OPERATION VOLCANO
THE HERCEPTIN CASE

story, lesson learned, proposals

AIFA | AEMPS | AGES | IGZ | MHRA

Agenzia Italiana del Farmaco
AIFA

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Director of the Publication: Domenico Di Giorgio.
Editorial production: Italian Medicines Agency - AIFA.
Editorial Staff: Annalisa Berselli (AIFA), Gianpaolo Derossi (AIFA), Belén Escribano Romero (AEMPS), Marta Gramazio (AIFA), Paul Hargreaves (MHRA), Manuel Ibarra Lorente (AEMPS), Marcel Moester (IGZ), Serena Panicale (AIFA), Andrea Ungersbäck (AGES), Hannes Wuerkner (AGES).
Book design and Illustrations: Gianpaolo Derossi.
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Compiling a book is a complex operation, which requires repeated checking of the text, the figures and the relations between these. Experience shows that it is practically impossible to publish a book free of errors. We will therefore be grateful to readers who will point out such errors.

ABBREVIATIONS

AEMPS	*Spanish Agency for Medicinal Products and Medical Devices*
AGES	*Austrian Agency for Health and Food Safety*
AIFA	*Italian Medicines Agency*
BASG	*Federal Office for Safety in Health Care (Austria)*
CAP	*Centrally Authorised Product*
DHPC	*Dear Healthcare Professional Letter*
DRA	*Drug Regulatory Authority*
EMA	*European Medicines Agency*
EU	*European Union*
FIMEA	*Finnish Medicines Agency*
FMD	*The European Union Falsified Medicines Directive 2011/62/EU*
GDP	*Good Distribution Practice*
GMDP	*Good Manufacturing and Distribution Practice*
GMP	*Good Manufacturing Practice*
HMA	*Heads of Medicines Agencies*
IWG	*Inspectors Working Group*
MAH	*Marketing Authorisation Holder*
MHRA	*Medicines and Healthcare Products Regulatory Agency (United Kingdom)*
MoH	*Ministry of Health*
MS	*Member States of the European Union*
NUI	*Non Urgent Information*
OTC	*Over the counter*
RA	*Rapid Alert*
RAS	*Rapid Alert System*
WGEO	*Working Group of Enforcement Officers*

The so-called “Operation Volcano”, also known as “Herceptin case”, originates upon receipt of an alert by a German parallel distributor, soon followed by further investigations in respect of which emerged that vials of the cancer medicine Herceptin (trastuzumab), stolen from Italian hospitals, have been manipulated and falsified and re-introduced under false credentials by unauthorized wholesalers into the legal supply chain. Seizures of falsified vials have been carried out by authorities in Germany, Finland and United Kingdom (UK). The distribution of the falsified vials to other European Union (EU) Member States (MS) was also proved.

Upon further investigation by the Italian authorities, additional medicinal products have been identified as stolen in Italy and, subsequently, re-introduced under false credentials by a criminal organization connected to Italy.
This has been facilitated through unauthorized wholesalers connected with the Italian criminal organization, formally based in Cyprus, Hungary, Latvia, Romania, Slovak Republic, Slovenia and Greece issuing fake invoices to sell the stolen medicines to authorised Italian and Maltese operators. These authorised operators have subsequently exported these to other EU markets.

A similar scheme, involving operators from other countries, was also discovered.

The vulnerability of the parallel import channel to this kind of attack and the lack of enforcement actions with respect to Good Distribution Practice (GDP) (e.g. inspections to wholesalers) were major causes for the case; strong protection of the network via strict importing rules for parallel distribution and traceability systems for medicines, cooperation between enforcement and health authorities, sharing of information and intelligence knowledge (also via web tools such as the AIFA/Fakeshare ones) allowed Italy to counteract criminals and to avoid the infiltration of illegal medicines and up to July 2015 led to the arrest of more than 60 people in 8 different police operations in Italy,

UPDATE AUGUST 2015:

police operations related to the "Operation Volcano" criminal network in italy.

		Arrested people	Seized products
2013	**November** Police (Lodi)	**20**	**236 boxes**
2013	**December** Carabinieri (Caserta)	**0**	**52.251 packages**
2014	**February** Carabinieri (Naples)	**2**	**404 boxes**
2014	**April** Police (Bari)	**4**	**680.000 euros**
2015	**February** Carabinieri (Siena)	**9**	**ND (tons)**
2015	**April** Carabinieri NAS (Milan)	**19**	**16.000 packages**
2015	**June** Guardia di Finanza (Rome, Naples)	**10**	**68.000 packages**

and to the eradication of the hospital thefts in Italy (passing from 3 cases per week, until May 2014, to zero, from June 2014), but were not enough for preventing further possible theft/falsification/exporting criminal plot, as demonstrated by the recent RA issued by Germany and other MS with respect to the possible infiltration of counterfeit medicines in the same channels targeted in this case.

By explaining the case in detail, summarising the key lessons learned and the possible preventive actions, this White Paper calls for **a stronger enforcement effort against pharmacrime, with more resources at MS level and an ad hoc coordination at EU level**.

I.
THE STORY (SO FAR)

I.I Thefts of medicines in Italy

Theft of medicines (from hospitals and in the field – i.e. from lorries and pharmacies) had a big increase in Italy after 2011; the number of thefts in hospitals, in particular, was so big as to become a "media emergency", with weekly articles and reports, and even University research ("Transcrime: the thefts of medicines from Italian hospitals", http://www.transcrime.it/pubblicazioni/the-theft-of-medicines-from-italian-hospitals/) being published and promoted on the general press.

This emergency situation resulted in AIFA (Italian Medicines Agency) Counterfeiting Prevention Unit setting up a **project** with industry in Italy in order to feed a shared database.

One of the primary functions of this project was for industry to share with AIFA information about stolen medicines, i.e. name, manufacturer, "Bollini" number, batch details, etc.: the database is being fed and the gathered data are analysed in order to understand the real framework.

Another function was to organise those information in order to let AIFA both investigate and respond to theft cases, and refer to those data against pharmaceutical crime in general, being the phenomenon more complex and articulate than isolated thefts.

THEFT PROJECT: TIMETABLE

- **Beginning 2013:**
  increase of thefts of medicines in Italy since 2012.
- **Spring 2013:**
  set up of the "Theft project" in order to share the data of the phenomenon – AIFA, Farmindustria (manufacturers association), ASSO-RAM (warehousing services association), Carabinieri NAS (specialised police force), supported by the Ministry of Health.
- **Summer 2013:**
  set up of a shared database through a platform managed by AIFA.
- **Autumn 2013:**
  gathering of data (from MoH, Industries, Distributors) and analysis.

"Where are the stolen medicines from the hospital thefts and truck thefts going to?" To help answer the question were examined and tested six **possible scenarios**:

1. Black market in the field

National distribution on "grey/black channels"
(i.e. to private hospitals, clinics, etc. or to doping network/beauty centers)

2. Black market on the web

Specialised distribution via the Internet
(e.g. athletes networks...)

3. New supply to hospitals

Mere financial damage
(i.e. creation of a shortage to be re-fulfilled)

4. Black market to EU/non EU MS

where medicines are cheaper or less accessible. Transfer (undercover export) to eastern Europe for distribution through pharmacies, etc.

5. Infiltration of the legal supply chain in Italy

National distribution into the legal network
(i.e. to Italian pharmacies, OTC pharmacies and hospitals)

6. Infiltration of the legal supply chain in EU

Transfer (overt export) to northern Europe
(e.g. parallel trade)

AIFA set up indicators for testing the different scenarios:

1. Black market in the field

Blacklist of stolen products and related batch numbers to be shared and **training** (police)
Winter 2013

2. Black market on the web

IT **intelligence activities** (AIFA, private companies)
Winter 2013

3. New supply to hospitals

Evaluation of data (low incidence)

4. Black market to EU/non EU MS

Blacklist of stolen products and related batch numbers to be shared and **training** (customs)
January 2014

5. Infiltration of the legal supply chain in Italy

Evaluation of data, **blacklist** and **training** (police)
Winter 2013

6. Infiltration of the legal supply chain in EU

Watchlist for EU MS, set up of an **alert procedure** (DB/signals)
Winter 2013

AIFA developed all listed instruments, and involved Carabinieri NAS, Customs and other stakeholders in the test verifications: the plan was to use these tools for triggering and "filtering" signals coming from the different involved actors – e.g. customs, police, industries, health professionals.

After some test in the field, the most probable scenario was considered the last one (6): a “blacklist” of stolen medicines was prepared and circulated to interested DRAs and stakeholders in Europe, asking to report AIFA any suspect signal about incidents involving the listed products.

The database was also made available to industries and operators as a tool for processing signals from the field: any suspicion about a medicine could be processed by using also the data regarding stolen medicines.

When in March 2014 the signal arrived, the system helped to identify it in a timely manner: a manipulation occurred in Germany on a medicine in AIFA blacklist was forwarded to the Marketing Authorisation Holder, that informed AIFA in real time, since the reported batch number matched an entry of the database.

I.II The case

A “signal” was received on March 31st, 2014, from a German parallel distributor who received Herceptin 150 mg from a wholesaler in UK, concerning what initially looked like a defective vial that had been traded in the Parallel Import system.
On March 31st the signal was forwarded to the manufacturer (Roche) and to AIFA.

