GPIE EIPG

Pharma Serialisation Deadlines

Pharma IQ has created this easy-to-assimilate summary of serialisation requirements around the world, whether they are already being followed or have impending deadlines (e.g. much of Europe due to the Falsified Medicines Act). You can keep it as a handy reference, share it around your colleagues or even stick it on your wall!

Questions asked

A DEADLINE DATE
(If applicable. If country already serialised, please simply state 'current')

B METHOD OF SERIALISATION
(e.g. 2D datamatrix, RFID, linear barcodes, e-pedigree, etc)

C ANY ADDITIONAL RESTRICTIONS OR REQUIREMENTS?
(e.g. special labels? Where from? etc)

D LEVEL OF SERIALISATION REQUIRED
(e.g. country, lot, package, etc)

FRANCE
A - as per EU Directive – possible extension to 2022 pending
B - 2D Datamatrix, 2D required for CIP code
D - GTIN, lot, exp, Serial nr

BELGIUM
A - Current
B - 2D - Sequential Barcode, 1D barcode Code-128C, linear barcode
C - Special Labels - IPEX. Labels applied by "Vignette labeller"
D - Package no lot info, GTIN, lot, exp, Serial nr, Package, reimbursed medicines

UK
A - as per EU Directive
B - 2D datamatrix
D - GTIN, lot, exp, Serial nr

NORDIC COUNTRIES
A - as per EU Directive
D - GTIN, lot, exp, Serial nr

SCANDINAVIA
A - as per EU Directive
B - 2D Datamatrix
D - GTIN, lot, exp, Serial nr

SPAIN
A - 2016, Pilot project finished
B - Datamatrix (pending Delegated Acts in EU Directive & their transposition into Spanish laws)
C - All reimbursed medicines
D - Unit/package level

USA
A - 2015-16 on some pharma
B - e-pedigree, 2D as per GS1, e-ped (Rf or barcode)
C - possibly (if RF then encoding important)
D - sales pack, Lot - Potency - EExpiration - NDC - eProduct Code - Manu - DC/Pharmacy - UID

RUSSIA
A - 2015, current
B - linear, 1D barcode Code-128C
C - Serials provided by Government (not GS1-compliant)
D - Serial Nr, every packaging level

GREECE
A - Ongoing
B - Bollini label 1D barcode: Code-39, linear barcode
C - Labels applied by "Vignette labeller"
D - GTIN, lot, exp, Serial nr, Package, reimbursed medicines

GERMANY
A - as per EU Directive; National legislation by Jan 2013, enforced by Q4 2016
B - 2D Datamatrix
C - Pilot project to be run in 2013 to decide widespread implementation strategy
D - likely to be package level

CHINA
A - 2015, although some started April 2010
B - 128 Barcode
C - Need to obtain barcode from Government

CALIFORNIA
A - 50% of product by Jan 2015 and 50% by Jan 2016
B - e-Pedigree, 2D Datamatrix, RFID, Linear
D - Item, smallest saleable unit, every level of packaging. Saleable unit point of sale, e-pedigree, full track and trace

INDIA
A - Not applicable, only Expiry Date required. Primary level Packaging: 1/07/2012, Secondary Level Packaging 1/01/12, Tertiary Level Packaging 1/10/11
B - Method of RFID, 2D Barcodes. Change only one tag FDA (Green/Approval). 2D or 1D barcode as per GS1. Primary level Packaging : GS1 2D DataMatrix , Secondary Level Packaging : GS1-128 i.e. 1D or GS1 DataMatrix i.e. 2D or GS1 Databar Tertiary Level Packaging '1D Barcode (GS1-128). 2D datamatrix
C - No more 'Tag/Details' of prescription drug packages, unique serial number, product identification code, batch number and expiry date
D - FDCA: For Domestics not for Export: chain of approval all dealers, doctors and pharma authorization, every packaging level. As per DGFT notification, package

BRAZIL
A - January 2012 (Please note: this is being contended and may change - TBC)
B - 2D as per GS1
C - Additional tamper evident label to seal carton, auto-adhesive labels with the 2D code
D - Package, secondary and tertiary packages

ITALY
A - Ongoing
B - Bollini label 1D barcode: Code-39 (2D under discussion)
C - Labels applied by "Vignette labeller" purchase of Bollini from Italian Mint
D - GTIN, lot, exp, Serial nr, Package related to Batch id

ARGENTINA
A - 15/12/2011
B - 2D, The Health Authority don't give any specific recommendation. The laboratories could choose between optical technologies (Datamatrix & GS1-128) or RFID EPC, Not fixed, GS1 standard. (Bar code,datamatrix or RFID) Prefered: Datamatrix
C - Security labels are required. The labels used must leave marks when removed. Visual code in the label.
D - GTIN + SERIAL

Pharmaceutical Serialisation & Traceability 2011

This infographic was developed for the Pharmaceutical Serialisation & Traceability summit in Geneva on November 2-4th, 2011. The event features expert speakers from industry leaders, EFPIA and GS1 and will bring attendees up-to-date with the latest serialisation developments. To find out more, visit **www.pharmaserialisation.com**

All data and information depicted was collected from an industry survey conducted by Pharma IQ in September 2011. This information is accurate to the best of the respondents knowledge at that time, and may subsequently have changed. Pharma IQ cannot take responsibility for the accuracy of this information.

