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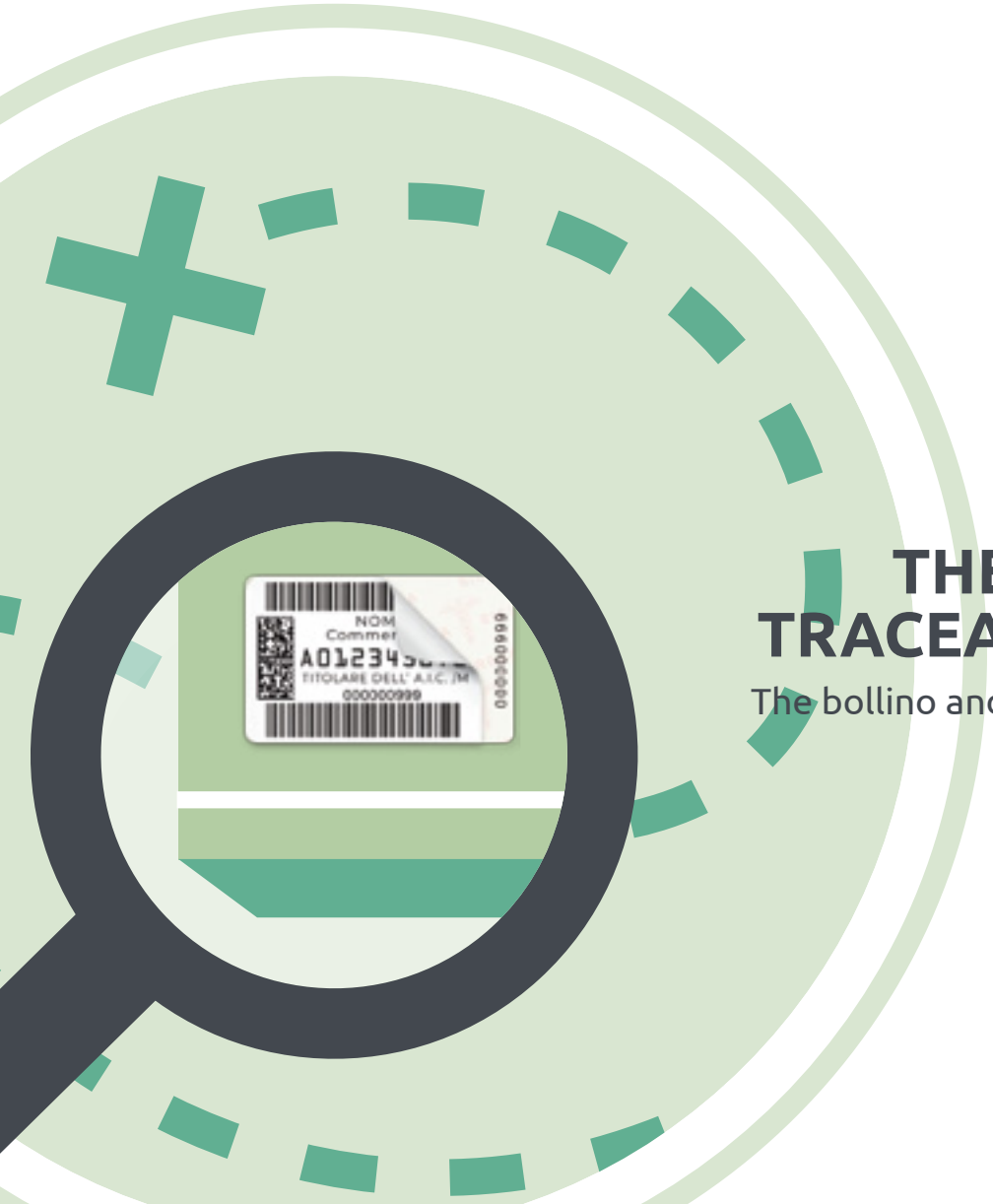

THE ITALIAN DRUG TRACEABILITY SYSTEM

The bollino and pharmaceutical verification

Ministero della Salute

AIFA
AGENZIA ITALIANA DEL FARMACO

Collana Tracciabilità Sanitaria

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ABBREVIATIONS

AIC – Autorizzazione all'Immissione in Commercio (*Marketing Authorisation*)
AIFA – Agenzia italiana del Farmaco (*Italian Medicines Agency*)
CDB – Central Database for Pharmaceutical Track & Trace (at the Ministry of Health)
IPZS – Istituto Poligrafico e Zecca dello Stato (*National printing house/Mint*)
MAH – Marketing Authorisation Holder
MoH – Ministry of Health
NSIS – Nuovo Sistema informativo Sanitario (*New Health Information System*)
SSN – Servizio Sanitario Nazionale (Italian National Health Service)

The Italian Drug traceability System has been in operation for years now.

In this period Italy has had to face a whole series of practicalities such as the **operational implementation by step,** the development of data and **process validation systems**, the activation of **warning signals**, the **integration with the GDP and the GMPs**, all experiences that could be configured as "good practices", to be shared at European level.

The competent institutions, then, have been able to use this system for a whole series of ancillary activities, such as **intelligence** activities to counteract and **fight against pharmaceutical crime**, the collection of **pharmacovigilance signals**, the management of shortages... even these experiences can provide the European Commission and the Member States with good practices in the implementation of the European traceability foreseen by the EU legislation.