As reported in the NUI that Paul-Ehrlich Institute (released on April 2nd), during the delivery control of medicinal products from the UK wholesaler the following was observed:

- the batch number of the primary and the secondary packaging differed;
- the products were partially liquid (although it is a powder);
- residue of product was observed on the outside of the vial;
- some products seemed to have been reopened and closed.

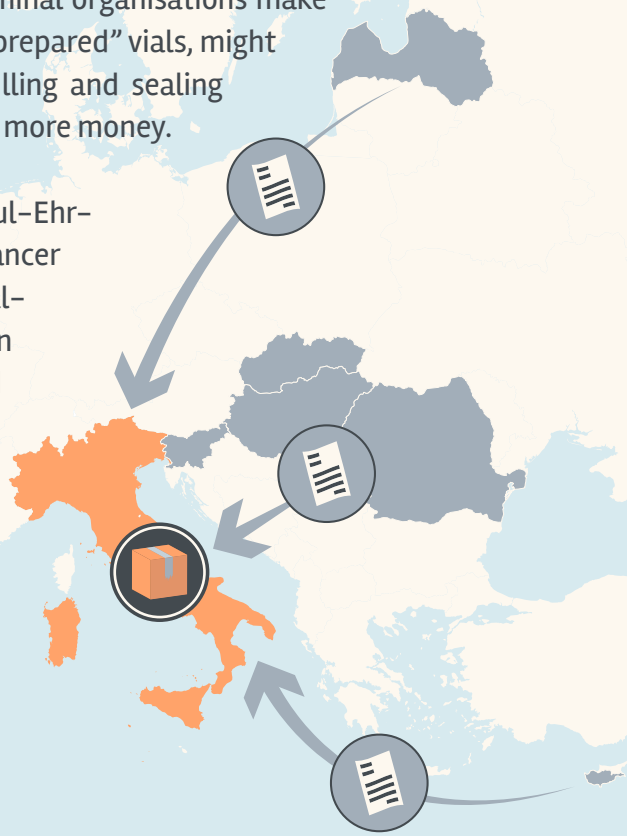
Samples from each of the affected batches (H4319B02; H4129B01; H4284B04) were seized.

Further investigation of the case was performed by involving also the manufacturer and the AIFA Counterfeiting Prevention Unit: data were evaluated by using also the theft database tools.

The check determined that the batch number could be related to a theft from a truck in Italy.

The quality signal and the theft data gave a possible explanation to what had been observed: the mix up of batch numbers can be caused by the assembly of single stolen vials in big packages, easier to replace on the market since importers prefer single batch numbers; the manipulation may be explained since criminal organisations make use of infiltrators and those, besides stealing intact or "prepared" vials, might recycle also products' packages from garbage by refilling and sealing them in a way acceptable to non experts, in order to get more money.

Following the above mentioned initial NUI issued by Paul-Ehrlich Institute (April 2nd, 2014), whereby vials of the cancer medicine Herceptin (trastuzumab), stolen from Italian hospitals/distributors, were reported to have been re-introduced under false credentials by unauthorized operators as falsified medicines into the supply chain, a number of Member States have taken action where required.



Seizures of manipulated vials have been carried out by national competent authorities in Germany, Finland and UK, while the MHRA inspected the UK wholesaler and the Carabinieri NAS inspected the Italian wholesaler who supplied to the UK: AIFA sup-

IDENTIFIED UNAUTHORIZED ("BOGUS") WHOLESALERS

- **CARNELA LIMITED**
  str. Michalaki Karaoli 8, Nicosia, Cyprus, VAT CY10308068X
- **ABLE POWER INTERNATIONAL HOLDINGS**
  str. Podmaniczky Utca 57. 2/14, Budapest, Hungary
- **AVIMAX HEALTH AND TRADE KFT**
  Fòti U. 4 Szàm, HU–2161 Csomàd, Hungary, VAT HU24206028
- **MARS DISTRIBUTIONS KFT**
  Tompa M. Utca 9, HU–8360 Keszthely, Hungary, VAT HU11779074
- **EURORIGA MED Import Export**
  str. Akademika Mstislava Keldisa Iela 12–158, Riga, Latvia,
  VAT LV40103517211
- **LATVAMED INTERNATIONAL Imp. Exp**
  str. Akademika Mstislava Keldisa Iela 12–158, Riga, Latvia,
  VAT LV40103572887
- **PERSONAL COMMODITY RINGSIDE**
  Municipiul Arad, str.Tribunal Dobra n.18 Judet Arad, Romania,
  Fiscal code RO31031066 dated 19.12.2012
- **ZEAPHARMA S.R.L**
  Municipiul Targu Jiu, Victoriei, bloc196, scara 3, etaj 2, ap. 10,
  Judetul GORJ, Romania *(note: Zeapharma is authorised as pharmacy, not as wholesaler)*
- **EXIMP AZ – sros**
  Bratislava, Slovak Republic
- **PIRAMID D.O.O**
  Brniceva Ulica 31, 1231 Ljubljana, Slovenia, VAT 61869937
- **TAIN D.O.O**
  Nova Gorica, str. Kridiceva Ulica n.19, Slovenia, VAT 76488632
- **HILDONS**
  Feidiou 3, Thessaloniki, Greece, VAT number EL 800528668
- **NIXERTRON IBERICA S.r.l.**
  via Novara 123, 20153 Milan, Italy, VAT 01063770323

ported the identification of the products as "illegally exported", and "falsified" with respect to the origin (as for the Dir. 2011/62 definition of "falsified medicine"). The distribution of similar vials to other EU MS was also verified.

In the invoices from the UK wholesaler two other products were detected, namely Alimta and Remicade. The evidence pointed firmly at a significant distribution channel having been discovered and not just a one-time case.

Upon further investigation by the Italian authorities, additional medicinal products were identified as stolen in Italy and subsequently re-introduced under false credentials. This was facilitated through the unauthorized operators operating in Cyprus, Hungary, Latvia, Romania, Slovak Republic and Slovenia issuing fake invoices pretending to sell the stolen medicines legally to authorised Italian operators.

These authorised legal Italian operators subsequently exported these to other EU markets.

Apparently, there was a consolidated scheme: the criminal organisation behind

this criminal operation hired local criminals in Italy to break into hospitals and to hijack distribution trucks.

The stolen products were transferred to an Italian licensed wholesalers and it appears that falsified receipts were created for the shipments. Fake non licensed wholesalers were set up in numerous EU Member States, e.g. Hungary, Latvia, Cyprus, Czech Republic.

Authorised wholesalers in Italy received (fake) invoices from one of the "bogus wholesalers" in another country, e.g. Hungary, and received the stolen medicinal products: It is likely that the medicinal products never left Italian territory during this stage, the unauthorised operators' *modus operandi* was aimed at legitimise the supply chain. The whitewashed shipment was then sold by the licensed Italian wholesalers, e.g. in the UK.

LIST OF OPERATORS WHICH DIRECTLY BOUGHT MEDICINES FROM THE "BOGUS WHOLESALERS"

- **FARMA GLOBAL Srl**
  Via Boscofangone Snc, 80035 Nola, Napoli, VAT 06474151211
- **FARMACEUTICA INTERNAZIONALE Srl**
  Via Dell'industria Snc, 83030 Pietradefusi, Avellino, VAT 02715470643
- **FARMACIA COZZOLINO DI MARIO & CIRO S.N.C.**
  Corso Italia 15, 80056 Ercolano, Napoli, VAT 02778921219
- **FARMACIA DELLA ROCCA**
  Via Sottotenente Ernesto Cirillo 207, 80041 Boscoreale, Napoli, VAT 06345681214
- **PHARMA-TRADE SPA**
  Via Roma,12 (Operative site: Via S.Abbondio, 158), 80045 Pompei (NA), VAT 07034161211
- **PHARMASEA Ltd.**
  11, Dingli Street, Sliema, Malta

The non Italian wholesalers, apparently, never asked anything more than the Italian authorisation of the legal wholesaler[1]; they apparently believed they bought from a genuine wholesaler for selling the medicines to other MS in that belief.

Since organisations in e.g. Latvia, Hungary etc. are unauthorised operators, the products were considered as "falsified"; due to the falsification of the origin, they were not considered safe or effective, and consequently quarantined.

1 According to GDP guidelines, wholesalers have to verify only the direct wholesalers they are buying from (see FMD).

With respect to the already investigated products, Italy traced all internal transactions: the Italian operators that were supplied, directly or indirectly, by the unauthorised wholesalers mentioned above were also inspected.

Member States were requested by AIFA in a NUI launched on May 14th to contact wholesalers, relevant organisations and parallel distributors in their territory to temporarily quarantine medicinal products bought from the unauthorized operators above, until the outcome of the current investigations provide evidence of their safety and efficacy, and to inform AIFA of any medicine bought from the Italian operators listed in the NUI, in order to allow the "validation" of the purchase with the data made available to AIFA by the Traceability System of the Ministry of Health.

Follow up NUIs were launched by AIFA on 28th of May, 1st and 25th of July and 26th of August, aimed at disseminating a list of specific batches of medicinal products that were confirmed as affected by the case, updating the list of involved operators and proposing specific activities of verification and inspection, when required, to the competent authorities of other MS.

