SD COLLECTION

2022 SPECIAL

PHARMACOVIGILANCE, MDR AND QUALITY

SafetyDrugs
PHARMACOVIGILANCE SOLUTIONS

SUMMARY

HOW TO MANAGE COMPLAINTS AND THEIR IMPACT ON SAFETY

COMPLAINT MANAGEMENT IS A PROCEDURE THAT AFFECTS EVERY COMPANY, BUT IN THE PHARMACEUTICAL FIELD IT CAN ALSO HAVE CONSEQUENCES ON THE PATIENT'S HEALTH.

Dr. Eleonora Corbetta spoke about **complaint management** at the AFI webinar “Pharmacovigilance and quality session”.

The coming of the complaint is a matter that, due to its potential impact on patient safety, must be managed and analyzed following targeted processes, useful for resolving the dispute.
Dr. Eleonora Corbetta, Qualified Person and Quality Assurance manager for the penicillin and sterile lines of ACS Dobfar, shared with the participants in the AFI webinar "Pharmacovigilance and quality session" what is her experience in handling complaints in her own business reality.

RECEIPT OF THE COMPLAINT AND IDENTIFICATION OF THE TYPE

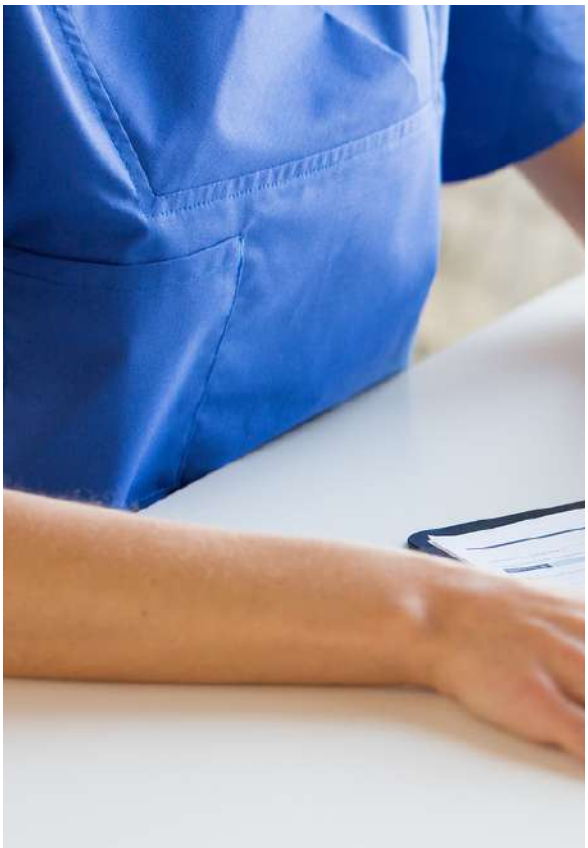
The complaint usually arrives via email by filling in a form by the customer from which it is possible to understand the **type of complaint**. In the reality of ACS Dobfar, which produces sterile products, in particular injectable antibiotics, these can concern positive sterility, foreign material, out-of-specification chemical analyses, out-of-specification microbiological analyzes and non-compliance packaging.

For any pharmaceutical company, in any case, knowing the type of non-compliance found by the customer is essential to make a first hypothetical estimate of the misunderstanding that occurred and it is also essential to ask the customer as many details as possible to better address the internal analysis. For example, in the case of an out-of-specification situation, the customer must provide the tests performed by him.

IDENTIFICATION OF THE ORIGIN OF THE COMPLAINT

It is therefore important to know the **origin of the complaint**, which may be due to:

- problem on Advance Samples
- problem during the stability stations
- problem after filling / packaging the batch not yet released on the market
- problem on the batch released both by ACS and by the customer and already placed on the market



IDENTIFICATION OF THE COMPLAINT CLASSIFICATION

The type and origin are essential to determine the **classification of the complaint**. This must take place immediately after the receipt of the complaint by the customer in order to determine the most important aspect, that is the impact on the SISPQ (Safety Identity Strength Purity and Quality of the product). The complaint has **three classifications** based on its severity in relation to the potential harm to the patient:

- **critical complaint**: the complaint has a very high priority as it has an impact on the customer (for example it has already been placed on the market). In this case, complaint handling times must be very fast. ACS Dobfar internally established a maximum limit of 7 days for the investigation.
- **major complaint:** the complaint has a high priority as it has a potential impact on the patient (for example, it has not yet been placed on the market or has already been placed on the market, but has not yet reached the patient). ACS Dobfar internally established a maximum limit of 14 days for the investigation.
- **minor complaint**: if the complaint does not have an impact on the SISPQ, it will have a low priority. ACS Dobfar has internally established a maximum limit of 30 days for the investigation of the complaint.

INTERNAL ANALYSIS

Upon receipt of the complaint, the QA will carry out an initial risk analysis and immediately afterward a more **in-depth investigation is carried out in a meeting** with the departments concerned and with the Qualified Person, responsible for placing the lot on the market and therefore, also of his future life.