CONNECT TO A GLOBAL PHARMA IQ SOCIAL NETWORK

Pharma iQ a division of IQPC

EIPG position: Safety features

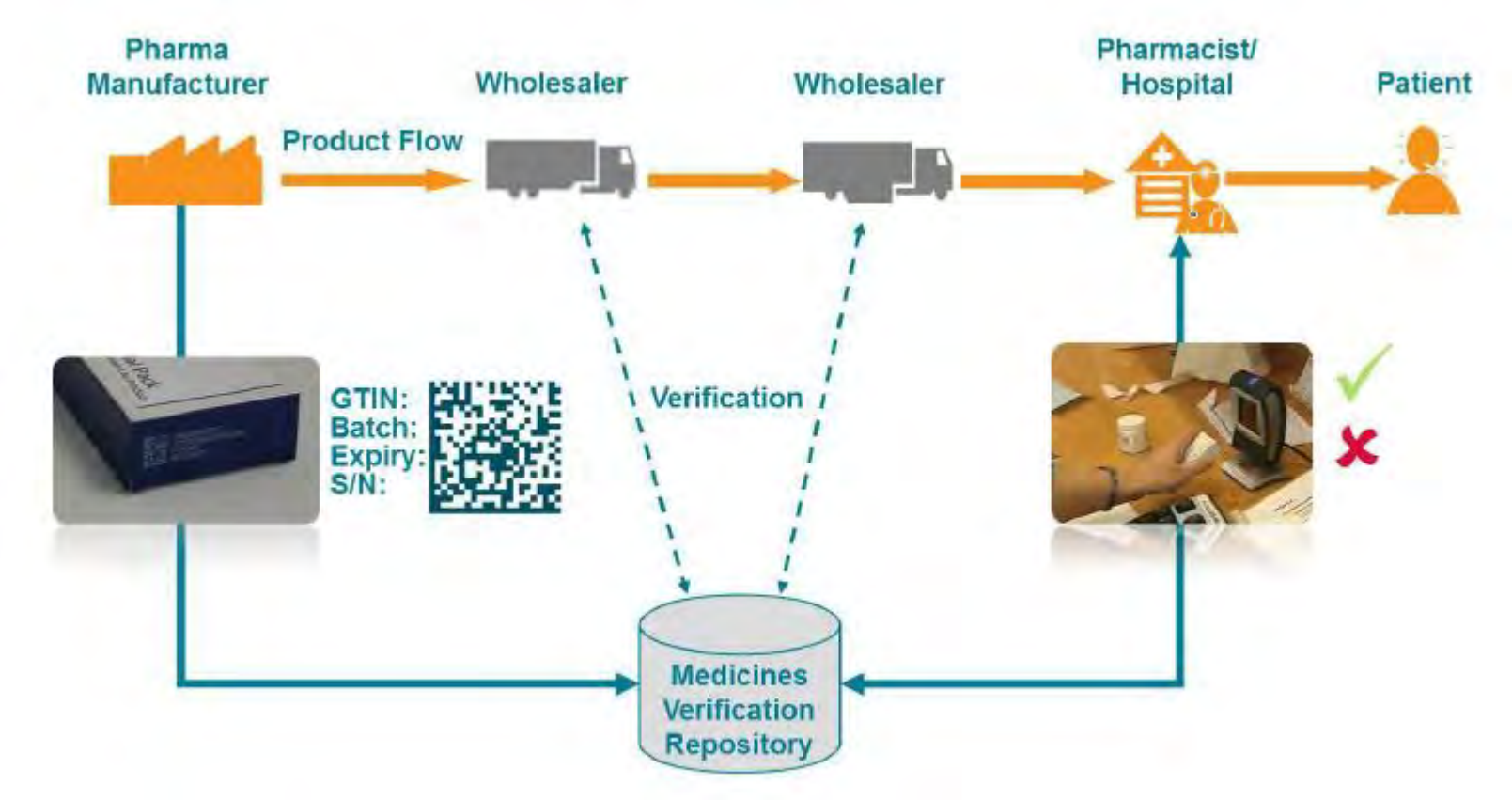
- EIPG key positions:
  - Harmonisation through regulation: harmonised systems will ensure uniform technical specifications and hence control capital investment requirements in hardware and software at point of dispensing. Will also reduce the number of countries that need to adapt their systems.
  - Serialisation number should include manufacturer product code, unique identification number, batch number and expiry date (the latter in particular to facilitate traceability and stock control in FEFO systems)
  - Reimbursement numbers and reimbursement systems differ significantly from one country to another, therefore inclusion of the reimbursement number is more challenging and is not recommended.