Further investigations allowed to discover that the "undercover distribution network" sourcing stolen medicines from Italy was applying similar schemes also in other MS (a Malta/Romania connection was demonstrated) and with other kind of illegal products (falsified Herceptin, Pegasys, Avastin were spotted between 2013 and 2014, in channels clearly related to this one).

THE SUPPLY CHAIN MODELS

A) Bogus Operator sells to Italian Operator who sells to German operator.

B) Bogus Operator sells to Italian Operator who sells to operator in another MS who subsequently sells to a German operator.

At this stage it is estimated that this has been going on for three years at least and involves hundreds of medicines.

The list of operators which directly bought medicines from the "bogus wholesalers" mentioned above was also released as an Annex to NUI issued on the 14th of May, and updated in the follow up NUIs (see box for the list)

Italian and Maltese authorities are progressing with regulatory action against the wholesaler authorisations of the above listed operators.

To date, the licence for three of the operators was suspended for three months by the competent local authority, Regione Campania:

- **FARMA GLOBAL** (degree n. 161, 29/7/14),
- **FARMACIA DELLA ROCCA** (n. 160, 29/7/14),
- **PHARMA-TRADE** (degree n. 162, 29/7/14).

Two of the operators are no longer active:

- **FARMACEUTICA INTERNAZIONALE** ceased its activities (as stated in the Regione Campania degrees n. 72, 27/5/14 and n. 111, 3/7/14);
- **PHARMASEA** license was revoked by the Maltese authorities.

Between April and July 2014, Italian Prosecutors and joint investigation teams coordinated by AIFA and Carabinieri NAS identified the involved operators, the distribution/export channels and, moreover, even the undercover warehouses of the criminal organisations.

In July 2014 three warehouses were found near Naples; police forces enforced the withdrawal of the stolen medicines from the exporting channels, and local authorities acted against the operators which directly bought from the bogus wholesalers.

It is now known that some wholesalers are not adhering to the regulations and this has permitted falsified medicines to contaminate the parallel import/distribution network.

II.
CASE MANAGEMENT

II.I The verification process

II.I.I Validation of trades

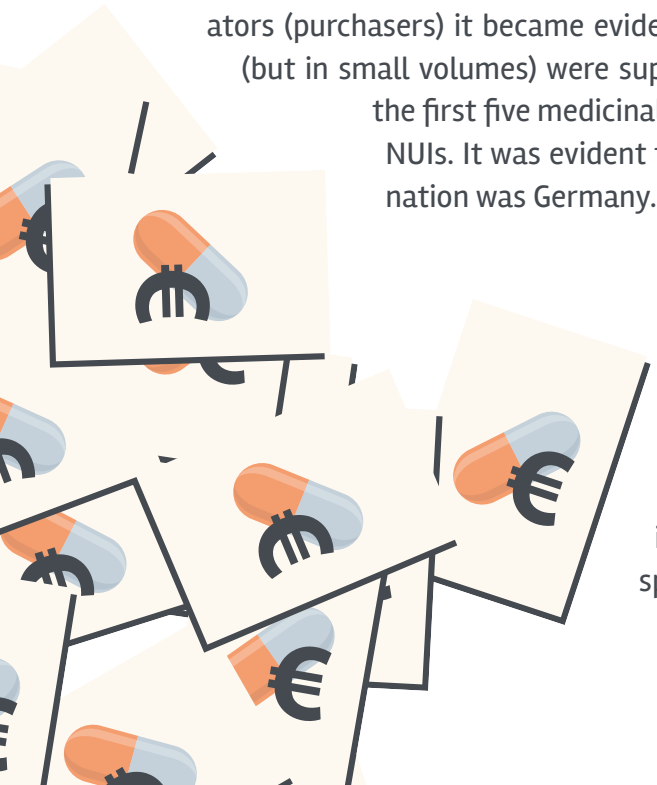
Since the NUIs launched by AIFA recommended quarantining all products sourced by operators that were "contaminated" by the bogus wholesalers, all EU MS started an in-depth check of all trading activities which were in connection with such operators; AIFA, Carabinieri NAS and other competent authorities performed targeted inspections of the whole supply chain and, after the July 1st NUI, all available invoices related to possibly "contaminated" trades were forwarded to AIFA and EMA for a systematic verification of the legitimacy of the trades.

The result of this exercise was double:

- AIFA worked on the data disclosed by the competent Prosecutor, following the trades from the bogus wholesalers to the first EU MS outside of Italy, with EMA and other MS followed up the next steps up to the final customer (**top-down approach**: final goal, RA/seizure of the illegal quarantined goods).
- EMA and AIFA filed all invoices received by the MS, trying both to reconstruct the full picture of the illegal trades (since some of the bogus wholesalers related transactions appeared to be missing in the available seized documentation), and to validate the legitimate trades, by verifying the origin of the products and the traceability of the supply (**bottom-up approach**: final goal, release of the quarantined products non related to the illegal network, and reconstruction of the full picture of the illegal trades for the next follow up RA/seizures).

On the basis of the data collected and disclosed by Carabinieri NAS and by the competent Prosecutor, AIFA have painstakingly identified the medicinal products that were supplied via Route A listed above. They are involving other MS in the supply chain review when one of the 5 authorised Italian wholesalers supplied product to a non-German wholesaler/PDs (Route B above).
EMA and other involved EU MS authorities supported the verification and trades reconstruction exercise, finalised at the compilation of the annex to the RA that AIFA issued on August 8th.
The investigation has identified 100 products that have been supplied via the bogus operators listed in the previous table. The products are listed in the RA issued by AIFA on August 8th, including an Annex that was updated on August 14th, September 1st and January 29th, 2015. This Annex will be furtherly updated as more information becomes available.

Italian authorities continued to identify the supply chains for the medicinal products concerned. On review of documentation from the bogus operators to Italian Operators (purchasers) it became evident that a large number of various medicines (but in small volumes) were supplied utilising the same supply chains as for the first five medicinal products identified and listed in the previous NUIs. It was evident that in most cases the country of final destination was Germany.



AIFA proposed recall of the medicines confirmed as falsified related to specific trades, as listed in the RA Annexes, and not the entire batches. Each Member State had to search for trades in which they are the last customer in the supply chain. Once identified, these trades form the basis of a specific MS recall.

It is important to note that AIFA proposed recall of the specific trade not the entire batch referenced.

II.I.II Validation of operators

As part of the general investigation, AIFA and Carabinieri NAS enforced the proposal included in the previous NUIs: Italian wholesalers were inspected by Carabinieri NAS and all invoices related to the "bogus wholesalers" were filed, and their trades traced to the first non Italian customer, as for the RA annex development process.
This inspection exercise was extended to all Italian operators who bought products from the operators listed, and all new data regarding trades and operators were disclosed in real time to all MS, via EMA mail list and AIFA restricted "fakeshare" web platform: the new bogus operator HILDONS was for instance identified in July 2014 during the inspection campaign, its nature confirmed through direct contacts between AIFA and Greek authorities, and the distribution of the information to the network authorised in real time by the Prosecutor.
After the RAs were issued, a new inspection campaign was launched as a result of the new data gathered by EMA and EU MS authorities; the results of the new campaign will be disclosed by AIFA through the same authorisation process and distribution channels used previously.
The results of this campaign should confirm the security of the distribution network in Italy, allowing all EU MS to consider as "safe" any trade related to the validated operators, with no need for further statements by the competent Italian authorities. There are no illegal activities recorded and confirmed after the third NUI launched by AIFA (July 1st, 2014). Invoices forwarded by EU MS authorities have been confirmed as legitimate.

It is likely that this new campaign, in combination with the RA follow up activities, will trigger the identification of new actors and trades. For example, Italian authorities have suspended the licence of another operator (ITAFARM SRL, Strada del Piano 49/E-51, 06135 Ponte S. Giovanni, Perugia, VAT 04944591009), even if for infringements that currently seem unrelated to the targeted illegal channels, whilst Italian and other EU

MS authorities are currently investigating suspect movements connected with the "bogus wholesalers" activities.

II.I.III Triggers for new signals

One of the key lessons learned during this phase of the investigation is that since the counterpart is a criminal organisation, it is impossible to rely on information sourced from the paperwork facade.

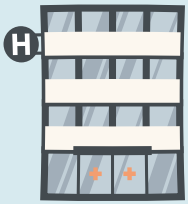
Moreover, some of the information related to the illegal channels emerged only after repeated police inspections and in depth IT verifications; and since the comparison between the number of stolen medicines (as for the available Italian data), the disclosed invoices and the "Italian sourced medicines" highlighted visible outliers and unbalances, it is likely that there are still more undercover channels to be discovered.

In order to generate more signals to be investigated, AIFA asked MAHs and the Ministry of Health for support in order to identify products that were not legally exported after April 1st 2013: this exercise was aimed at giving all MS new references for identifying suspect invoices and trades.

AIFA then checked all available traceability data, and asked MAHs of hospital

PRODUCTS SOLD MOSTLY TO HOSPITALS

These are products for which the dispensation is exclusively at hospital level. AIFA contacted the MAHs of these products in order to verify the distribution chain and validate the data through the Italian Traceability System of the Ministry of Health. This let AIFA identify the products sold directly to hospitals without any wholesalers' involvement. Hospitals are not allowed to export or resell these products: **any of these products found at level of wholesalers' channel should be regarded as "suspect" at least, and evaluated further**.