The following **phases** will take place during the meeting:

- **Confirmation and reassessment of the seriousness of the complaint and its classification**: the complaint will be assessed in an interdisciplinary manner and may be downgraded if further useful information is received by re-evaluating, or if during the time elapsed between receipt of this and the in-depth assessment meeting to decline this claim.
- **planning of activities for investigation**: once the complaint has been classified, the activities necessary for its investigation will be planned. These will obviously adapt according to the type, so for example in the case of a complaint about a foreign body, it will be necessary to conduct the investigation also at the laboratory level to verify the nature of this particle. It would be a good idea - suggests the doctor - to have the specific spectra of all the materials present in the company in their laboratory libraries, in order to reduce time and resources to find the corresponding material.

Once the material has been identified, it will be possible to plan the activities that always include the control of the batch record and the analytical sheet of the batch involved and the training of operators who have developed over the production and analysis of batches.

It may also be necessary to perform analytical tests again in order to verify the compliance of the product with the specifications and to confirm or not the data found by the customer.

- **planning and verification of stocks in the warehouse and possible segregation**: activity necessary to check if the entire quantity of the batch has been sold. If so, it will be necessary to investigate who the buyers were, in order to be able to notify all interested parties of the ongoing investigation; in the negative, the segregation of stocks will proceed.

INVESTIGATION

At this point the most important part is identifying and **analyzing the root cause**. To do this you can use the various tools offered by the guidelines, such as the "5 why", rather than the Ishikawa diagram. A fundamental thing, also for inspection purposes, is to never underestimate any probable root cause: if the problem is recurring (easily highlighted by the KPIs) you cannot always limit the attribution of the issue to the usual cause, but, every time it is necessary to analyze every probability and possibly, if any evidence collected allows it to be discarded, report the reasons why it was excluded, otherwise keep it and evaluate it together with the others. For each of these it is necessary to analyze your own Quality System in order to determine whether it allows you to totally eliminate it or not. In the event that the probable root cause is eliminated from the Quality System, but the investigation reveals that there are failures in our system, it will be necessary to fill these failures by identifying the **CAPAs**.

CAPAs can emerge both due to failures and probable root causes. As well as the complaint, these will be managed with a data integrity system in compliance with CFR 21 part 11, which allows us to track both the complaint, the CAPAs, and any deviations related to it.

At this point you can proceed by **determining whether the complaint is justified or not justified**.

Once the complaint investigation/management process has been completed, It is possible to **analyze the trend** on a quarterly and annual basis both with QA and with upper management and QP.

COLLABORATION BETWEEN PHARMACOVIGILANCE AND QUALITY: HOW TO MAKE IT POSSIBLE WHEN THE AFFILIATES HAVE DIFFERENT NATURE

DURING THE AFI WEBINAR "PHARMACOVIGILANCE AND QUALITY" ON 27TH NOVEMBER, DR. DONATA SADDEMI AND DR. BARBARA BELLONI RESPECTIVELY PHARMACOVIGILANCE MANAGER & REGULATORY ASSOCIATE AND QA MANAGER & QUALIFIED PERSON OF THE PHARMACEUTICAL COMPANY RECIPHARM ITALIA, ILLUSTRATED THEIR COMPLAINT MANAGEMENT FLOW.

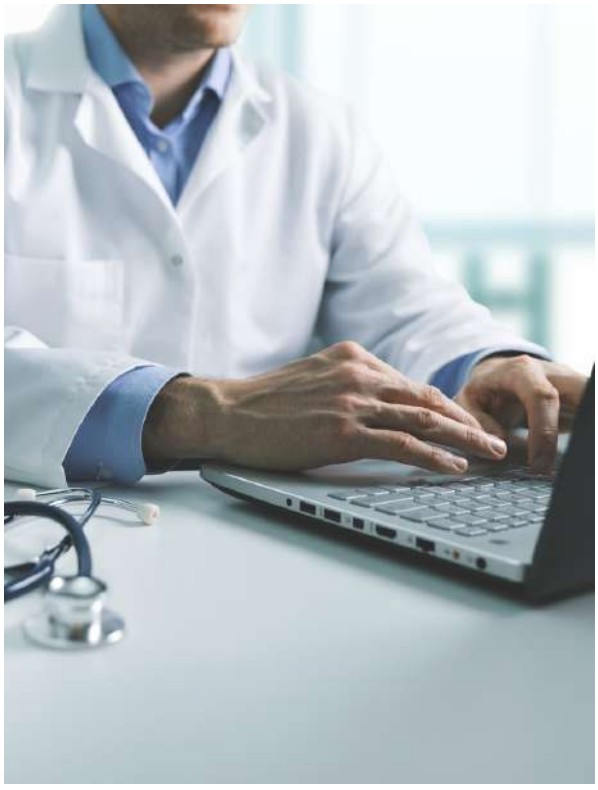
The reality of Recipharm Italia can be more complicated than other situations as it is a group composed by four production sites, two of which are Marketing Authorisation Holders.
For the complaint management has been developed a flow that meet the two variables: involvement of the company as a production site, therefore in the event that the object of the complaint is the product of a customer, or involvement as MAH.