Current state of play: Safety features

- Delegated Act on the Detailed Rules for a Unique Identifier for Medicinal Products for Human Use, and its Verification (Concept Paper issued Nov 2011; responses Apr 2012)
  - Modalities for verifying the safety features: systematic check-out of the serialisation number at the dispensing point, random or systematic verifications at the level of wholesale dealers
  - Provisions of the establishment, management and accessibility of the repositories system: stakeholder, EU or national governance?
  - Other issues: Commercially sensitive information, personal data, repackaging.

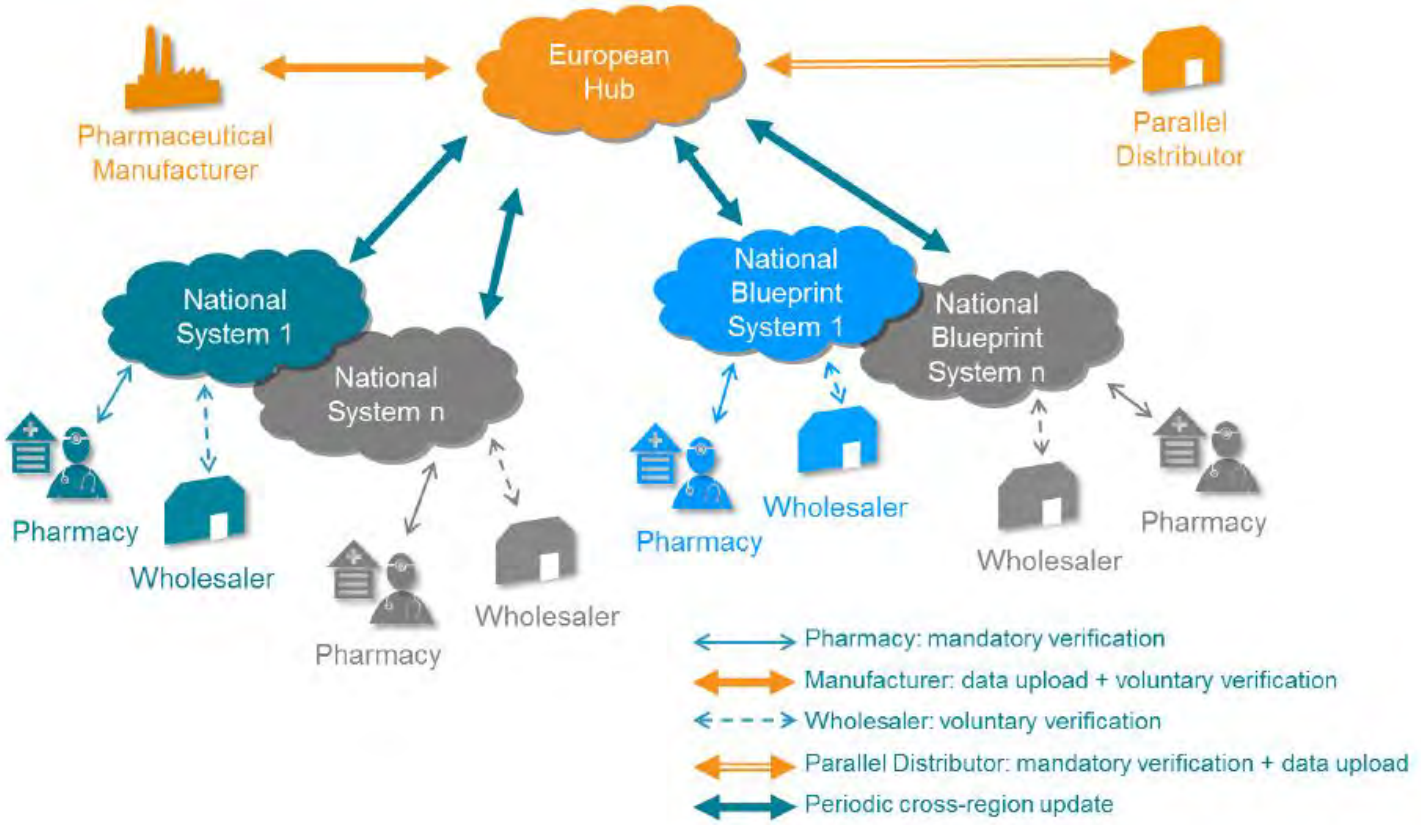
Modalities: eTACT (EDQM anti-counterfeiting traceability service for medicines)

Modalities: EAEPC-EFPIA-GIRP-PGEU Point of Dispense European Medicines Verification System