BRAND	MAH	MAH STATEMENT
AFINITOR	Novartis Farma S.p.A.	Note to AIFA, 3 September 2014
ATRIPLA	Gilead Sciences S.r.l. (for Bristol Myers Squibb)	Note to AIFA, 8 August 2014
AVASTIN	Roche S.p.a.	TWIMC 16 May 2014
CAELYX	Janssen-Cilag SpA	Note to AIFA, 28 August 2014
ECALTA	Pfizer Italia S.r.l.	Note to AIFA, 3 September 2014
EVIPLERA	Gilead Sciences S.r.l.	Note to AIFA, 8 August 2014
EXJADE	Novartis Farma S.p.A.	Note to AIFA, 3 September 2014
FASLODEX	AstraZeneca S.p.a.	Note to AIFA, 6 August 2014
GILENYA	Novartis Farma S.p.A.	Note to AIFA, 3 September 2014
HERCEPTIN	Roche S.p.a.	TWIMC 17 April 2014
IRESSA	AstraZeneca S.p.a.	Note to AIFA, 2 September 2014
MABTHERA	Roche S.p.a.	TWIMC 16 May 2014
NPLATE (250mg)	Amgen S.r.l.	Note to AIFA, 11 August 2014
PREZISTA	Janssen-Cilag SpA	Note to AIFA, 28 August 2014
ROACTEMRA	Roche S.p.a.	Note to AIFA, 7 August 2014
STELARA	Janssen-Cilag SpA	Note to AIFA, 28 August 2014

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BRAND	MAH	MAH STATEMENT
SUTENT	Pfizer Italia S.r.l.	Note to AIFA, 3 September 2014
TASIGNA	Novartis Farma S.p.A.	Note to AIFA, 3 September 2014
TRUVADA	Gilead Sciences S.r.l.	Note to AIFA, 8 August 2014
TYSABRI	Biogen Idec Italia S.r.l.	Note to AIFA, 6 August 2014
VELCADE	Janssen-Cilag SpA	Note to AIFA, 28 August 2014
VIRAMUNE	Boehringer Ingelheim Italia S.p.a.	Note to AIFA, 6 August 2014
VIREAD	Gilead Sciences S.r.l.	Note to AIFA, 8 August 2014
VOTRIENT	GlaxoSmithKline S.p.a.	Note to AIFA, 7 August 2014

medicines listed in the RA annex to specify if they sold products to wholesalers (i.e. the only wholesalers legally exporting medicines) after April 1st 2013. MAH declarations were validated using the traceability data gathered by the Italian Ministry of Health through the medicines track & trace system in place in Italy.

On August 26th, a list of products for which the distribution was intended for Italian hospitals (which are not allowed to export these medicines) was released via NUI: since any trade related to the above mentioned list of products should be regarded as "suspect" at least, and evaluated further, AIFA asked all operators to send any information regarding trades of those products which occurred after 1st April 2013, that were not already listed in the 8th August RA, and recommends to quarantine the suspect goods until further verification of the trade.

The goal of this exercise is to support the research of any other illegal channel that is still out of the investigation: any signal will be evaluated (through traceability data and verification with MAH) and, if confirmed as "suspect", forwarded to police/prosecutor for the follow up activities (e.g. inspections and seizures), in preparation of further update of the RA Annex.

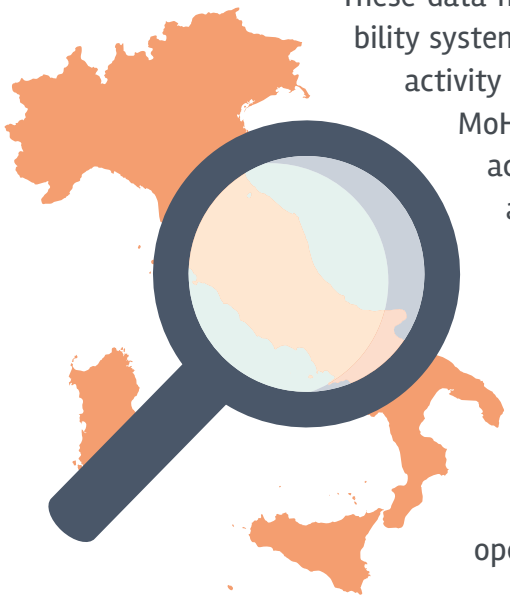
II.I.IV Restoring of the security of the italian supply chain beyond the Herceptin case

During the crisis period, Italy put in place additional checks and verifications that are currently guaranteeing the safety of the supply chain: NAS inspections, reinforced verification on MoH traceability data, cooperation with MAHs and wholesalers associations for data verification and invoices check, support to other MS in invoices verification were all major triggers for the enforcement of the proper GDP processes validation, with respect to the criminal infiltration that was highlighted by the AIFA/NAS investigation.

Since GDP inspections are not specifically targeting criminal behaviours, Italy is putting in place extra verifications to be applied in order to avoid the possible resurfacing of this kind of criminal infiltrations: the inspection systems will be strengthened through the cooperation between NAS and competent authorities, allowing to maintain the degree of confidence on the validation that was confirmed through the extraordinary procedures put in place during the investigation, and the already established procedures for tracing legal operations will be put in transparency, in order to allow other EU MS to easily check by themselves the legitimacy of the supplies.

With respect to this, it is important to note that legally distributing/exporting operators are currently obliged to send to the Traceability System of the Ministry of Health all data about the medicines they export: products, number of pieces, batch numbers, dates and MS of destination.

Lack of communication of those data is considered as a relevant infringement, since it impacts on the traceability of the medicines; specific sanctions are already considered in the Italian regulation, and could trigger not only administrative fines, but also licence suspensions.



These data may be automatically correlated by the traceability system to the MAH supplies, highlighting any suspect activity (i.e. export non related to previous supplies); MoH and AIFA will develop a system for giving MSs access to the validation data and will also prepare an ad hoc "certification file" that all MS operators could request from their Italian suppliers, as an official confirmation that the distribution/export is traced and legal.

AIFA currently publishes on its website alerts, blacklists and data about stolen medicines: the restricted "fakeshare" web platform, active since January 2014, was made available to operators and authorities for the sharing of infor-

mation during the crisis, and will be developed further as a current tool for operators, whilst the ad hoc "open" webpage (already active: *http://www.agenziafarmaco.gov.it/en/content/falsified-illegal-and-stolen-medicines-0*) will be used for the dissemination of guidance documents, such as guidelines (e.g. the "WGEO due diligence" for wholesalers, a "list of suspect signals for wholesalers" that AIFA is currently developing, and a list of available web resources for checking the National authorisations of wholesalers), alert on stolen medicines, and the explanation of the verifications on the Italian supplies for the interested operators.

Some of the measures could be easily implemented at EU level as preventive actions against the resurfacing of the contamination.

II.II Coordination activities

Upon the first alerts for Herceptin, BASG/AGES required the parallel distributors, which are located in Germany, to recall the batches identified (April 16th to 18th, 2014). Within the recall correspondence BASG/AGES not only asked for delivery data, but also for purchase data (name of the supplier). For getting an overview EMA set up spreadsheets to collect the delivery routes of Italian-origin Herceptin batches. By checking the spreadsheets and contacting the relevant DRAs, the original supplier in Italy could be identified for mostly all quantities of Herceptin which were distributed to Austria within few days. One route was traced back to a Maltese supplier, and after contacting the DRA in Malta, an inspection took place which revealed that this supplier sourced Herceptin from an unauthorized supplier.

In the mid of May 2014, all parallel importers based in Austria were inspected or officially contacted to provide the names and status of their suppliers for special parallel traded medicinal products. Afterwards a check was done whether the named companies under suspicion were on the circulated list of the bogus wholesalers.

A focus project was started to collect all purchase data of all medicinal products affected in this case to check whether all actors involved in the distribution chain possess an authorization according to Directive 2001/83/EC.

BASG/AGES coordinated and required all data relevant for the Austrian market (e.g. asked DRA to provide data on suppliers for Herceptin delivered to Austria) and analysed the data.

A coordination of all investigative measures and outcomes (e.g. collecting the analyses reports) as well as asking for required data all over Europe (which was partially done by EMA) and an analysis of the data given with investigative measures to follow on DRA side would be useful. In this case, analysis of data was done on DRA level only by those DRAs affected as end user countries – to different extent.

II.II.I Roles of different entities during this case

Role of EMA

- Coordination and set up of spreadsheets completed by member states;
- Providing data on parallel distribution notifications;
- Coordination activities and requests to affected DRAs from DRA side for CAPs.

Role of WGEO Task Force Volcano (founded in Vienna during the annual WGEO – Meeting)

- Discussion of next steps and recommendations from enforcement side;
- Keeping in mind the broader involvement of other branches of the illegal net-work in other MS.

Role of AIFA

- Providing data and analysing data, primarily related to the Italian case;
- Linking the prosecutor in Italy to European DRAs and EMA;
- Summarising all information and coordination of discussion/joint activities between DRAs and investigators (via organisation of webinars, teleconferences, development of documentation, publication of NUIs, RA and press releases);
- Sharing of information between DRA/enforcement activities through the "fake-share" web tools (restricted web area, webinar platform, etc.).