This text intends to illustrate the characteristics of a mature system and its success story in managing both ordinary activities and critical issues in pharmaceutical distribution.

THE CENTRAL DATABASE FOR PHARMACEUTICAL TRACK & TRACE

The tracking system for the packaging along the intermediate and final distribution chain in Italy

In the past few years, a small number of countries have developed systems for tracking sanitary products (in this definition being included medicine, vaccinations and medical devices) as useful and efficient tools to contrast the counterfeiting and illicit distribution on the market.

"Tracking" is defined as t**he possibility of identifying the origin and the different steps in the production processes**. In the health sector, there are two reference models:

- **E– pedegree**, a model of traceability which allows the full traceability of a single packaging from the beginning to the end of the distribution. This model requires significant investments and changes in the working processes for each player of the distribution chain.
- **End to end model** allows identifying the authenticity of a package only at the end of the distribution chain. This model has a significant impact on the producers and on the finals steps of the distribution chain (pharmacies, public and private health facilities, businesses, professional offices, etc) but it also accounts the all distribution chain in a sort of *black box*.

The tracking system adopted in Italy for medicines was conceived by the legislator in article 40 of Law 39/2002 according to an E–pedegree model. Article 40 provided for the establishment at the Ministry of Health of a Central Database (CDB) with the aim of strengthening measures in contrast to possible frauds against public health and the National Health Service. The same law has referred to decrees of the Minister of Health for the operational discipline of the BDC feeding methods.

During the preparation of the first implementation decree, in the phases of confrontation with all the players involved, adopting immediately the E–pedigree model turned out too complex. A gradual implementation of the system was therefore envisaged, divided into phases: in exchange for this gradualness, requested by the stakeholders, an additional information charge was added, not envisaged by Article 40, concerning the economic values of the supply of medicines to the public facilities of the NHS. Moreover, the principle of trust between the actors of the supply chain is been applied, in order to reduce the data at the level of outbound movements.

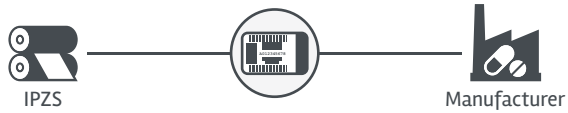
The Italian Traceability system currently adopts an intermediate model that is placed in between the "E-pedegree" and the "End to end model".

It is possible to identify two types of provisions: the first relating to the rules for unambiguous identification of the packages, the second relating to the methods of supplying the Central database. It is also interesting to observe the amount of time necessary to reach the current configuration:

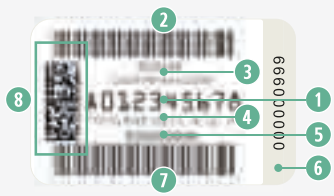
Unique identifier of an individual pack of a medicinal product	
2001	Decree of the MoH – 2nd August: introduction of an adhesive label with a progressive numeric ID code ("Bollino") for all medicines reimbursed by the NHS as unique identifier to a given pack of a medicinal product
2002	Decree of the MoH – 1st February: introduction of the "Bollino" for all medicines for human usage
2012	Decree of the MoH – 30th May: Progressive numbering of the labels affixed to the packaging of medicinal products placed on the Italian market
2014	Decree of the MoH – 30th May amending the Decree of the MoH – 2nd August 2001: introduces the "Datamatrix" as component of the "Bollino"

A secure repository: the Central Data Bank	
2002	Law 39 – 1st March (art. 40): creation, at the Ministry of Health, of a Central Database recording, on the base of the "Bollino" system, all movements of each drugs' package through the distribution chain, according with an "E-pedigree" model
2003	Law 14 – 3rd February: implementation of EU Parliament and Council Directive 2001/83/CE and adoption of the expected univocal drug coding system by the 1st July 2004
2003	Decree Law 269/2003 (art. 40): introduction of data recording related to the NHS drugs prescription
2004	Decree of the MoH – 15th July: definition of technical specification for the implementation of the traceability project in production and distribution (Phase 1)
2007	Decree of the MoH – 31th July: creation of a Central Data Bank recording data related to direct distribution of drugs through NHS facilities and pharmacies
2009	Decree of the MoH –4th February: creation of a Central Data Bank recording data about internat uses of drugs in NHS facilities
2011	Decree of the Ministry of Economy and Finance – 2nd November: Dematerialization of the NHS paper medical prescription, referred to in Art. 11, paragraph 16 of Decree.

In Italy, **the first step** to ensure control over the entire distribution chain of medicines, from their manufacture or import to the supply to the public, was been the **definition of the rules for identifying the packaging of medicines**. The National Mint Institute (IPZS) produces, at the request of the pharmaceutical company, adhesive labels ("Bollino") containing the progressive numbering to be applied to the packaging of medicines on the market in Italy. This choice currently ensures the uniqueness of progressive numbering and print quality.



The second step saw the involvement of different **players**, albeit operating in a unified vision, **of the distribution and dispensation of medicines** and the definition of the technical rules for the transmission of the data to the Central Database, data organized in more "Information Flows".