Modalities: EAEPC-EFPIA-GIRP-PGEU Point of Dispense European Medicines Verification System

efpia
European Federation of Pharmaceutical Industries and Associations



Modalities: EAEPC-EFPIA-GIRP-PGEU Point of Dispense EMVS – 10 Core Principles

- Combining tamper-evident packaging with a unique serial number.
- Guaranteeing continuity of protection throughout the entire supply chain.
- Ensuring a single coding and identification system on each pack across the EU.
- Ensuring product verification database systems can work together across the EU.
- Verifying every serialised pack at pharmacy level.
- Maximising all the potential benefits of mass serialisation.
- Focusing on securing patient safety and protecting patient privacy.
- Using safety features that are simple, robust and cost-effective.
- Working together in the interests of patient safety.
- Involving other stakeholders.

Modalities: EAEPC-EFPIA-GIRP-PGEU Point of Dispense European Medicines Verification System

- Wholesale distributors must verify that the medicinal products received are not falsified by checking the safety features on the outer packaging. (*Art. 80(ca)*)
- "If significant individual pack scanning is involved it presents major practical and costly challenges to the smooth operation of the distribution chain and will severely impact the speed of delivery of vital medicinal products to pharmacies and ultimately to patients."

Monika Derecque-Pois, Director-General GIRP european Industrial Pharmacy, March 2012

EIPG position: Safety features

- EIPG key positions:
  - In keeping with the requirements of the Directive, particularly on wholesale distributors, to be alert for counterfeit penetration, EIPG recommends systematic check-out of the serialisation number at the dispensing, but with additional random verifications at the level of wholesale distributors.
  - EIPG feels that the repository system should be one of national governance – EU governance will probably be too expensive, and national governance will allow addressing specifics of wholesale distribution in different Member States
  - In repackaging, the system should allow for linking of the repackaged serial number to the original serial number.

Current state of play: Safety features

- Delegated Act on the Detailed Rules for a Unique Identifier for Medicinal Products for Human Use, and its Verification (Concept Paper issued Nov 2011; responses Apr 2012)
  - 'White' and 'black' lists of medicinal products: the risk of falsified medicines, and the risks arising from falsified medicines.
  - Criteria: price, sales volume, number and frequency of previous incidents, specific characteristics of the product, seriousness of conditions intended to be treated, other potential risks
  - Identification criteria: ATC, brand name, API or case-by-case?
  - Classification criteria

Current state of play: Safety features

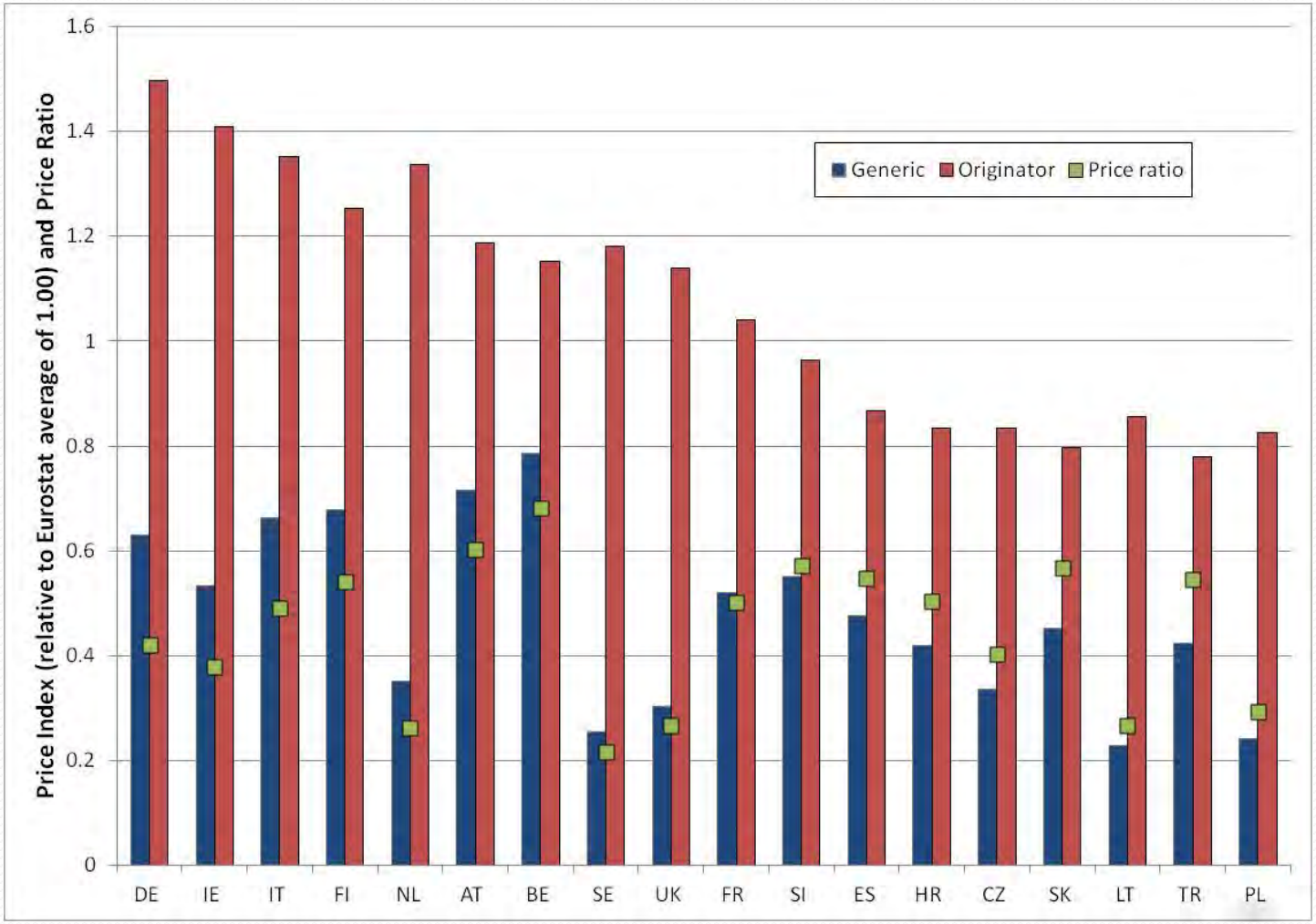
Criterion	Quantification	Topic
Price	High	5 points
	Low	1 point
Volume	High	5 points
	Low	1 point
Incidents in EU or 3rd countries	Several	5 points
	None	1 point
Characteristics	Risk of falsification	5 points
	No risk of falsification	1 point
Severity of treated conditions	Severe	5 points
	Not severe	1 point
Other risks	-	Max. 5 points