Role of DRAs

- Providing data on distribution of medicinal products affected in this case follow-ing requests from EMA, Italy or other concerned MS;

- Some DRAs are not affected as target country, which may have influence on setting priorities in corresponding.

Investigative Coordination

- Is currently done by AIFA for the Italy case which is a heavy workload;
- Information is missing whether further suspicions are addressed/followed–up/coordinated from enforcement side (e.g. the Romanian/Malta case, the Romanian Herceptin/MabThera/Sutent cases, evaluation of notifications of parallel distributed medicinal products and trade that gain no financial benefit for the involved companies when legally bought).

III.
KEY LESSON LEARNED

The management of the "Operation Volcano" made it clear that additional enforcement resources are necessary to tackle any cross-border illegal trafficking of this magnitude. These resources have to be allocated within DRAs to handle such cases adequately in order to protect public health.

GMDP inspections are mostly focused on the pharmaceutical quality system. Empirically, signals of criminality cannot be found that way. Although irregularities might be addressed by GMDP inspectors, further enforcement investigations are necessary to tighten the suspicion. DRAs are well staffed with personnel to narrow down the risk and danger to public health caused by falsified medicines. GMDP personnel is competent to set up guides and measures to prevent falsified medicines entering the legal supply chain, but when this occurs many different professional experiences in the pharmaceutical area have to be considered before a case can be fixed. Only specialised DRA enforcement personnel are trained to address and prove irregularities especially of the provisions of FMD. Coordinated surveillance of the market and communication between these two groups is necessary. Finally, each other's experiences have to be implemented in prevention programs to secure public health.

Another evidence stands out: there is no common procedure for handling in a coordinated way transnational enforcement cases in healthcare. The "Herceptin case" proved how spread and interconnected illegal activities in Europe are, while the operations set in motion proved the importance of sharing a common procedure at a European level to tackle such activities which have European impact and require proactive measures to identify signals by all involved MS.

Training of GMDP inspectors should attract more attention to finding signals of irregularities/illegal practices and criminalities, which can never be found by using standard procedures. Every inspector should be aware, that no criminal case is like the last one.

The supply chain to parallel importers and distributors can be complex and there is currently no system that enables visibility of the full audit trail, even in MS where existing regulations support traceability.

Looking closer to complex criminal cases will mostly end up in finding several other non compliant activities conducted by well known and inspected authorised companies, like the fact that vials were detected during delivery control as manipulated but no notification was carried out to the National Competent Authorities or buying from not authorised wholesalers.

The same illegal structure can be driven in another country at the same time, following the same set up, like the Romanian signals indicate. Awareness raising and the will to preserve confidence in the parallel trade system can strengthen the ambition for compliance.

IV.
PROPOSALS

IV.I Enforcement coordination

The medicines supply chain is constantly being challenged by criminal activity and this paper and associated proposals appear to be a positive step towards managing this risk. It is clear from the lessons learned that well-coordinated, effective and efficient enforcement collaboration by member states is key in fighting medicines crime. It is therefore suggested that, in complex cross border cases involving more than two member states, an ad hoc medicrime enforcement taskforce, comprising of staff from enforcement departments within drug regulatory agencies and associated bodies, should be formed.

The formation of an enforcement taskforce will enable members to share information and partake of intelligence and best practice, as well as gauge enforcement capabilities/limitations and provide assistance in capacity building and training. Tools and guidelines can also be developed, for example the WGEO due diligence document, and shared with appropriate stakeholders. The ad hoc enforcement taskforce will also endeavour to co-operate with competent international bodies such as EMA, EUROPOL, INTERPOL, and others at eye level.

One of the primary roles of the medicrime enforcement taskforce will be to gather intelligence by collection and analysing each signal and supporting national competent authorities such as police, DRAs and customs with concrete questions to be able to conduct investigations in a timely and efficient manner, share information and focus on evidence. The team should also adopt proactive measures and move away from the traditional reactive enforcement activities, which stand the risks of losing relevant evidence and investigative leads

In terms of setting up and implementing the taskforce the following issues will be addressed:

- A task force leader similar to a Rapporteur shall be appointed.
- Reassure that the WGEO SPOC system is in place in each country.
- Support from the highest level (HMA) must be provided to influence member states to provide requested data within the set time frame and to actively collaborate.
- Members shall be assigned to prioritise their work on the taskforce in order to protect the public health within Europe.
- Financing for the taskforce personnel should be guaranteed and provided by the respective agency.
- Training is available for specific enforcement duties.
- A joint communication strategy should be agreed.
- Cooperational meetings, webinars and telecons can be performed.
- Mapping and structured intelligence gathering can be guaranteed.
- Recommend actions for member states affected will be documented.
- A focused enforcement project shall be set up to proactively collect and document all data in the case (as done during this case by using the AIFA/EC "fakeshare" platform and tools).

IV.I.I Further proposals

The MHRA collaborated with AIFA, and other agencies, to produce this document with a view to formalising a process that would allow effective joint working in relation to complex, European, cross border investigations. In terms of enforcement coordination, **the MHRA support the formation of an ad-hoc taskforce approach to manage this type of enquiry**.

In relation to regulatory coordination, the MHRA support the closer cooperation with the EMA GMDP Inspectors Working Group in relation to improving the due diligence requirements for wholesale dealers and enhanced cold chain provisions.

The paper clearly addresses matters from an "enforcement" perspective which would include collaboration in relation to the investigative strategy. However, an area that does not seem to be clear, and that the paper may benefit from, is in relation to the management of the higher level strategic issues. The question arises, **should there be a strategic group that sits above the operational taskforce to ensure appropriate coordination of the issues?**

It is suggested the group could maintain an overview of the emerging issues, draw up terms of reference for the operational taskforce, ensure sufficient resources are available, consider transnational risk and strategic linkages with other agencies. This strategic group could also review progress of the taskforce and would provide a useful structure to escalate critical issues.
Depending on the nature and the scale of the event, it would be drawn from the member states most affected by the incident.

It is suggested to pull a steady strategic group out of senior DRA enforcement officers alongside the active WGEO taskforce, whose members would change case by case. Only a few of the European agencies could facilitate a bigger operational group with their resources. Smaller countries could handle cases better with the supervisory help of both the strategic group and the active colleagues involved in the taskforce. Financing and resources for both strategic group and WGEO taskforce have to be ensured in order to better tackle criminal activities at a European level.

IV.II Regulatory approach

The current regulations and controls are clearly insufficient with regard to due diligence by wholesalers in order to prevent the criminal penetration of the legitimate supply chain. It is recommended that the EMA, GMDP IWG and HMA-WGEO be requested to develop common position documents to explain how to apply the due diligence requirements in the EU GDP Guide by wholesalers and strengthen its compliance providing examples of how to carry out this activity, e.g. requiring financial credit checks, confirming VAT num-

ber, checking Duns number, confirming EORI number and confirming that the address is a registered business premise, like listed in the WGEO Due Diligence paper.
The creation of the EMA GMDP database will help resolve the problem of wholesale dealers unknowingly purchasing from unlicensed sources. However, it will take approximately five years for the database to be fully operational as it depends upon the inspection of wholesale dealers and the issue of a GDP certificate. One possible proposal could be for an enhanced inspection programme by all MS with a commitment to complete the database within an agreed time limit. This would have significant resource consequences for most MS and may detract from their GMP inspection programmes.

In order to make out of the thefts' database a useful tools at a European level, there should be legal obligations for all stakeholders to report stolen medicines to the DRA. The "Operation Volcano" highlighted the importance of such a tool in support of investigations.

Ways should be sought to see if a quicker implementation of the serial number system introduced in FMD would be possible, along with the permission to use this structure for all medicines and medical products.

Lastly, in order to ensure the quality of products, it is recommended that the Commission, through the auspices of the EMA GMDP Inspectors Working Group, be requested to review the current requirements in the EU GDP Guide for cold chain medicines and determine whether the current requirements can usefully be strengthened by requiring a temperature data logger (or similar) to accompany all shipments so as to assure a complete temperature audit trail.

IV.III Preventive measures

Prevention can only be based on tools to gather and share information among authorities involved in law enforcement. The following tools currently appear to be the most useful ones:

- A constantly and timely updated database (similar to EudraGMP) and/or web platforms of thefts of medicines where data about stolen medicines are published: AIFA already started a project on this involving authorities, administrations, associations and operators in the pharmaceutical and healthcare fields.
- Real time alert on stolen/illegal medicines (AIFA will start using new ad hoc pages for that – http://www.agenziafarmaco.gov.it/it/content/furti-di-medicinali, and will promote the use of the AIFA/EC "fakeshare" platform as tool for investigators).
- Development of risk profiles on suspect offers as included in the HMA-WGEO due diligence document in Annex VI.
- Guideline for wholesalers how to proceed when a batch listed in the "Stolen Medicines Database" is offered.
- Training for DRA enforcement employees and for GMDP inspectors.

All of these measures should be discussed by involving the appropriate international fora (e.g. Inspectors Working Party – EMA, PIC/S, PDA, ISPE etc.).