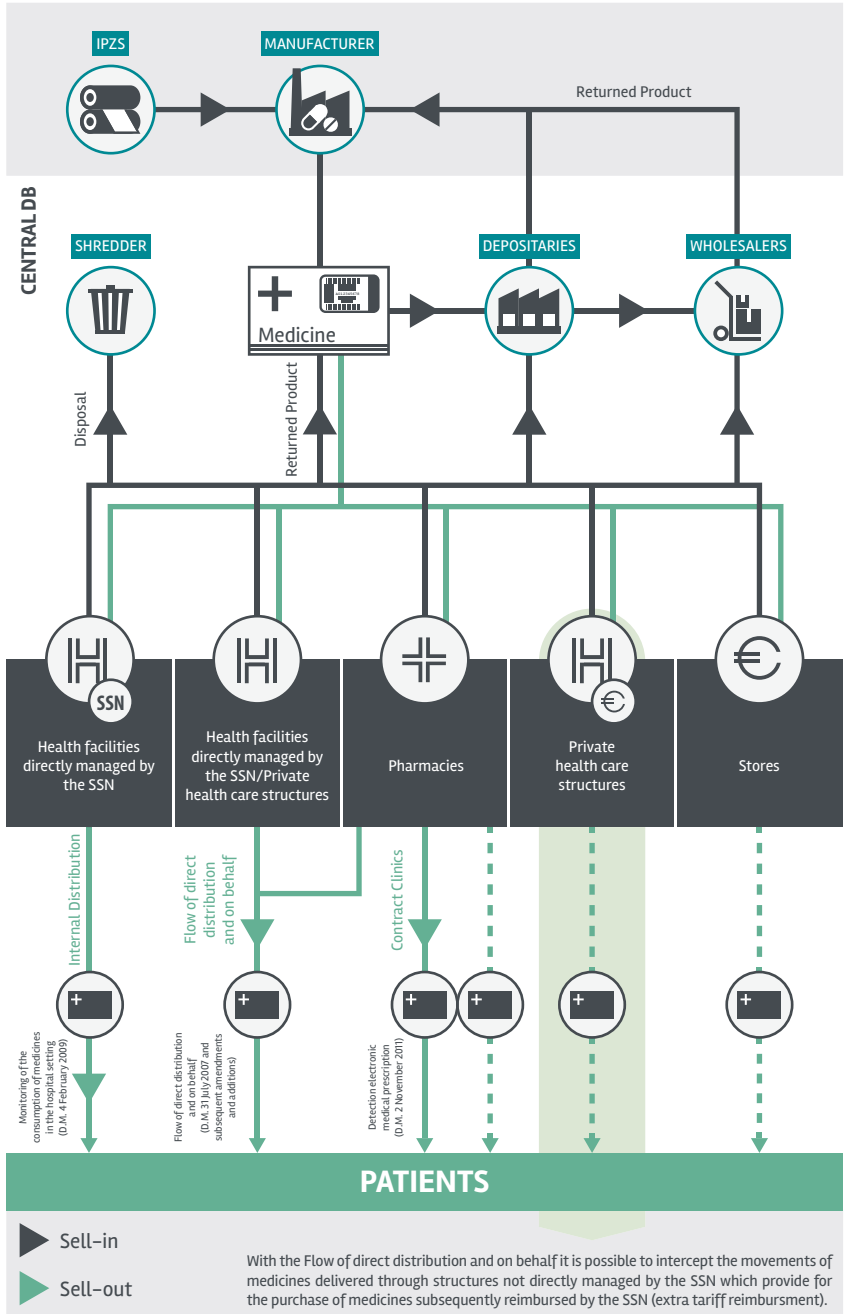


- The AIC code in both clear text 1 and 39 barcode 2 form;
- the name of the medicine with pharmaceutical form, dosage indication and number of dose units 3;
- the company that holds the AIC 4;
- the unique serial number (UID) in both clear 5 6 and barcode form 7;
- the two-dimensional representation (Datamatrix) 8 that contains the AIC code and the "Bollino"'s serial number according to the symbology Datamatrix ECC-200 (Decree of the MoH 30 May 2014).

"Bollino" information contents

As previously stated, in 2005 it has been decided to allow the supply of the Central Database in a sustainable way by all the players involved. After a detailed study of the main operations in charge to manufacturers and wholesalers about the activity of registration of medicines entering and leaving, the original model has been simplified and organized in a way that caused the loss of part of the detailed information respect the e-pedigree model, but has allowed the full launch of the project in short time.

The connections between the various information flows that govern the supply of the Central Database: intermediate production and distribution (D.M. 15 July 2004)



Decree of the MoH of 15 July 2004
The main simplification interventions of the e-pedigree model

- **Transmission to the CDB of outbound movements only:** the assumption is that there is a trust's relationship among actors, thanks to which addressee can consider reliable the data transmitted by the sender;
- **reduction in the number of players involved in the transmission of outbound movements:** MINT, manufacturers, wholesalers. Furthermore, because of the presence of manufacturers in other countries, the concept of "productive cloud" was introduced: the transmission of outgoing movements by the manufactures shall be ensured at least by the deposit that first inserted the packages on the Italian territory;
- **no transmission of the unique identification number of the package** (AIC code + progressive numbering) by the different players, with the exception of the IPZS and Manufactures. The serialization of the progressive numbering is a further simplification of the system: the MINT transmits to the CDB the range of labels supplied to the industry and not the single unique identifiers (from single unique identifier 1 to single unique identifier N) and the Manufacture transmits the range of labels (from single unique identifier M to single unique identifier P) used in a specific batch number with the relative expiration date.