The **flow**, developed **in synergy by the quality and the pharmacovigilance department**, evolves as follows:

1. **Receipt** by the quality department of a **complaint** about a defect and/or adverse event
2. **Registration** of the complaint by the quality department
3. **Internal notification** to the pharmacovigilance department. If, on the other hand, pharmacovigilance receives the report directly, then it has to report to the quality department, which will register the complaint.
4. **Execution of the analysis**. The pharmacovigilance department looks for any safety information. If so, the second variable will be analyzed, which is the ownership of the product. If Recipharm is involved only as a manufacturer, it is necessary to transfer the information to the client company according to agreed times and methods; if the ownership is of Recipharm, then the pharmacovigilance department records the data in the pharmacovigilance database. The quality department, in parallel, starts the qualitative investigation which includes: document review of everything that may concern the defect; review of historical data to highlight any Trend (analysis both by product and by defect); analysis of counter samples and claimed samples;

5. After the analysis, we proceed with the **determination of whether or not the complaint is confirmed**.

In both cases, the investigation is closed and a final report is issued which is sent to the customer. However, if the complaint is confirmed, it is possible to intervene with actions on the batches and, in extreme cases, it may be necessary to recall the batch. All activities are tracked in the quality system. The customer, especially in the case of subcontractors, can comment and possibly addendum to complaints. In any case, the information passes through the pharmacovigilance, if there is an impact on safety it must integrate the information that emerged through follow up. In the event that the subject of the complaint is a product owned by Recipharm, the pharmacovigilance will update the data in the database, if instead the product is a third-party account, all the information is transferred to the customer's pharmacovigilance within the agreed timescales.



Beyond the individual complaint submission cases, there are **several other activities that the Quality and Pharmacovigilance departments must carry out**, including: **reviewing and linking complaints and pharmacovigilance procedures, staff training, review of the Quality Agreement, the revision of the SDEA** (Safety Data Exchange Agreement), **the reconciliation between departments and between customers, and finally the analysis of trends**. The latter, to be carried out annually, checks the number of complaints, the number of adverse event, the type of events and root causes. In the event that a trend emerges, it is necessary to proceed with the definition of the additional actions that must be traced in the quality system.

These are all activities necessary to guarantee the safety and efficacy of the products, as well as their quality.
Patient safety is a very complex world - the two doctors conclude - the collaboration and integration of the quality and pharmacovigilance departments is therefore fundamental.

MDR AND INFORMATION FROM THE MANUFACTURER: ALL THE NEWS

WITH THE ENTRY INTO FORCE OF THE MDR THERE ARE SEVERAL AREAS THAT HAVE BEEN REVISED AS THEY ARE TREATED MORE ROUGHLY IN THE OLD DIRECTIVE, AMONG THESE THERE ARE ALSO THE INFORMATION SUPPLIED WITH THE DEVICE: IN ORDER TO PRESENT THE CORRECT USE OF YOUR DEVICE , EACH MANUFACTURER IS IN FACT REQUIRED TO AFFIX ON LABELS, PACKAGING AND INSTRUCTIONS FOR USE, ALL THE INFORMATION NECESSARY FOR ITS USE, SUCH AS THE RISKS AND BENEFITS, OPERATING METHODS, CE MARK, ETC. LET'S SEE THE UPDATES.

THE NEW OBLIGATIONS OF THE ACTORS

The obligations of the actors foreseen in the old Directive have not changed, however the new Regulation adds some. Here they are divided according to the reference person:

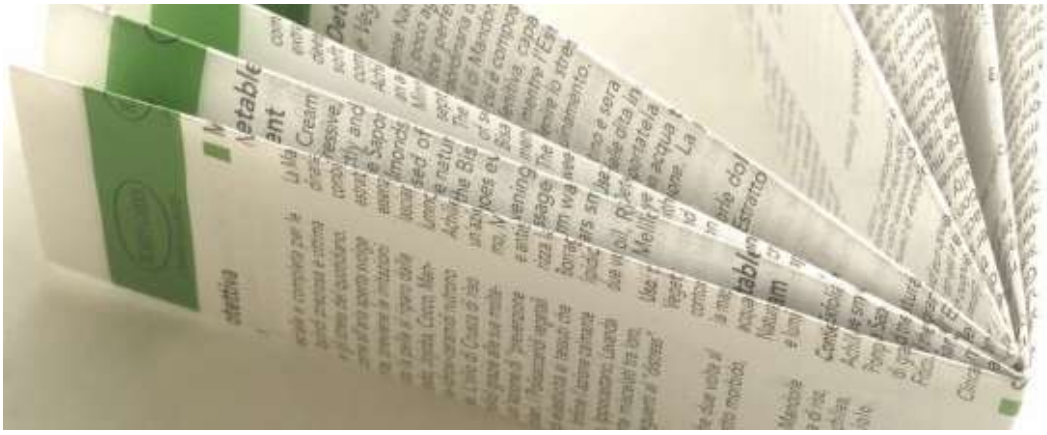
- **Manufacturer.** The manufacturer must ensure that the device is provided with the necessary information in the official language of the Member State where the device is made available. In addition, he must ensure that the information on the label is indelible, easily legible and clearly understandable to the user or recipient patient.
- **Importer**. The importer is required to verify that the device is equipped with the instructions for use, that it is labeled in accordance with the Regulations and that the related information is visible and not covered by any other labels. Furthermore, he must indicate on the device, on its packaging or on a document supplied with the device his data such as name, trade name or registered trademark, registered office and address.
- **Distributor**. Before making a device available on the market, the distributor is required to verify that the CE marking has been affixed, the EU declaration of conformity has been drawn up and that the information that must be provided by the manufacturer is present. The distributor must therefore ensure that the manufacturer has carried out his duties and cannot for any reason distribute a product whose requirements have not been met.