PoM with ≤6 points in 'white list'; non-PoM with >10 points in 'black list'

EIPG position: Points allocation lacks scientific rationale.

Where are we headed?

Where are we headed?



Farrugia and Savvas, Journal of the Malta College of Pharmacy Practice, 2009

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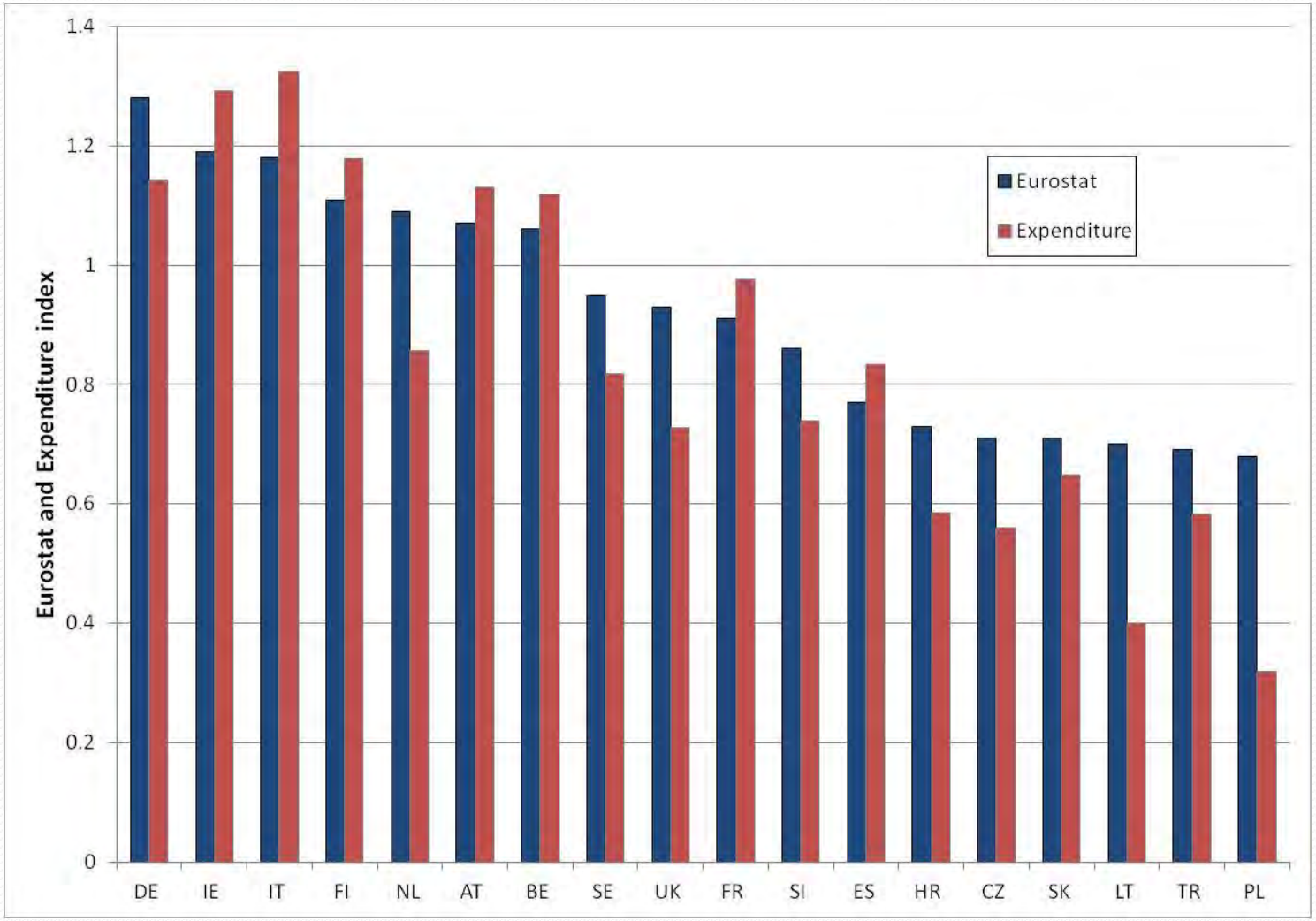