Afterwards (Decree of 31 July 2007 and amendments, Decree of 4 February 2009 and Decree of the Ministry of the Economy 2 November 2011), the same methodology was applied to allow the detection of the data to end of distribution chain for the NHS: specific feasibility studies have allowed identifying data and technical specification about the distribution by the pharmacies and consumption of medicines in hospital: these data are collected by the Local Health Units of the NHS and transmitted to the Central Data Bank.

Transmission to the BDC of the data of the pharmaceutical prescriptions charged to the SSN, including the unique identifier of the package. The automatic reading of the unique identifier by pharmacies or hospitals is carried out at the time of the supply to the public (or at different times for what concerns the hospitals). However, the verification of the authenticity of the unique identifier is applied only at a later time.

This choice was determined by some considerations. First of all, the production and supply of the "bollino" stickers from the National Printing House to the MAH is strictly controlled and this ensures that the labels are available only to the producers. The second aspect is the cost/benefit assessment of the development of a technological infrastructure for online verification of the authenticity of the unique identifier due to the significant size of the pharmaceutical market in Italy.

This choice, obviously, was strongly conditioned by the forecasts in the Directive 2011/62/EU of the European Parliament and of The Council of 8 June 2011 and implemented in the recent EU Regulation 161/2016 which defined a

uniform system at European level for the fight against the counterfeiting of medicines, a system created through the inter–European integration of databases at national level and the definition of new mechanisms for the unambiguous identification of medicinal packages.*

But what is the size of the Central Database? The data set forth below may allow to understand the complexity of the system (update 2019).

Manufacturers	499
Agents	536
Wholesalers	1.378

Hospital/Facilities	2.807
Pharmacies	20.035
Stores	6.718
Sites for destruction	160

Number of packages recorded/month (the same pack is tracked more times)	~480.000.000
Number of transmitted files/month	>20.000
Number of transmitted records/day	~3.900.000

The development and management of the Central Database are in charge of the Ministry of Health. The Central Database is fully integrated into the technological infrastructure of the Ministry and is interoperable with the database of the medicines managed by the AIFA. The Central Database uses secure tools for data communication (digital and electronic signatures and secure protocols). In addition, it benefits from the security and protection measures envisaged for public administration data centres (high reliability, disaster recovery).

* Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use

In order to guarantee data confidentiality, a specific user authorization process is active for transmission and consultation. The Ministry of Health and AIFA can consult the data at a national level, while the Regions can consult data referring to their specific territory, as well as numerous benchmark reports at national level concerning data on pharmacies and hospital consumption. The other actors can consult the data they themselves transmitted to the Central Database. Furthermore, each addressee can consult the data transmitted by another person who has indicated it as a recipient.

All the technical information for the correct supply of the central database is made available to the public on the website of the Ministry of Health (www.salute.gov.it> Drug traceability section).
The elements which allowed the realization of this system, unique at international level for the national coverage that it covers, can be briefly summarized as follows

- Organization of the project in phases, but with a clear overall reference scheme. The formalization activity described in the feasibility studies prepared with the collaboration of all the actors was important.
- The subdivision into phases has also allowed the introduction of different players at different times, according to the indications provided for by the various implementation decrees.
- Complete and stable documentation for all the players, to reduce the impacts on the feeding systems over time.
- Evaluation of the impact of the verification of the unique identifier on the IT systems of the different players and, rather than anticipating it, harmonize it with the prescription.
- Availability of an efficient user support service.
- Where possible, ensuring the direct involvement of the players through the involvement of the associations. Over the years, there have been many sharing and comparison initiatives to fully understand the power supply rules of the central database.

The main uses of the data in the Central Database are briefly summarized as follows:

National Health Service's (SSN) expenditure analysis (pay back measures, expense caps monitoring)

Sunset Clause (lapse of the marketing authorisation in Italy) Monitoring

Analysis by the regulatory bodies in order to verify the authenticity of found or under investigation packages

Monitoring of distributive deficiencies

Verification of the export of medicines

Remote control of the supply chain

Since last April 2019 the CDB is been extended to the veterinary sector in order to monitor the distribution and the use of veterinary medicines for the animals.

BOLLINO
The Italian Security Label for Pharmaceutical Products

The IPZS prints 2.5 billion of Bollini per year, constantly committing to meet the needs of pharmaceutical companies, providing a dedicated service focused on continuous improvement. The Bollino system is perfectly integrated with all the production systems of pharmaceutical companies, since its appearance in the 90s.
The stickers are sold exclusively through a web platform based on a governmental authorization procedure. It is possible to operate on the web platform only after an exclusively digital approval process. The web platform allows the orders tracing, from the moment of the request until the delivery, with the possibility of checking the order status in real time by the customer himself.
Furthermore, the web platform allows companies to buy only the labels for which they have the necessary marketing authorizations.
The information on the "Bollino" (e.g. Commercial name, dosage of the medicine and the type of cancellation) are personalized by the customer in the web platform. Each artwork is associated to a unique identifier managed and deposited by the Poligrafico in a special repository system that represents an additional blocking element to the purchase in the absence of legal authorizations for placing on the market.