THE LABELS

Un'importante novità riguarda le etichette: l'apposizione del vettore UDI, il codice alfanumerico di identificazione univoca del dispositivo, che ricordiamo deve essere presente sia nel formato leggibile (HRI - Human Readable Information) sia nel formato per la trasmissione elettronica (AIDC - Automatic Identification and Data Collection).

The affixing of further details is provided only in the case of particular devices:

- The labels of **reprocessed disposable devices** must **indicate the number of cycles already performed** and any restrictions on the number of reprocessing cycles allowed.
- The labels of devices consisting of one or more substances must report the overall **qualitative composition of the device and quantitative information on the main components** responsible for carrying out the main action envisaged.
- Active implantable device labels should include **serial and lot numbers** if applicable.



THE PACKAGING

The only type of packaging subject to implementation is sterile: the MDR states that **information such as sterility certification and sterilization method must be present**; description of the device; date of manufacture and limit of use / plant; warning that refers to the instructions for use in case of damage to the packaging or inadvertent opening; manufacturer data; possibly indication "intended exclusively for clinical investigations" or "custom device".

INSTRUCTIONS FOR USE

As regards the instructions for use, the changes with respect to the MDD concern the **affixing of** the following information: expected clinical **benefits and risks** associated with the use of the device; summary of **safety and clinical performance**; **date** of publication of the instructions for use or any revisions; notice indicating the need to r**eport any serious accident to the manufacturer and the competent authority of the Member State** in which the user and / or patient is located; requirements regarding particular infrastructures, specialized **training or specific qualifications** of the user of the device and / or other people.

Additional information needs to be added in case of specific categories of devices:

- **refurbished devices**: notice about the **reusability of the device** only if it has been refurbished under the responsibility of the manufacturer
- **devices consisting of substances or combinations of substances**: warnings and **precautions** relating to the general profile of interaction of the DM and its metabolic products with other devices, medicines and other substances as well as **contraindications**, unwanted side effects and the risks related to overdose
- **implantable devices**: overall **qualitative and quantitative information** on the materials and substances to which patients may be exposed
- **devices intended for use by lay users**: information on when the user should **consult a healthcare professional**
- **devices that contain programmable electronic systems**, including software, or for software that are devices in their own right: minimum hardware requirements, characteristics of **IT rules and IT security measures,** including protection against unauthorized access, necessary to make the software work as intended.

CONSIDERATIONS AND DECLARATIONS

Each manufacturer, in drawing up the information, must take into consideration the target users by analyzing the type of intended consumers (doctor, nurse, patient, etc.), the relative characteristics (functional capacities, levels and behavior of experience and knowledge) and the their level of training.

In addition to paying attention to the end user, the manufacturer must keep in mind that, according to Article 7, "In the labeling, instructions for use, making available, putting into service and advertising the devices it is prohibited the use of texts, names, trademarks, figurative or other images and signs that could mislead the user or patient as regards the intended use, safety and performance of the device:

- attributing to the device functions and properties it lacks
- creating erroneous impressions about the treatment or diagnosis, functions or properties that the device lacks
- failing to inform the user or patient about a potential risk associated with the use of the device according to its intended use
- proposing uses of the device other than those declared as part of the intended use for which the conformity assessment was carried out "

MDR AND THE DELEGATION LAW: THE AREAS TO BE REDEFINED

A LITTLE MORE THAN A MONTH FROM THE DATE OF FULL APPLICABILITY OF THE REGULATION ON MEDICAL DEVICES 2017/745, THE TRANSPOSITION OF THE EUROPEAN DIRECTIVES AND THE IMPLEMENTATION OF OTHER EUROPEAN UNION ACTS, IN ITALY PASS FROM PARLIAMENT TO THE GOVERNMENT, AS SANCTIONED BY THE DELEGATED LAW N. 53 OF 22 APRIL 2021.

The art. 15 of this **Delegation Law establishes the principles and criteria for the adaptation of the national legislation to MDR 2017/745.** We remind you that the Regulation on Medical Devices is actually already in force from 26/05/2017, but that its full applicability took place on 26/05/2021, after the transition period initially envisaged of 3 years and then extended for a further 12 months due to the Covid-19 pandemic.

The Government must adopt, , within 12 months from the date of entry into force of the Delegation Law, one or more legislative decrees for the redefinition of the following areas: surveillance and supervision, communication, sanction system, unique device identification system (UDI), Health technology Assessment (HTA), General Data Protection Regulation (GDPR) and, finally, the financing system.

VIGILANCE AND POST-MARKET SURVEILLANCE

It is necessary to implement coordination and reorganization of the national provisions in force with those of the Regulation, with particular focus on the **methods and procedures of vigilance** , **market surveillance and of safety control** of medical devices, fundamental adjustments if we consider the proactivity of these procedures dictated by the MDR .

COMMUNICATION

The Government will have to establish the **contents**, the **timing** and the **modalities of recording the informations** that the manufacturers, the distributors users are required **to communicate to Ministry of Health**.

SANCTIONING SYSTEM

The sanctioning system will have to be **redefined** on the basis of the new and wider **obligations** for manufacturers imposed by the MDR. **Administrative penalties, which must be "effective, dissuasive and proportionate to the seriousness of the violations** of the provisions of Regulation (EU) 2017/745 and Regulation (EU) 2017/746", will ber educed by one third in the event of violation by micro-enterprises.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

Subject to agreement between the State, the Regions and the Autonomous Provinces, it will be necessary to **strengthen the functions of HTA and adapt the activities** of the Observatory on the purchase prices of devices di in order to make the purchasing procedures more efficient.