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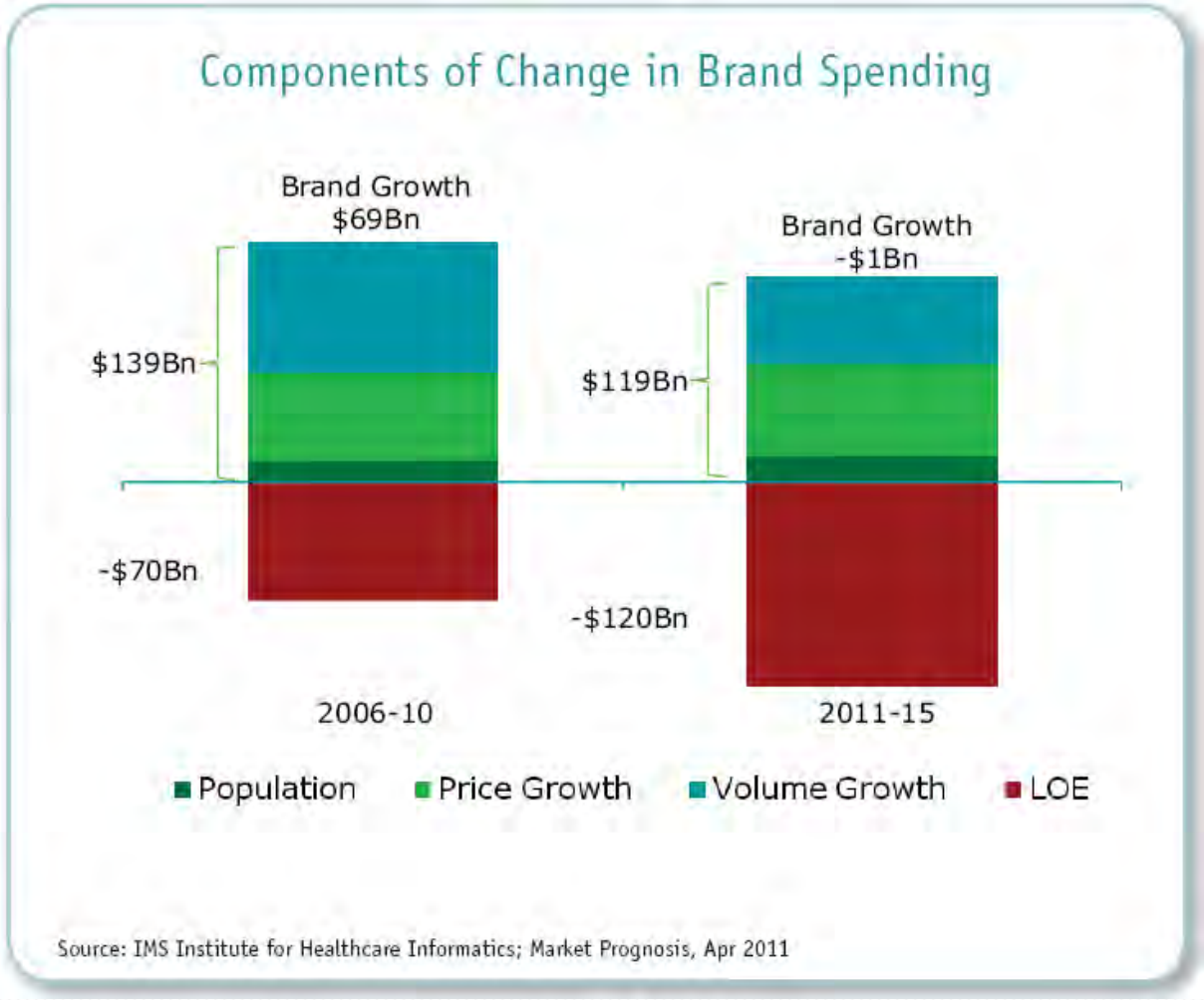
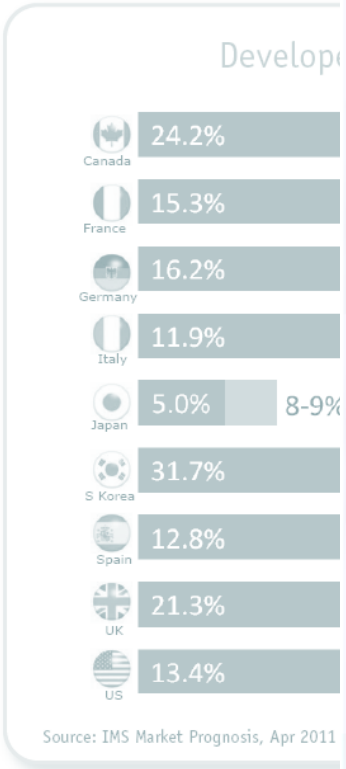
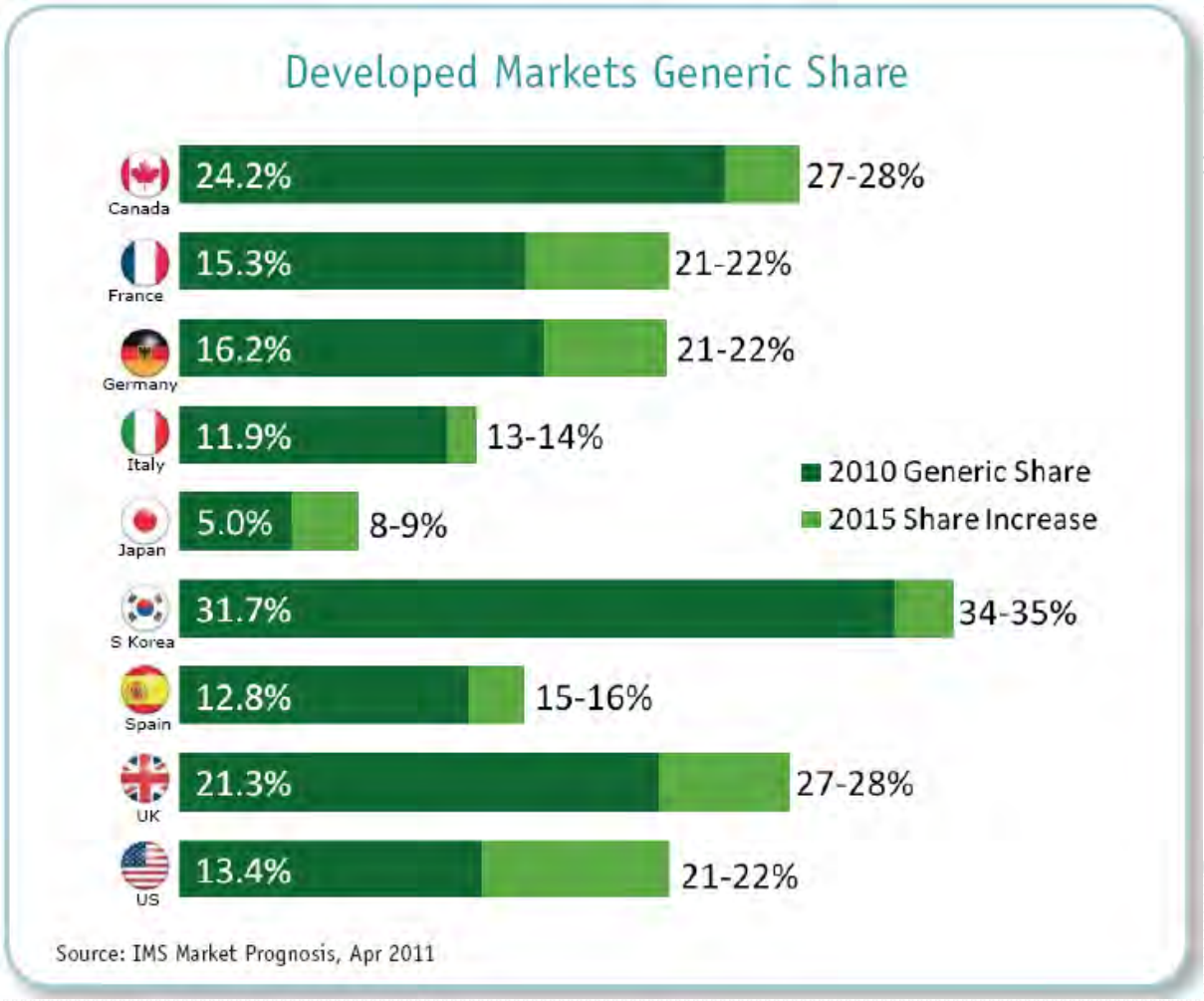
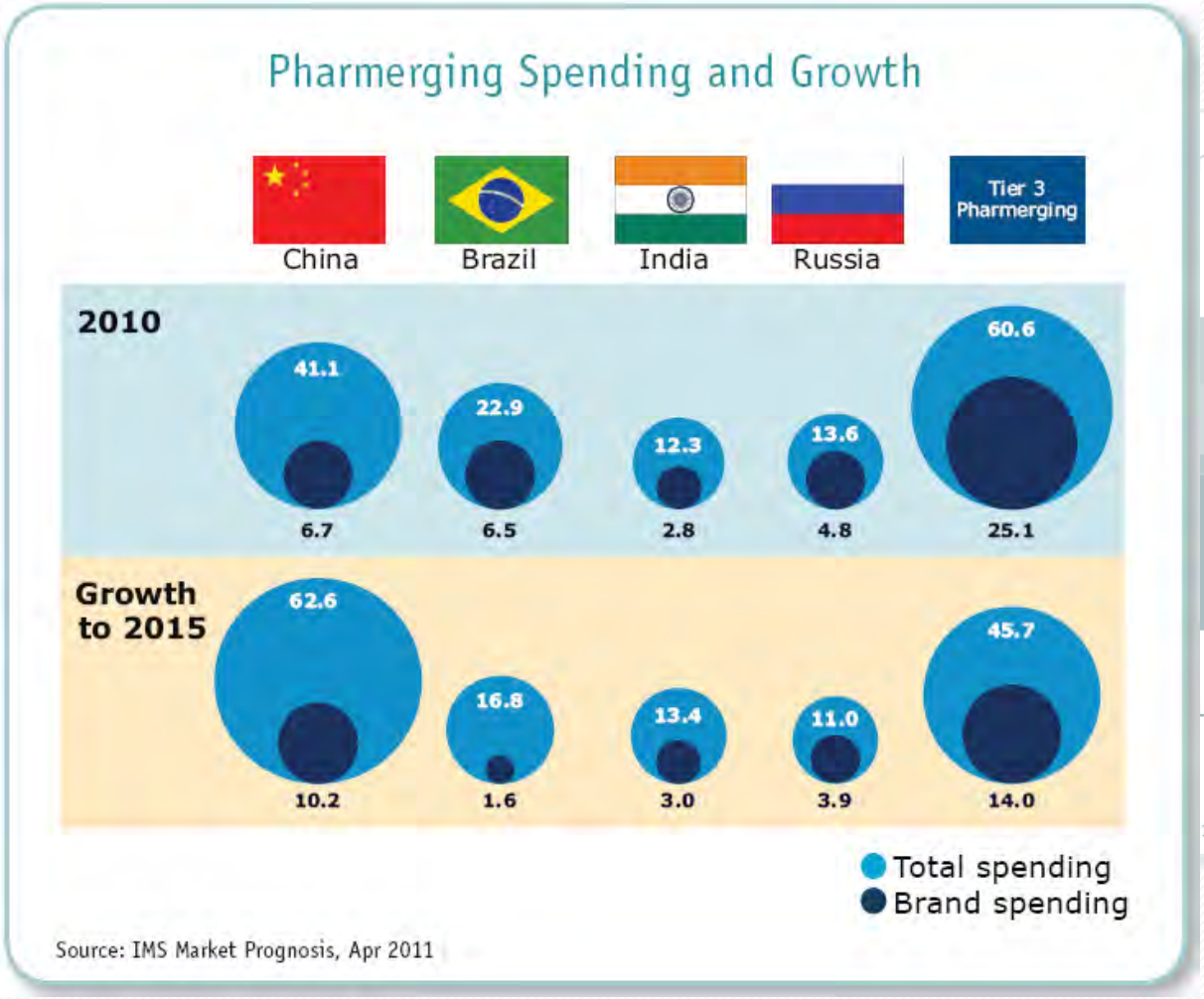




Where are we headed?



Where are we headed?



Conclusions?

- Legislation is only the first step – implementation will be a major challenge that must, however, be undertaken to protect public health.
- The latest proposed amendments to the Directive reflect an attempt to juggle the need for the raising of standards to counteract the direct and indirect negative costs of counterfeits, whilst trying to mitigate the cost of implementing such standards.
- Half measures will be worse than no measures – they will give the false illusion of security. Failure to invest decisively and comprehensively in ensuring this objective will ultimately be much more costly.
- Ensuring availability and accessibility of medicines of guaranteed quality, safety and efficacy is a paramount professional obligation.

Where are we headed?