The italian traceability code issuing system is independent from the pharmaceutical industry. It meets the requirements of neutrality and completeness of information for traceability of the medicine, for the protection of the patient, for the monitoring of health status and levels of assistance, performing a further, very important, function: it is the instrument by which the Italian Ministry of Finance monitors the annual pharmaceutical expenditure, thanks to the fact that the unique identification code printed on the sticker is also the reimbursement code for drugs dispensed by the National Health Service.

TECHNICAL DESCRIPTION

Security features

The “Bollino” is a three–layer paper label.

The size of upper layer is 35x25 mm and it has been submitted to the UV dull paper treatment. The layer is printed on watermarked paper with addition–al security features as rhombus shape visible when the upper layer is held against the light and security fibers in light blue and yellow colours that react to UV light. The watermarked upper layer therefore ensures the authenticity of the bollino in case of specific evaluation.

Upper layer

The upper layer shows the following information:

- the AIC code in both clear and code 39 barcode form
- the company that holds the AIC in the Italian regulation system
- the name of the medicine with pharmaceutical form, dosage indication and number of dose units
- the unique serial number (UID) in both clear and barcode form.

The removed self–adhesive “Bollino” will be applicated on the medical pre–scription of the National Health Service without the use of other tecniques that could compromise the automatic reading of the codes thanks to a usage of water based acrylic glue on the layer.

The size of the lower layer is 40x25 mm. It consists of a silicone paper, not watermarked, with both functions of joining to the packaging of the medi–cine and allowing the separation of the upper layer for the application on the medical prescription. This layer is semitransparent with the text *“SICUREZZA”* and symbol of the caduceus printed in flexography with red ink on the whole

background. This layer shows the unique serial number (UID) in clear printed perpendicularly and covered by a transparent special coating.

Lower layer

It remains attached to the pack of the medicinal product for the entire period of its validity and in case of the attempts of removal it acts as anti-tampering device. In this way, every single pharmaceutical package is fully traced from the production to the final disposal, including the after-sales lifetime.

Security checks

The production is done according to GMP and ISO standards and the ISO-14298 Intergraph for security printing (Government Level). Productions subjected to the Security Printings control are identified and tracked, both for the compliant and non-conforming product, with the verification and the count of the single sample, in each processing phase, up to the delivery to the customer.

Poligrafico pursues customer satisfaction through the implementation of a Quality Management System certified according to the UNI EN ISO 9001

standard, under which it provides forensic test for authenticity if requested by the investigative authorities.

Traceability codes

Each package of medicine is uniquely identified through the combination, not repeatable for 10 years, of the AIC code (the marketing authorization code issued by AIFA the Italian National Authority responsible for human drugs regulation) and a progressive 9–digit numbering.

The unique serial number is issued by IPZS, the Italian National Printing House, and represents both the traceability unique identifier and the reimbursement code. The robust issuing system, developed under the ISO/IEC 27001 standard for the technologies of technical safety information, combined with a security printing solution is the only way to have a secure and reliable link between the digital world and the material one. This code, together with the AIC code, is able to be the guarantee of authenticity of each medicine pack.

Moreover, a further element of deterrence to counterfeiting is represented by the barcode interleaved 2 of 5 regulated by the ISO/IEC 16390. This element encodes the progressive number in clear plus the check digit. This check digit is not humanly readable and assures the correctness of the number, thus adding an element of security to the coding system.

IPZS designs and produces special features and technologies for secure identity and products, in particular security papers, security printing, identity documents, watermarked and security paper. Designs and develops installation and maintenance of infrastructure and application solutions related to IT services, digital archiving and preservation of electronic documents.

All products are made according to the with national and EU standards and according to the UNI EN ISO 9001 standard and in accordance the FSC–STD–40–004 certification “FSC – Chain of custody”. Thanks to this certification, IPZS guarantees the traceability of materials coming from FSC certified forests. IPZS guarantees the origin of the wood and paper used for its products and therefore demonstrates correctly and transparently its active

contribution to responsible forest management. It certifies that all chemicals, used for any kind of internal production, are fully compliant with the REACH guidelines. It means that IPZS carefully checks that all the chemicals purchased for the production of security paper are registered REACH. The productions subjected to the Security Printings control are identified and tracked, both for the compliant and non-conforming product, with the verification and the count of the single sample, in each processing phase, up to the delivery. In case of productions with numbering of the single specimen, it is possible to extend the identification and traceability up to the final use phases.

IPZS obtained also the UNI EN ISO 14001: 2004 certification, introducing an Environmental Management System and the ISO 27001:2017 Certification which proves its customers and stakeholders that the Poligrafico is able to effectively manage the information security. The ISO 27001:2017 provides a framework for information security management best practices. It has also obtained various certifications to attest the high quality standards of the work done. In addition to ISO 9001: 2015 "Quality management systems", the OHSAS 18001: 2007 "Occupational Health and Safety Assessment" has recently been B.U. Integrated Solutions Development obtained: ISO 14298: 2013 "Printing process management system with safety elements" and the FSC: Forest Stewardship Council and the ISO/IEC 27001: 2013 was also certified on the technologies of technical safety information.