FINANCING SYSTEM

There will also be a system of government financing of medical devices through the **payment** by companies that produce or market medical devices **of a quote** not exceeding 0.75% of the turnover, net of VAT, **deriving from the sale of medical devices and of large equipment to the National Health Service**.

GDPR

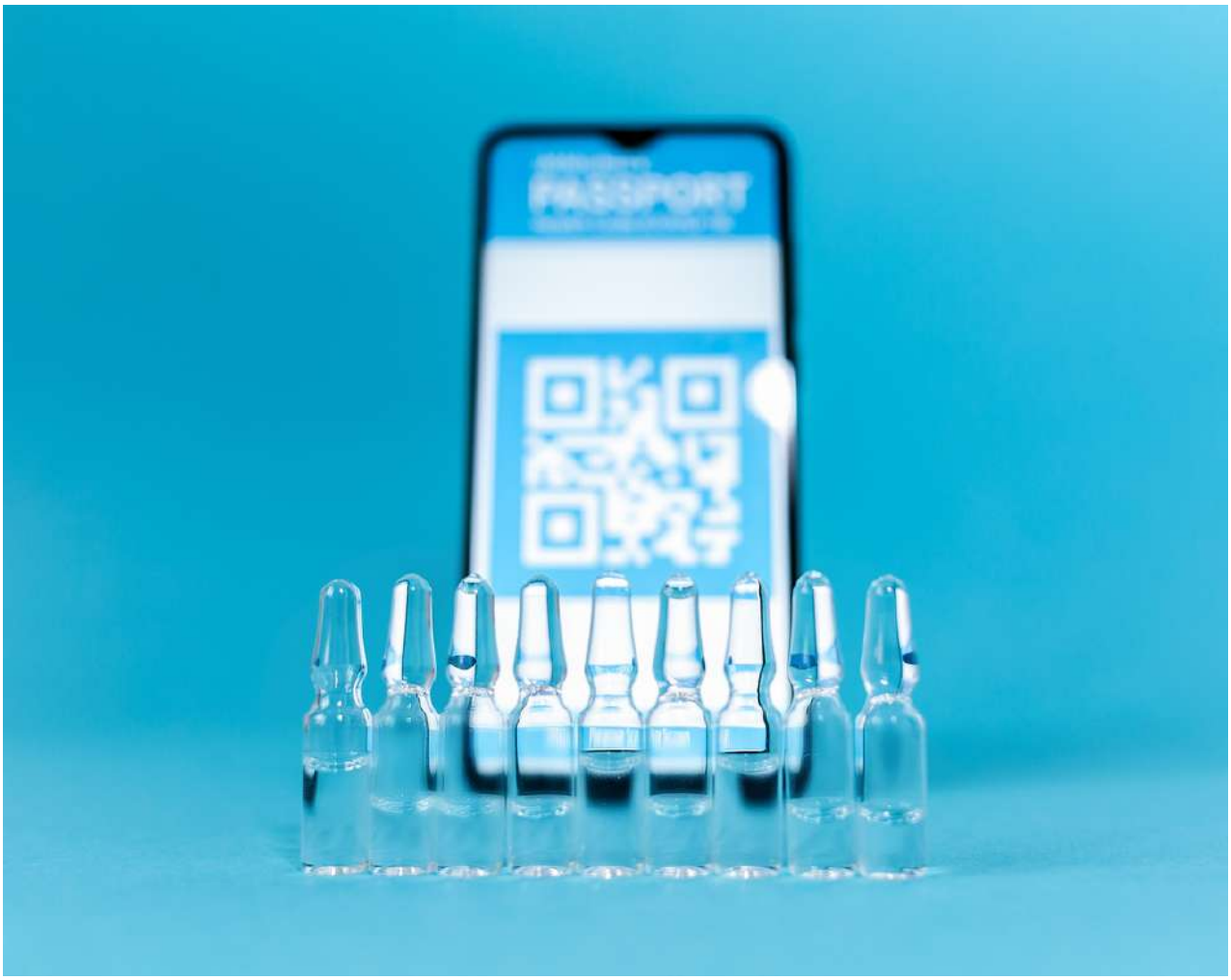
The activities envisaged by the MDR, such as clinical evaluation and post-marketing surveillance, with an attached monitoring system, measurement of results and data analysis, involve extensive processing of personal data and must therefore be compliant to the GDPR. Particular attention should be paid by the adaptation decree on the passage of data collected by health professionals and hospitals to manufacturers.

UNIQUE DEVICE IDENTIFIER (UDI)

The government is entrusted with identifying the methods of **traceability** of the DM through the reordering and connection of databases in accordance with the **Unique Device Identifier - UDI**, so as to safeguard the most complete information level.

MANAGEMENT

It will be necessary to reorganize and coordinate the activities of the public bodies responsible for the governance of medical devices.



MDR: THE MAIN NEWS

THE MDR, REPLACING THE OLD DIRECTIVE, IMPLEMENTS NEW FEATURES. HERE THEY ARE.