V.
RAs and NUIs

RAs issued by AIFA

August 8th, 2014 | IT – Italian Medicines Agency (AIFA)

AIFA triggered a wide recall of illegally medicines through a list of verified trades where the primary source was a bogus wholesaler. The document was updated on August 14th, September 1st 2014, January 29th 2015 and on July 2nd 2015.

Other RAs

April 2nd, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Suspected counterfeit of Herceptin (Trastuzumab) 150mg. The document was updated on August 12th.

April 8th, 2014 | FI – Finnish Medicines Agency (FIMEA)

Suspect counterfeit herceptin.

April 11th, 2014 | European Medicines Agency (EMA)

Herceptin 150mg Powder for concentrate for solution for infusion.

April 17th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Falsified Remicade batches and the actions taken in Germany.

May 23th, 2014 | CZ – State Institute for Drug Control (SUKL)

Notification of a Quality Defect/Recall. The document was updated on June 26th.

July 1st, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Concerning falsified syringes of Gardasil.

July 28th, 2014 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Recall, notification for parallelimported medicinal products of the Company CC–Pharma in Germany.

July 28th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall, notification for parallelimported medicinal products of the Company CC–Pharma in Germany.

August 4th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of batches of products of Italian origin.

August 6th, 2014 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Concerning falsified Viramune.

August 8th, 2014 | N – Norwegian Medicines Agency

Recall of falsified medicinal products (Ipstyl, Orifarm). The document was updated on August 11th.

August 14th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Concerning the company Haemato Pharma Gmbh, regarding recalls of batches of products of Italian origin.

August 14th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Concerning the company Inopha GmbH, regarding recalls of batches of products of Italian origin.

August 19th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recalls of parallel distributed medicines of Italian origin (RA CC–Pharma).

August 19th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of suspected medicinal products of Italian origin (Remicade 100 mg).

August 19th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of suspected medicinal products of Italian origin (Humira 40 mg).

August 26th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of illegal products of italian origin (RA Orifarm).

August 26th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of illegal products of Italian origin (RA Milinda).

August 26th, 2014 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Recall, notification for parallel imported medicinal product Celebrex 200 mg of the parallel distributer CC–Pharma in Germany.

August 26th, 2014 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Recall, notification for parallel imported medicinal product Viramune 400 mg of the parallel distributer CC–Pharma in Germany.

August 26th, 2014 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Recall, notification for parallel imported medicinal products of the parallel distributer Orifarm GmbH in Germany.

August 27th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of illegal products of Italian origin (Clexane e Remicade).

August 29th, 2014 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Quality defect, Class II, medicinal product Cialis 20 mg tablets of the MAH Eli Lilly Niederlande, parallel distribution by Orifarm GmbH, DE.

September 9th, 2014 | DK – Danish Health and Medicines Authority (SST)

Illegal supply chain (Zonegran and Ipstyl).

September 25th, 2014 | FI – Finnish Medicines Agency (FIMEA)

Truvada parallel trade.

November 5th, 2014 | UK – Medicines and Healthcare Products Regulatory Agency (MHRA)

Suspected Falsification, Symbicort Turbohaler 320/9. The document was updated on November 6th.

May 18th, 2015 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Recall of suspected counterferit medicinal products of italian origin (Spiriva Respimat)

May 18th, 2015 | DE – Federal Institute for Drugs and Medical Devices (BfArM)

Recall of suspected counterferit medicinal products of italian origin (Clexane 40 mg)

NUIs

April 4th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Follow–up information on suspected counterfeit of Herceptin 150 mg.

May 14th, 2014 | IT – Italian Medicines Agency (AIFA)

Identification of the "bogus wholesalers" and first list of operators having traded illegal medicines.

May 28th, 2014 | IT – Italian Medicines Agency (AIFA)

List of involved batches for some of the products traded by the bogus wholesalers (Mabthera, Avastin, Herceptin).

July 1st, 2014 | IT – Italian Medicines Agency (AIFA)

Update of the list of involved operators, proposal of inspection and verifications aimed at discovering other possible channels and triggering new signals.

July 25th, 2014 | IT – Italian Medicines Agency (AIFA)

Update of the list of operators and summary of the case.

August 26th, 2014 | IT – Italian Medicines Agency (AIFA)

Update on the status of the Italian distribution network, summary of the ongoing verifications and proposal of follow up.

October 14th, 2014 | IT – Italian Medicines Agency (AIFA)

Update on the status of the Italian distribution network.

RAs related to similar patterns

September 3rd, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Counterfeit/manipulated Mabthera 500mg (Bactch: H0656B03) with romanian origin.

September 9th, 2014 | RO – National Agency for Medicines and Medical Devices (ANMDM)

Notification–products distributed by Chemomed Intertrading.

September 11th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Notification–products distributed by Chemomed Intertrading.

October 2nd, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall, illegally traded/counterfeited medicinal product Abilify; wholesaler Chemomed in RO, manufacturer hvd medical GmbH in DE.

October 8th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Recall of falisied medicines by parallel distributor InophaGmbH.

October 22nd, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Notification on Tarceva 150mg.

November 19th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Falsified Avastin Romanian origin.

December 4th, 2014 | DE – Paul–Ehrlich–Institut (PEI)

Suspected falsified MabThera of Romanian origin.

VI.

WGEO DUE DILIGENCE

by wholesalers and other actors involved in the purchase and sale of medicinal products in the legal supply chain

VI.I Introduction

The legal supply chain of medicinal products has become increasingly more complex during recent decades, with more and more actors being involved. Brokers are introduced and more than one distributor is usually involved in the purchase and sale of the same batch of product. Consignments of medicinal products are often moved across several countries' borders before entering the market they are intended for. One important reason for this being the large extent of movement/change of production sites producing medicinal products from Europe to third countries.

This ever increasing complexity calls for a well regulated and monitored supply chain. As the saying goes "a chain is as strong as its weakest link", and to this end every player, every actor in the supply chain has a crucial responsibility and role to play to ensure that the right medicines of the right quality reach the right market and thereby also ensuring that no falsified medicines penetrate the legal supply chain. Falsified medicines enter the legal supply chain either by someone's criminal intentions, by negligence of actors in the legal distribution chain or by both. So though one cannot eliminate the former, which will be dealt with through the enforcement systems of the respective countries, there is much room for improvement in the latter.

One of the key issues one has to address in order to ensure a safer supply chain is to exercise appropriate due diligence. Due diligence involves ensuring that the person with whom wholesalers are dealing and thus sourcing (in case of purchases) and supplying to (in case of selling) are duly authorised in line with required legislation to handle (receive and supply) the medicinal products involved in the transaction. Though this might

seem as a simple and quite straight forward task, experience has shown that this is often overseen or poorly adhered to.

VI.II Scope

The scope of this document is to list a set of questions with recommended answers which will help wholesalers to highlight the risk areas and thus exercise necessary due diligence when entering into deals especially with new potential suppliers and/or customers.

VI.III Questions and Answers

Q. Do you have a procedure available for Qualification of Suppliers?

A. A procedure delineating how a potential supplier should be assessed before becoming an approved supplier from the point of view of your business operations should always be available and followed up. A person should be identified within the company, ideally the Responsible Person, who should be responsible for the execution of this procedure and thereby approving new suppliers.

Q. What should be checked before a new supplier can be approved?

Does the company actually exist? Was the verification documented?

A. To ascertain that the company does indeed physically exist, ask for the UID or VAT number and check this against appropriate country registers, before documenting that the verification has taken place.
Alternatively, or additionally, search for the number on:
(*www.ec.europe.eu/taxation_customs/vies/vatRequest.html*). In this way you will at least ascertain that the company is actually a registered one (and thus a legal entity subject to legal proceedings). Open source checks on the internet can often be very useful too.

What is the licensing status of the company?

A. Once the company has sent you a copy of their licence or a GDP-certificate, then the authenticity of the document and the validity of the authorisation are very important. This verification can be done by checking the website of the competent authority issuing the licence or if it is registered in the EUDRA-GDP/GMP database as GDP/GMP compli-

ant. If the licence has an expiry date and it is expired, or if it has no expiry date and was issued more than 3 years ago, check if it is still valid. The process of how and when such verification is to be done should be described in your procedure and the verifications documented. It is crucial that the company licence status is confirmed before you issue a purchase order.

Was an audit performed of the supplier?

A. You should have a policy of auditing your suppliers, especially new suppliers with whom you have not previously had any business dealings with and which are not known as trusted sources to your medicinal supply trading network. There should be a documented policy of audits including whom and when to audit based on a risk assessment approach. Frequency of such audits is also to be listed. An audit should, as a minimum, include a check of the supplier's procedure for supplier qualification, ensuring that the supplier has a process in place to verify that licences/certificates are checked prior to any purchase orders being issued.

Q. Is the product offered a new product for your company?

A. Verify that the product has a Marketing Authorisation in an EEA country. You have to consider if this product by nature or by source may be falsified. If so, do not assume that the Marketing Authorisation number on the packaging is authentic/legitimate, check with MAH or with the competent authority of the destination country to confirm the products marketing status. Your quality system should have a procedure which incorporates a mandatory provision to notify the authorities in cases of suspicious products.

Q. Is the product being offered available in quantities or volumes unusually high or is the price being offered considerably lower than the usual price?