CASE STUDIES

Use of traceability data in Italy, for the purpose of intelligence and investigation of potential incidents of falsification

The pharmaceutical verification/authentication system was implemented in Italy to ensure control over the entire chain of distribution of medicines, from their manufacture/import to their supply to the public, through the serialisation and traceability of all marketed packages.

Nowadays "The medicinal products' Traceability System" allows monitoring of about 2.45 billion packages of medicine and is definitely an effective tool to struggle possible fraud in the trade of medicines, which could be a risk for public health and a detriment to the NHS and treasury.

Traceability data are currently used for investigation and intelligence purposes: Ministry of Health, AIFA and enforcement bodies (mainly Carabinieri NAS – the specialized police force dealing with health related issues, but also Customs, financial police and others) cooperate in analyzing and evaluating the available information, with the goal of targeting possible infiltrations of illegal products, frauds and other kind of pharmaceutical crime, as for the following case examples:

- Volcano Operation
- "Car trunk" case
- Illegal export of "lost" packages
- Distribution disruptions and shortages
- GDP verifications
- Rapid Alert from the UK on fake or missing "bollino" stickers

Volcano Operation

Theft of medicines (from hospitals and on the ground –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 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: the goal was to gather and analyze data, by using also the existing ones (such as traceability data), in order to develop scenarios for understanding the channels where the stolen products were recycled.

AIFA then set up indicators for testing the different scenarios, in order to be ready to process any signal from the field giving clues about the recycling channels.

In March 2014, a signal about a suspect/manipulated products was received from Germany, with respect to a parallel trade products originating from Italy: the problem was related to batch numbers, not matching the ones on the outside box.

Verification of the unique identifier(s) confirmed the supposed destination of the product in Italy – an hospital. The verification on the batch numbers vs AIFA database on thefts also allowed to identify the possible events related to the "mixed up products".

German invoice allowed to discover that the German product was sourced through a UK trader; the UK supplier bought the product from an Italian wholesaler. Checking the invoice of the Italian wholesaler allowed to identify other hospital only products, that were checked in the Italian T&T system.
All transactions related to the above mentioned products were verified in the T&T system.
The result of the verification was a list of operators (trading the suspect products) and transactions for exporting/supplying the products: all transactions were traced back to the first visible source.
MAHs were then involved in verifying if the first visible source was actually supplied by them: the confirmation of the absence of supply allowed the identification of a list of "contaminated operators".
Verification triggered an "avalanche effect": AIFA/MoH started by verifying one product (Herceptin, in Germany), identified as illegal through T&T; UK invoice led to five products (the ones in the Italian operator invoice to UK), also identified as illegal.

Checking the transactions regarding the five products in the T&T system allowed to identify more operators, and their transactions led to the development of a larger list of products, object of a first Rapid Alert.

In order to generate more signals to be investigated, AIFA asked MAH and 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 MAH of hospital medicines listed to specify if they sold products to wholesalers (IE 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.

As a result of this exercise, a list of product for which the distribution was exclusively intended for 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 previous RAS, and recommends to quarantine the suspect goods until further verification of the trade.

The goal of this exercise was to support the research of any other illegal channel that is still out of the investigation: any signal was evaluated (through traceability data and verification with MAH) and, if confirmed as "suspect", forwarded to police/prosecutor for the follow up activities (EG inspections and seizures), in preparation of further update of the Rapid Alert.
The final figures are summarized in the "Volcano Operation White Paper" for the EC (published on November 2015): thousands of illegal trades, tenths of police operations, tenths of millions of euros of seized products, etc., with impressive short term results in terms of reduction of the criminal phenomena (eradication of hospital thefts, strong reduction of pharmaceutical thefts as a whole).

All Rapid Alerts, black lists of operators, NUI for suspect products/operators were developed by **using data from the Italian T&T system**, as a data source for preventive intelligence and for reactive initiatives.

“Car trunk” case

A side case related to the Volcano Operation: during a search, police forces found hundreds of packages of an Italian medicine in the car of a foreign operator.

Checking the batch number in the database on thefts allowed to identify them as “suspect” – then an in depth verification in the T&T system and in the MAH database was performed.

T&T system and MAH data allowed to identify the unique identifiers connected to a specific theft, corresponding to the ones found by the police. The identification of the products as “stolen”, and their connection to a specific filed event, allowed police forces to immediately seize the product and the car, and to charge the operator for illegal trade, laundering, etc.

Illegal export of “lost” packages

AIFA received an informal signal about “non registered thefts” (single packages “lost” in hospitals) being used for gathering products to be exported: a possible “model” for controlling this kind of trade was then developed (IE: when checking export activities during inspections in the field, pay attention to supplies involving small quantities of many different batches of the same product).

A first supply of this kind was found a few weeks after the signal: Carabinieri NAS sent AIFA/MoH information about a suspect trade, providing also the available unique identifiers.

T&T/MAH data confirmed that at least some of the identifiers were related to a supply to a specific hospital: the products proposed for export were then not available to wholesalers.

In another case, two separate occurrences products found on the market of third Countries, bearing unique identifier that were already considered as “decommissioned”, since the product were sold to an hospital (and already transferred from the hospital pharmacy to the departments – from where the medicines were probably stolen), allowed to identify a possible scheme for diversion, involving insiders from an hospital and other distribution operators.