THE PERSON RESPONSIBLE FOR COMPLIANCE WITH THE LAW

in order to e**nsure full compliance with the Regulations, a professional figure must be appointed** in charge of supervising the various corporate **tasks**, such as:

- **Compliance of devices with the quality system**
- **Drafting and updating** of the technical documentation and the **EU declaration of conformity**
- **Compliance with post-market surveillance** and reporting obligations
- Release of the **declaration in the event of an investigation** into the medical device

This person must be i**nternal to the company**, with the exception of micro-enterprises (companies with less than 50 employees and a turnover of less than 10 million euros) which can have an external figure.

CLASSIFICATION OF MEDICAL DEVICES AND NOTIFIED BODIES

The new Regulation adds a new class for reusable surgical instruments, **the Ir**, and implements a more stringent classification of devices: there are many devices whose risk class has been updated and which consequently must be recertified. Responsible for this task are the Notified Bodies, which under the MDR are in turn subject to the obligation of requalification. According to the old MDD 93/42 directive these were 56, while to date, there are only twenty qualified Bodies.

THE TRANSITIONAL PERIOD

To allow manufacturers to adapt to certifications, a **transitional period** has been envisaged.

Here are the expiration dates:

- Until 25/05/2021: all certificates issued in accordance with the AIMDD and MDD directives are valid until the expiration date.
- From 05/26/2021 to 05/25/2024: certificates issued in accordance with the AIMDD and MDD directives before the full application of the MDR (05/26/2021) remain valid until 05/24/2024 provided that there are significant changes in the design and intended use.
- Until 25/05/2024: devices that according to MDD were class I, but which under MDR pass to a higher category and therefore require the intervention of a Notified Body, can continue to be placed on the market until that date on condition that there are no MDRs and significant changes in design and intended use.
- From 05/26/2024 to 05/27/2025: MDD devices already placed on the market can continue to be made available
- From May 2024, all devices placed on the market must be MDR compliant.

In this regard, we remind you that the various stages of supplying a device, from launch on the market to reaching the user, have been defined as follows:

- **placing on the market**: it is the first making available of a device on the Union market;
- **provision**: is the supply of a device for distribution, consumption or use on the Union market;
- **commissioning**: phases in which a device has been made available to the end user as it is ready for first use on the Union market according to its intended use.

INFORMATION PROVIDED BY THE MANUFACTURER

Several changes also concerned the information that manufacturers must provide on labels, packaging and instructions for use.

For the labels, the real novelty will be the affixing of the UDI carrier; as far as packaging is concerned, new requirements have been envisaged only in the case of sterility; finally, the instructions for use are those that have received more updates, all aimed at greater safety and information for the user.

DECLARATION OF CONFORMITY

Another novelty with respect to the MDD is the n**ew declaration of conformity, the mandatory document certifying compliance with EU requirements**, which with the MDR is enriched with information.

IDENTIFICATION AND TRACEABILITY: THE UDI CODE

Particular attention was paid to the MDR regarding the identification and traceability of medical devices. In fact, 10 articles have been foreseen in this regard (art. 25 - 34). The focal point is the **UDI code, the new Unique Identification Code, whose purpose is to identify and track the device with absolute certainty**.

The obligation to affix the code on the label of the DM started on:

- 05/26/2021 for implantable and Class III devices
- 26/05/2023 for Class IIa and IIb devices
- 26/05/2025 for Class I devices

Direct marking on reusable devices is mandatory from:

- 05/26/2023 for implantable and Class III devices
- 26/05/2025 for Class IIa and IIb devices
- 26/05/2027 for Class I devices

SUPERVISION AND POST-MARKETING SURVEILLANCE

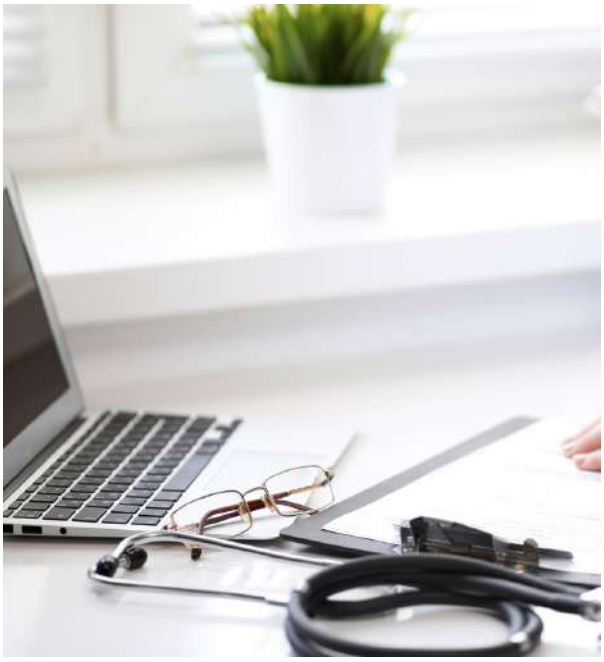
Post-market surveillance is becoming more stringent, manufacturers are now required to plan, establish, document, implement, maintain and update a post-market surveillance system for each device, in order to collect, record and analyze quality data, on performance and safety of the device during its entire life.

This system will have to be based on a post-market surveillance plan.

Consequently, manufacturers are required to draw up a post-market surveillance report for Class I devices and a PSUR for Class IIa, IIb and III devices.