A. If the answer to any of these questions is 'yes', as part of due diligence, the wholesaler accepting the deal should investigate the reason why, to try to establish a plausible explanation before entering into a transaction. This holds true especially for products which one does not usually come by in large quantities, or it is a known fact that currently there is a shortage of a particular product (example GMP problems in a site / sites

where the product is manufactured). Low prices should also raise a red alert and the wholesale dealer should enquire the reason as to why such a low price is being offered.

Q. Is the supply chain of this transaction transparent?

A. The supply chain, i.e. the movement of goods from the storage of your supplier until they reach your warehouse should be as transparent as possible. Is the complete chain accountable? If not, it may pose a risk. A risk assessment should be conducted in this regard to establish whether all points and handlers involved in the consignment journey are known. If brokers are involved, check whether these brokers are adequately registered with the competent authority where they are established. Brokers must register with the competent authorities of the country in which they are situated. If a broker involved who is situated in the EEA is not registered, you should not enter into an agreement but notify the competent authority.

Q. What will be the method of transportation? Will there be groupage?

A. The transport of the consignment should be well planned and it should only be handled by shipping/transportation companies with whom there are written agreements and with whom you have experience and confidence in. Another important point to consider is whether there would be groupage. If this is the case this should be known prior to shipping so that adequate measures are taken by the handlers/shippers not to leave the consignments exposed which increases the risk of someone tampering with the consignment. For products requiring special storage conditions such as cold chain medicines the transportation has to be well planned in advance.

VII.

OFFICIAL WEB RESOURCES

allowing to check if a wholesaler is authorised to trade in medicines by the competent authorities of the MS where it is established

EMA

The Community database EUDRAGMDP may not be fully populated as Member States are currently working to bring it into operation so the database can be complimented with further information from the sources listed above and even through direct contact with the concerned National Competent Authorities if no listing can be found.

- *http://eudragmdp.eudra.org/inspections/logonGeneralPublic.do*

AUSTRIA

- *http://www.basg.gv.at/inspektionen/good-manufacturingdistribution-practice/arzneimittelbetriebe/*

CYPRUS

Cyprus Regulatory authority, Pharmaceutical Services/Ministry of Health, has published a catalog of all authorized wholesalers in Cyprus. Here is the relevant link:

- *http://www.moh.gov.cy/MOH/phs/phs.nsf/All/B67DD58A5E16809AC2257B2E0026D869?OpenDocument*

All authorized wholesalers are also registered in the EudraGMDP database.

DENMARK

Information about Danish companies with a valid WDL can be found at the link:

- *http://sundhedsstyrelsen.dk/en/medicines/regulation/company-authorisations-and-registrations/wholesale-distribution*

By clicking at “Companies authorized to distribute medicines by wholesale in Denmark” an excel file will be downloaded.

Another list for companies authorized to manufacture and import medicines and intermediates in Denmark can be downloaded here:

- *http://sundhedsstyrelsen.dk/en/medicines/regulation/company-authorisations-and-registrations/manufacture-and-import-of-medicines-and-intermediates*

A manufacturer must hold a wholesale dealer's authorisation if it wholesale deals medicines that are not manufactured at an address approved on the MIA, or if the manufacturer chooses to wholesale their own manufactured medicines from other addresses than those authorised on the MIA (e.g. separate storage addresses).

FINLAND

Name list of authorized wholesale license holders in Finland (for more detailed requests, contact *qdefect@fimea.fi*)

- *http://www.fimea.fi/valvonta/laaketehtaat_ja_-tukkukaupat/toimiluvat/kotimaiset_laaketukkukaupat*

FRANCE

List of authorised pharmaceutical companies in France, including notably wholesalers, importers and exporters.

- *http://agence-prd.ansm.sante.fr/php/etapharm/index.php*

ICELAND

List of Information about Icelandic companies with a valid WDL:

- *http://www.lyfjastofnun.is/Eftirlit/Lyfjaheildsolur_og_dreifing/Listi_yfir_lyfjaheildsolur/*

All authorized wholesalers are also registered in the EudraGMDP database.

ITALY

Permalink to the updated page:

- *http://www.dati.salute.gov.it/dataset/distributori_farmaci.jsp*

Download link (refences: *D – Depositario* = warehousing service shipping/distributing medicines on behalf of manufacturers; *P – Produttore* = manufacturer; *G – Grossista* = wholesaler):

- *http://www.dati.salute.gov.it/imgs/C_17_dataset_4_download_itemDownload0_upFile.CSV*

MALTA

A webpage listing various pharmaceutical activities licensed/certified/registered after establishing that the relevant GxP requirements and provisions of the Medicines Act are achieved. This webpage lists various headings for facilities with a: GMP certificate, manufacturer's licence, wholesale dealer's licence, plus registered brokers and API importers and distributors. Clicking on the individual listed heading opens a document with the relevant listed entities under that heading.

- *http://www.medicinesauthority.gov.mt/licensed-pharmaceutical-activities*

ROMANIA

The list of authorized Romanian wholesalers can be found at the following link:

- *http://www.anm.ro/anmdm/_/Lista%20depozite.pdf*

The suspended wholesalers are marked in red.

SPAIN

The list of authorized Spanish wholesalers can be found at the following link:

- *https://labofar.aemps.es/labofar/registro/entidadesDistribucion/consulta.do?metodo=detalleBusqueda*

By clicking in the name of the company, in blue, it is possible to access to more detail data. Some of these details are still missing pending of the update of the authorisations to the new format but all the authorised companies are listed. Also it is indicated whether the wholesale dealer's licence is temporarily suspended.

SWITZERLAND

Link to the authorized wholesalers in Switzerland:

- *https://www.swissmedic.ch/bewilligungen/00155/00241/00253/index.html?lang=en*

THE NETHERLANDS

There are currently 229 wholesale dealers listed on EudraGMDP under WDA – Nederland. There may be more wholesalers with a license that are not yet transferred to EudraGMDP, and for those you could search the list of licensed manufacturers and wholesalers at

- *http://www.farmatec.nl/geneesmiddelen/vergunningen/farmacie/Lijstvergunninghouders.aspx*

This is a pdf list that you could search for the name or address of the wholesaler. WDA is indicated by the letter G in the column "Registernummer" (number in the register).

UNITED KINGDOM

List of UK MHRA licensed wholesalers:

- *http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Manufacturersandwholesaledealerslicences/index.htm*

VIII.
Q&A

At the beginning of the use of the "fakeshare" web tools, AIFA gathered questions from all interested MS authorities, and prepared an ad hoc Q&A document, that was presented during the second "fakeshare" webinar, and shared through the restricted web area, in order to create common consensus on some issues related to the case: the following list of Q&A is an excerpt from that document, with the exclusion of the questions related to practicalities or to aspect that are now out of date.

Q. Can medicinal products, that are related to the illegal wholesalers outside Italy, be defined as falsified?

AIFA (ITALY). We consider these medicines as "supplied with fake documentation" (e.g. invoices stating that they were supplied by non authorized/non active wholesalers), and consequently FALSIFIED. See Dir. 2001/83, as amended by Dir. 2011/62. TITLE I, Definitions, Art. 1.

> *33. Falsified medicinal product:*
>
> *Any medicinal product with a false representation of:*
>
> *(a) 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;*
>
> *(b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or*
>
> *(c) its history, including the records and documents relating to the distribution channels used.*
>
> *This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.*

Q. Where in the European legislation can I find the right paragraphs to force the Parallel distributors/Wholesalers to give us the requested information?

POINT FOR DISCUSSION. Dir. 2001/83, TITLE IV considers together "Manufacture and importation"; TITLE XI ("Supervision and sanctions"), art. 111, states that

1g. Inspections shall be carried out by officials representing the competent authority who shall be empowered to (...)

(c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the description of the manufacturing method;

(d) inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX.

With respect to wholesalers, there are clear provisions under Art. 80:

Holders of the distribution authorization must fulfil the following minimum requirements: (...)

(e) they must keep records either in the form of purchase/sales invoices or on computer, or in any other form, giving for any transaction in medicinal products received, dispatched or brokered at least the following information:

- *date,*
- *name of the medicinal product,*
- *quantity received, supplied or brokered,*
- *name and address of the supplier or consignee, as appropriate,*
- *batch number of the medicinal products at least for products bearing the safety features referred to in point (o) of Article 54;*

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;

Q. What do we do if the Parallel distributors/Wholesalers refuse to give information or refuse to do a recall and send their lawyers against us?

AIFA (ITALY). Lack of compliance with Directive 2001/83 would be a major infringement with respect to any authorization.

Q. What measures are planned for the suspected Italian wholesalers, will there be a withdrawal of licences?

Q. Are the above mentioned Italian operators declared GDP non–compliant? If so, has this been entered into Eudra GMDP?

AIFA (ITALY). The ones who bought from "non authorized wholesalers" (i.e. the ones in Latvia etc.) will undergo sanctions from the competent authorities (i.e. local Authorities).

Article 80 Holders of the distribution authorization must fulfil the following minimum requirements:

(a) they must make the premises, installations and equipment referred to in Article 79(a) accessible at all times to the persons responsible for inspecting them;

(b) they must obtain their supplies of medicinal products only from persons who are themselves in possession of the distribution authorization or who are exempt from obtaining such authorization under the terms of Article 77(3) ;

(...)