The first police investigation on the case was recently completed (an operator was charged), whilst the second is currently ongoing.

Distribution disruptions and shortages

In European regulation there is no harmonized definition of "shortages of medicines" or "unavailability of medicines," nor of "critical and/or irreplaceable medicines": this is a key issue in setting up any law enforcement strategy against the phenomenon.

The two issues identified at European level as "main roots for shortages" should refer to two different situations, linked to different actors and macro-phenomena:

- manufacturing shortages (due to problems of drug manufacturers), often related to the non-profitability of low price / old medicines,
- distribution unavailability (due to distribution operators), often related to "parallel trade", IE sale between wholesalers operating in different MS, related to price differences on different markets, and in particular to higher average prices in countries such as Germany, where the parallel trade is fostered through regulatory tools.

The unavailability is due primarily to economic factors related to the distribution network, EG the parallel trade exploiting price differences within the European market.

Over the years, several strategies for combating this type of distortion have been proposed and implemented, and even the (definitely unlikely) imposition of an "average European price" comparable enough to discourage the export to more profitable markets has been from time to time mentioned in the discussion.

Italy started in 2015 an intersectorial cooperation between central/Regional authorities and manufacturers/ wholesalers/ retailers associations, aimed at verifying the roots for lack of availability of some medicines on the Italian market.

T&T data allowed to identify some "key products" to be used as a reference in ad hoc verification in the field, with respect to some illegal transactions, used for "raking" products to be exported.

T&T data and intelligence activities performed at central level by AIFA/MoH triggered inspections to wholesalers, identification of illegal trades (EG pharmacies selling to wholesalers) and sanctions to operators.

The interim result of the activity was a reduction of the impact of the phenomenon, and the prevention of the lack of supply for some key products.

GDP verifications

Traceability data may also be used in supporting the on site GDP verifications performed by Regional inspectors: the central traceabilty system developed ad hoc queries that may be launched with respect to operators and key products, that may be used by the inspectors as an extra resource for double checking trades and invoices. This tool was particularly useful in verifying non compliant trades related to processes generating shortages and marketing disruptions in Italy (see above), also with respect to signals received at an international level (see below): after a pilot phase started in 2018, some Regional authorities already incorporated the tool in their standard procedures for GDP verifications.

Rapid Alert from the UK on fake or missing "Bollino" stickers

Following two reports issued by Germany (October 08 and November 21, 2018), where bollini labels have been suspected to be manipulated and then confirmed as falsified, upon further investigation, the Italian authorities detected additional cases of bollini labels falsification related to hospital medicinal products, in particular

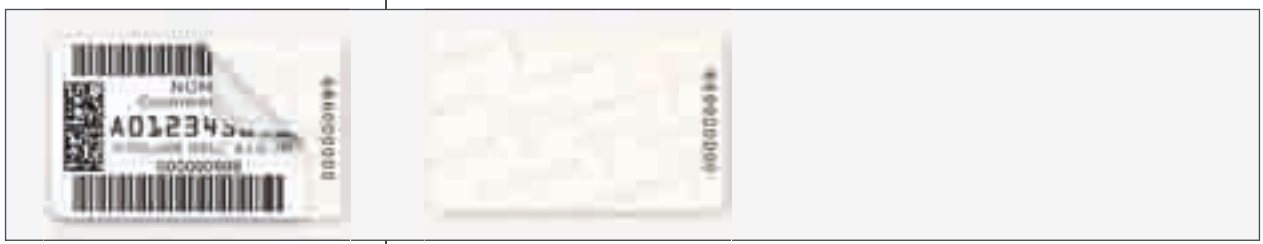
- Standard pharmacy medicines bought by wholesalers in "hospital package", and sold to pharmacies or exported after having substituted the stamped bollino with a fake one bearing the same unique code, but no indication regarding the hospital use;
- Anti-cancer drugs, sold without bollini stickers on the outer box/ carton:

In both cases, the products have been considered as possibly falsified medicines, as for the EU definition:

- Products bearing a falsified "bollino" bear a counterfeit component in the packaging;
- Products with no "bollino" could have been sourced via theft, and sold via fake credentials.

Then, in February 2019, two Non Urgent Information Documents were launched, in order to gather signal regarding suspicious products bearing Italian safety features, distributed in the European network, mainly through Parallel Distribution trades.

A second "Alert" activity was then performed in July 2019. Following the FMD ALERT MDR 123–05/19 issued by MHRA on June 27, 2019, where medicines have been suspected to be taken out of the regulated medicines' supply chain during distribution and later re–introduced, on Falsified documentation and without the "bollino" stickers, the Italian authorities asked for additional checks on the products object of the MHRA Alert.
In order to prevent the distribution of falsified medicines through the parallel distribution channel, AIFA asked to communicate any anomalies with regard to the offer of medicinal products missing the "bollini" labels or showing dif–ferent features from those described in the AIFA NUI dated February 6th, 2019.



A bollino sticker with upper (sticking) level and lower level (left) and the lower, serialized level of the bollino sticker (right): packages seized in UK were missing the upper level.