CLINICAL EVALUATION

Another important revision has been given to the area of clinical evaluation and clinical investigations: the MDR requires manufacturers to carry out a **systematic and continuous clinical evaluation for each medical device** on the market and to prepare clinical investigations in the event of gaps in clinical evidence of products, obligations already foreseen in the MDD, but now more detailed and filled with some gaps.



EUDAMED

Key figure of the MDR is **EUDAMED, the European database of medical devices, consisting of six modules**:

- Registration of the plaint if (manufacturer, authorized representative, importer and distributor)
- UDI and device registration
- Registration of economic operators
- Notified and certified bodies
- Clinical investigations and performance studies
- Supervision and post-marketing surveillance

The new **EUDAMED database, the aim of which is to improve general transparency and strengthen coordination between different Member States in the EU**, will only be available from May 2022.

DELEGATION LAW

Finally, we recall that in April the Delegation Law no. 53 was issued with which the parliament "passes the ball" to the Government for the reception of some European directives, including the MDR itself. The Government will have 12 months to apply the transposition directives.

The areas of adjustment are: post-marketing surveillance and surveillance, communication between manufacturers and authorities, management by public bodies, sanctioning system, traceability and UDI system, purchase of DM, GDPR and financing system.

MDR: APPLICABILITY IS OFFICIAL, IS EVERYTHING READY?

FROM TODAY, THE MDR, THE NEW EUROPEAN REGULATION ON MEDICAL DEVICES, THAT CAME INTO FORCE IN MAY 2017, HAS FULL APPLICABILITY. AFTER A ONE-YEAR POSTPONEMENT DUE TO COVID, IT WONDERS HOW THE VARIOUS ACTORS INVOLVED IN THE FULFILMENT OF THE NEW DUTIES REQUIRED BY EU REGULATION 2017/745 ARE.

Are the stakeholders ready? The answer is: not really! - says Dr. Maria Grazia Leone, (General Directorate of Medical Devices and Pharmaceutical Service, Italian Ministry of Health) during the AFI Symposium webinar this morning, 26/05/2021, the date of full applicability of the MDR.
In fact, there are still several gaps - explain the various speakers. Here they are below.

THE ITALIAN DELEGATION LAW

It is only last month that the new Delegation Law n.53, according to which the implementation of the MDR in Italy passes from Parliament to the Government. It is therefore the responsibility of the latter to adopt legislative decrees to adapt national regulations to the transposition of the Regulation. At your disposal 12 months for the adjustment starting from the release of the Delegation Law on 22 April 2021.

NOTIFIED BODIES

The Notified Bodies, responsible for the certification of Medical Devices, **under the MDR were in turn subject to recertification**. However, to date, not even half is ready: the long time required for redevelopment has generated a serious shortage of suitable institutions. In fact, the European Notified Bodies, that were 56 under the directive, are now only 20 and three are on the home straight.

DEVICE RECERTIFICATION

Several devices under the MDR change their risk class and are therefore subject to intervention by the NB for their recertification, however, this has been postponed due to the delay in the requalification of the Notified Bodies. With Regulation 561/2020, which amends the MDR regarding the dates of application, the placing on the market or putting into service of medical devices that pass from class I to a higher category is extended until 26/05/2024 and which therefore require the intervention of a Notified Body.

UDI

The **Unique Devices Identifier (UDI) code, whose purpose is to facilitate the identification and traceability of medical devices**, has as deadline for obtaining it the 26/05/2021, but its affixing obligation starts on 26/05/2021 for Class III DM, 26/05/2023 for DMs of Class IIa and IIb and 26/05/2025 for DMs of Class I.

EUDAMED

Also the new European database is late: it was supposed to be online in May 2020, the first date of application of the MDR, but the official news is that it will only be active starting from May 2022. For the moment, and only for some countries, the manufacturer registration form has been opened.

BREXIT AND DATA CIRCULATION BETWEEN THE EU AND THE UK: THE EUROPEAN COMMISSION DECISION ARRIVES

TWO ADEQUACY DECISIONS ADOPTED, HERE'S WHAT THEY SANCTION.

After **Brexit** there have been numerous doubts regarding the data protection system in the United Kingdom: since it is no longer part of the European Union starting from January 2021, it was necessary to find an agreement between the parties, so that European data could move safely on British territory.

On June 28, 2021, the European Commission finally announced the agreement between the two shores of the English Channel: two adequacy decisions were adopted, one under the General Data Protection Regulation (GDPR) and the other for the Directive on law enforcement.

The UK has fully incorporated the principles, rights and obligations of the GDPR and the Law Enforcement Directive into its post-Brexit legal framework, so its data protection system has not changed since it was a Member State of the EU and therefore remains equivalent to the current one guaranteed in Europe.

Access to personal data by public authorities in the UK is also no longer a particular concern, as strong safeguards are in place: data collection by authorities is subject to the prior authorization of an independent judicial body and any measures it must be necessary and proportionate to what one intends to achieve. In addition, the United Kingdom is subject to the jurisdiction of the European Court of Human Rights and must accede to the European Convention on Human Rights as well as the Council of Europe Convention for the protection of Individuals with regard to Automated Processing of Personal Data, which it is the only binding international data protection treaty.