(ca) they must verify that the medicinal products received are not falsified by checking the safety features on the outer packaging, in accordance with the requirements laid down in the delegated acts referred to in Article 54a(2) ;

(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned;

(e) they must keep records either in the form of purchase/sales invoices or on computer, or in any other form, giving for any transaction in medicinal products received, dispatched or brokered at least the following information:

- *date,*
- *name of the medicinal product,*
- *quantity received, supplied or brokered,*
- *name and address of the supplier or consignee, as appropriate,*
- *batch number of the medicinal products at least for products bearing the safety features referred to in point (o) of Article 54;*

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;

(g) they must comply with the principles and guidelines of good distribution practice for medicinal products as laid down in Article 84;

In particular, the Italian implementation of Dir. 2001/83 indicate the art. 80 requirements as "essential" for granting the wholesale authorization; this aspect will be covered even

before the trial, and (if relevant) the update of the EUDRA GDMP system will be considered.

Q. Is it true that in Italy hospitals have no licence as wholesalers?

AIFA (ITALY). Yes.

Q. Are Italian labelled medicinal products that are hospital only in Italy to be classified as falsified if they are in the legitimate supply chain elsewhere in EU/EEA?

Q. Is it illegal for an Italian wholesaler to export hospital only medicines to other EU-countries?

AIFA (ITALY). No: Italian wholesalers may legally export also hospital only medicines.

Q. Is there a list of Italian medicinal products that are hospital only?

AIFA (ITALY). Yes: it is published and updated regularly by AIFA, it is available on the web. http://www.agenziafarmaco.gov.it/it/content/tabelle-farmaci-di-classe-e-h-al-15052014 (Excel file: http://www.agenziafarmaco.gov.it/sites/default/files/Classe_H_per_Principio_Attivo_15.05.2014. xls)

Q. If Italian medicinal products that are hospital only are found in the legitimate supply chain in EU/EEA, what action should be taken, i.e. company to quarantine, National Competent Authorities to seize, company to return to marketing authorization holder, etc?

AIFA (ITALY). We should refine the question: since it is possible that hospital only drugs are legally exported, we should focus on ILLEGAL products. If Italian medicinal products that are hospital only and are confirmed as "falsified", e.g. paired to fake documentation with respect to the origin are found in the legitimate supply, the rules for falsified medicines should be applied.

Q. For the stolen cold chain medicines is there any evidence that the cold chain has been maintained, i.e. by data-logger records that cover the relevant periods of time?

AIFA (ITALY). No direct evidence. With respect to the medicines under investigation, as far as we know, up to now none reported EMA complaints/pharmacovigilance data/etc. clearly related to cold chain issues; the criminals were using a certain degree of care in handling things, apparently, since they were working on a "long term business"; and they wanted to avoid incidents. The "Herceptin incident" starting the case seems to be an indication of the "enlargement of the platform" – i.e. the central coordination unit of the criminal organization started using "non specialized burglars" for "supplying" the network, which was the cause for the incident. We know Police is studying the camera recordings of recent thefts, in order to identify "people carrying portable refrigerators".

Q. Can you confirm that the tampering/adulteration of Herceptin is a one–off incident and, in principal, is not related to the theft of medicines?

Q. How many of the involved medicinal products are at the moment confirmed to be manipulated? (I think it is only Herceptin!?)

AIFA (ITALY). The only manipulation we found up to today is the Herceptin one. We have a series of indications supporting the interpretation of the manipulation as a "bad quality supplier tampering": the very low incidence of the case, the bad quality of manipulation, the presence of water in all tampered vials, support this interpretation of the incident. We suppose that someone working in the targeted hospital took the medicines, some empty vials and some labels, and tried to arrange some "extra vials" to be added to the supply.

Q. What are the specific reasons for the Italian companies being on the list of concern?

Q. Does the Italian wholesalers mentioned on the list of operators identified as having supplied medicines sourced from the illegal operators identified outside of Italy have a valid WDA in Italy?

AIFA (ITALY). The list we published includes authorized operators, which according to the medicines traceability data/seized invoices/customs data, were directly or indirectly "victims" of the fake wholesalers, i.e. they exported medicines "arriving" from the Latvian/Hungarian/ etc. wholesalers – as the documents pretended. Please, note that since

they simply traded medicines from this network, they should simply considered as "under reinforced checks" – the Italian names in the list are not blacklisted.

Q. What is AIFA's recommendation to member states for any consignments of the products of its watchlist? Immediate recall or quarantine of all those products of Italian origin following precautionary principle as there is an illegal supply chain (unauthorised wholesaling activity)?

Q. Do you have batch numbers for any of the medicines on the list of concern?

Q. Of the 64 products identified by AIFA, is it possible for AIFA to differentiate this list of medicinal products into those that have a potential legitimate supply route out of Italy and those which have no potential legitimate supply route out of Italy?

AIFA (ITALY). AIFA (ITALY). The list was considered as a "support for inspections", a sort of watchlist, being based on documents issued by fake wholesalers; so, at this stage the recommendation is to use it for extra verification, not for recalls or seizures. In the examined documentation we have batch numbers, but since the batch numbers come from fake invoices, we are performing extra checks, connecting the purchase invoices with the selling ones. Our plan is to send MS Authorities data and copies of all confirmed invoices/trades by next week, including confirmed batch numbers; in this way, we will cover also the EMA point, i.e. the possible "final destination" of medicines. According to the picture we are building and to other ongoing investigation we are trying to liaise with, it seems that some specific medicines (doping substances and Botox, for instance) were destinated to the national black market, or to the web.

Q. What dates does your information regarding stolen medicines cover? i. e. how long have the companies been dealing in stolen/falsified medicines?

Q. When did this begin? What would be the recommended exclusion dates for consignments supplied to member states?

AIFA (ITALY). We have industry data for 2013–2014, and all Ministry of Health data from 2012 to 2014. According to our information, the case started at least 3 years ago (i.e. end of 2011, beginning of 2012). Since we are speaking about products with a very quick turnover, we performed a risk assessment, deciding to ask the Prosecutor the more re-

cent data; we would then recommend to focus on 2013–2014 purchases, at least for the moment.

Q. How can you state for a specific medicine (i.e. Mabthera and Avastin) that no legal export has taken place the last 12 months? Have you decided whether or not to extend the range of "12 months"? Also it would be helpful to know exactly when "12 months ago" is – is it April or May 2013, or what is behind this timeframe?

AIFA (ITALY). Italy has a full medicines traceability in place: all medicines packages are identified with an unique code, so we may check all trades/export/movements of medicines. You find some explanation (in Italian) and a picture (easier to understand) here *http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=1373&area=tracciabilita%20farmaco&menu=monitoraggio*. The "12 months" window means "after April 1, 2013".

Q. What kind of documentation does an Italian wholesaler need to export medicines to other EU–countries (special documents?, notification to authorities in Italy? Other?)

AIFA (ITALY). Only authorized wholesalers (authorized at local level; the authorization is notified to Ministry of Health) may export medicines; they may only export authorized medicines, obviously. There is an obligation to send all data about the export (i.e. medicine name and number of pieces) to the Traceability Repository.

Q. What enforcement measure is being undertaken against the Italian wholesale dealers involved? Have we an assurance that this pipeline has now been stopped?

AIFA (ITALY). They were inspected by the Police forces, all their transactions were examined and doublechecked by AIFA/Ministry of Health, and also the Italian Customs are verifying their trades. Some of the operators already stopped their activities, and the Prosecutors and the local authorities are planning direct actions on them. We noted a strong reduction in thefts after the beginning of investigations, even if we cannot be sure to have identified all channels – we still have thefts, but we don't know if they are related to a "delay" in stopping the "suppliers", or to another exporting channel. An update on the activities performed in Italy is already part of this White Paper.

Q. Is there any evidence of supply to the Italian market?

AIFA (ITALY). For the moment, we have no evidence with respect to the already evaluated products (i.e. the hospital ones), which we may confirm as being out of our legal distribution network. In Italy, parallel import procedures are related to a centrally issued authorization (managed by AIFA), so we already know that no parallel import was authorized for any of the already evaluated products. As mentioned above, according to the picture we are building and to other ongoing investigation we are trying to liaise with, it seems that some specific medicines (doping substances and Botox, for instance) were destinated to the Italian black market, or to the web (targeting Italian market) ; then, we will better evaluate this in the follow up investigations we are starting.

Afterword
Review by the HMA

On February 2015, this White Paper was provided to the HMA for evaluation, prior to submitting the paper to the European Commission.
Dr Ian Hudson, MHRA Chief Executive Officer, commented on the document as reported at p.27 under the heading “Further proposals”.

On May 11-13, 2015, in the occasion of the 80th HMA Meeting held in Ljubljana, Slovenia, copies of the publication were distributed to the participants. The publication of the White Paper on the HMA Website under the WGEO page was approved. Submission of the White Paper to the EC was also approved.

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TABLES

AIFA will keep in updating all documentation and databases related to the case, using the same web tools developed in the FAKESHARE/FAKESHARE II projects framework, already used during this crisis.
The restricted area of the *www.fakeshare.eu* website will be accessible to all registered users from interested institutions and stakeholders.