Italian medicinal products **without** the "bollino" sticker (i.e. with the serialized lower layer on the box, but missing the sticker – see image above) are consid–ered non–compliant with Italian requirements, and can potentially be linked to fraud in the "national health system" or to other illegal practices.
As some of the medicinal products listed in the MHRA's FMD ALERT are among those currently in "short supply" in Italy, AIFA specifically asked to check **in particular the packages of Neupro, Vimpat, Clexane and Spiriva** imported from Italy, due to the risk that the supply of these medicines could have orig–inated from not authorised sources.
In all the above mentioned cases, traceability data were then used for check–ing any reported export activity, validating those correctly traceable in the

system and in the Italian distribution chain, and starting an in depth investigation on the suspicious ones.

As a follow up to those investigations, two criminal networks exporting illegal medicins were dismantled:

- The first network was exporting hospital packages bearing a fake bollino, whilst the original sticker was sent to reimbursement through fake prescription: NHS was then paying for medicines that were never used in Italy, having been exported to other EU MS – mainly Germany and UK. In January 2019, two pharmacists were arrested and charged for the coordination of this criminal plot.
- The second network was exporting medicines obtained through fake prescription, traded out of the Italian traceability system, was dismantled. In November 2019, 14 people were charged for illegal behaviours related to the "missing bollini" case.

GMP-RELATED ASPECTS

The "Bollino sticker" is directly applied on the pharmaceutical package: then, being considered as part of the packaging, GMP rules are applicable to its management, from the manufacturing to its application to the pharmaceutical package, to be performed as for GMP labeling operations.

The technical requirement for the manufacturing of "Bollino" are defined in the regulation: all aspects related to adhesivity, quality of printing, compatibility with the materials used for pharmaceutical packaging were then considered in the development of the technical annex to the regulation, as for the qualification of materials defined in EU GMP rules (see 5.45 for qualification of materials).
When developing the technical annex, National Mint had to take into consideration aspects such as variations in labelling and storage conditions, physical characteristics of the application substrate, required levels of resistance to solvents, moisture, UV rays, performance requirements at different temperatures, and also specific technicalities such as the difficulties related to packaging materials and operations (e.g. bags used for some non standard products).
With respect to the application of "Bollino", EU GMP 5.46–5.50 (labeling) are applied, with a particular focus on accounting of UI and discarded materials. This is related to non GMP aspects, someway overlapping with the GMP ones: "Bollino" is also classified at the same level of security of banknotes and stamps, then accounting of the units used and damaged/discarded during the manufacturing process is required, in order to avoid frauds and other infringements related to financial regulation. Data about discarded unique identifier are then generated and stored in the manufacturing documentation, generating extra requirements to be harmonized with the GMP ones.

Since all the mentioned requirements for "Bollino" management are evaluated in the GMP framework, Italian GMP inspectors routinely evaluate them during inspections to manufacturing/packaging sites: this issue is considered by AIFA in the inspection procedures and in the training programs for GMP inspectors.

FUTURE DEVELOPMENTS

About safety features of medicines pursuant to Regulation 2016/161, IPZS has developed a project that concerns the realization of an anti-tampering device in cases where the packaging of the medicine is legitimately opened (for example for the replacement of the leaflet in case of parallel trade or for rework by the manufacturer).
In the event of repackaging, in accordance with Article 47bis of Directive 2001/83/EC, the ATD (Anti Tampering Device) must be replaced with an equivalent one, after verifying that the medicinal product in question is authentic and has not been tampered with.
Through the introduction of specific safety elements, this project merges the European Commission Directive 2001/83 according to which traders/producers who want to reseal the packaging of medicines must provide the competent authority of the Member State of destination with sufficient information to allow an evaluation on the effectiveness of the new anti-tampering solution of the device and on the equivalence with respect to the one legitimately tampered with. The Directive provides that:

- the holder of the manufacturing authorization checks that the medicinal product is authentic and has not been tampered with before removing or completely or partially hiding the safety features;
- the manufacturing authorization holder replaces the safety features with other equivalents in terms of possibility of verifying the authenticity, identification and possible tampering;
- the replacement of the ATD is carried out according to good manufacturing practices;
- the replacement of the safety features is subject to the supervision of the competent authority.

The solution could also be applied to OTC (Over-the-counter drugs) for which the EU Regulation does not provide any safety system.
In this case, the ATD would be configured both as a support tool for the identification code (to guarantee authenticity and traceability) and as an anti-tampering element.
This issue is particularly felt given that OTCs are the only drugs that can be sold on the Internet, the most dangerous distribution channel in terms of potential frauds among those active today. The label could therefore become a

voluntary system that can be implemented by “virtuous” companies as a sign of authenticity and quality.

It provides a tamper–evident label to safely repackage the medicine. The label has physical and logical safety characteristics (e.g. a unique identification code). The use of an anonymous label without an identification code would not guarantee the legitimacy of the replacement as anyone could apply it to close the packaging following tampering and fraud.
The ATD has a polypropylene adhesive plastic support with physical (hologram, UV inks) and logical (an identification code) safety features that guarantee the originality and uniqueness of the label. The identification code of the label is an 8–digit alphanumeric serial.
Since it could overcome the unique identifier of the medicine, provided for by the Regulation, the ATD is transparent so as not to affect its legibility.
The label has precuts that guarantee the breakup of the same only in the area where the package is opened and do not affect the reading of the code, the batch number and the expiry date, which are the most relevant information for the patient and must remain legible even after the box is opened.

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