A novelty consists in the introduction of the so-called "forfeiture clause" incorporated in the adequacy decisions: the latter will have a limited duration of four years from their entry into force. Upon expiry, they may be renewed, as long as the UK continues to ensure an adequate level of data protection and security. During the period of validity, the European Commission will in any case continue to monitor the legal situation of the United Kingdom and, in the event of deviations, it may intervene at any time.
To date, therefore, the full implementation of the GDPR and the solid guarantees placed on adequacy decisions in the event of future divergences, guarantee full freedom of data circulation between the EU and the UK.

COVID VACCINES: THIS IS WHAT THE DATA REVEAL AFTER 6 MONTHS OF ADMINISTRATION

IT WAS DECEMBER 2020 WHEN THE FIRST DOSES OF VACCINES AGAINST THE VIRUS THAT HAS BEEN INFECTING THE WORLD FOR A YEAR AND A HALF, ARRIVED IN ITALY. BETWEEN DOUBTS AND PERPLEXITIES, ALMOST 50 MILLION DOSES HAVE BEEN ADMINISTERED TO DATE. LET'S SEE WHAT THE DATA PUBLISHED BY THE ITALIAN MEDICINES AGENCY (AIFA) SAY.

REPORTING ADVERSE EVENTS FROM COVID VACCINES

It is the Italian Authority's concern to publish monthly a report on the data of the reports of suspected adverse reactions given by the four vaccines available in Italy for Covid-19: Astrazeneca, Pfizer, Moderna and Johnson & Johnson. In this sixth report, the data refer to the time range from 27 December 2020 to 26 June 2021, during which 76,206 reports were submitted, out of a total of 49,512,799 doses administered, with a reporting rate of of 154 for every 100,000 doses administered.

The 88.1% of the reports reported non-serious event such as fever, fatigue, headache, chills, nausea, muscle aches or simply pain at the injection site; the remaining 11.9% reported severe reactions, more frequently identifiable as symptoms of severe flu, resulting in complete resolution or improvement in most cases.

About l'80% of adverse events occurred on the same dayor the day after administration ,more rarely beyond the following 48 hours. The most serious events commonly occur after the second dose of the mRNA vaccines or after the first dose of the Astrazeneca vaccine.

AGE, SEX AND TYPE OF REPORTING SUBJECTS

The age group that counts the most reports is that from 20 to 29 years, then decreasing the following, resulting in an average age of 49 years.
However, for all groups, **most of the reports occurred after the second dose**.
As for the sex of the subjects, it is women who have **the highest number of reports, or 73% against 26% of men**, although the percentages of **doses administered are respectively 54% and 46%**.
About 77% of the reporter is a health worker of which 40% are doctors, 20% pharmacists and 16% other health professionals. The remaining 23% of the total is given **by patients / citizens**.
The 97% of these reports is are spontaneous.

VACCINE RANKING BY REACTIONS

The vaccine with **the most reports is the Comirnaty Pfizer**, with 69%, but it is also the most administered, in fact it boasts **70% of administrations.**
Following Vaxzevria **Astrazeneca with 24,7% of reactions and only 17%of administrations.**
In third position Spikevax **Moderna with 5,2% of reports for a total 9,6% of administrations.**
Finally, we find Janssen **Johnson & Johnson with1,1% of reports and e 2,5%of inoculated doses.**

SERIOUS EVENTS: REPORTING RATE, TYPE AND TIMING

The reporting rate for serious events is **18 for every 100,000 doses administered**, regardless of the type of vaccine, the dose administered (first or second) and the possible causal role of the vaccination.
In detail, **the reporting rate** is:

- Comirnaty **Pfizer: 14** for every 100,000 doses administered
- Spikevax **Moderna: 14** for every 100,000 doses administered
- Vaxzevria **Astrazeneca: 37** for every 100,000 doses administered
- Janssen **Johnson & Johnson: 12** for every 100,000 doses administered

According to the data, the onset of a **serious adverse event occurred in 60% of cases within 48 hours**, **in 18% within the first week** and in 19% in the following weeks. For 3% of cases, unfortunately, there is not enough data to establish the timing.

The reporting of **serious events**, which as mentioned above represent l'**11,9% of the total reports, refer to:**

- **7,0% other relevant clinical condition**, or they alerted the subject and / or reporter without determining a specific intervention in a hospital setting
- **3,2% hospitalization**
- **0,6% life-threatening**
- **0,6% death**
- **0,5% disability**
- **0,1% congenital anomalies**

The **60% of serious events resulted** in the "**complete resolution**" or "**improvement**" of the event, while 24% were not yet cured at the time of reporting.

VACCINE/SEVERE EVENT CORRELATION RATE

The causal link according to the **WHO algorithm was included in 69% of reports of serious adverse events**. It emerged that 46% % of these are correlatable, 33% are indeterminate, 19% are unrelated and 2% are unclassifiable.

FATAL EVENTS: AGE AND GENDER OF THE AFFECTED SUBJECTS

The total number of **fatal case reports** in this sixth report is **423**, with a reporting rate of 0.85 per 100,000 doses administered.

The average age is 77 and involved 51,5% women and 48% men; 0.5% of cases do not report the patient's sex.

Of these cases, **244 occurred after the first dose , while 127 after the second**. In 52 reports it was not specified.

The deaths occurred over a period of time ranging from two hours up to a maximum of 78 days. In most cases the correlation is due to pathologies already present before vaccination, to cases of clinical frailty and polytherapy.

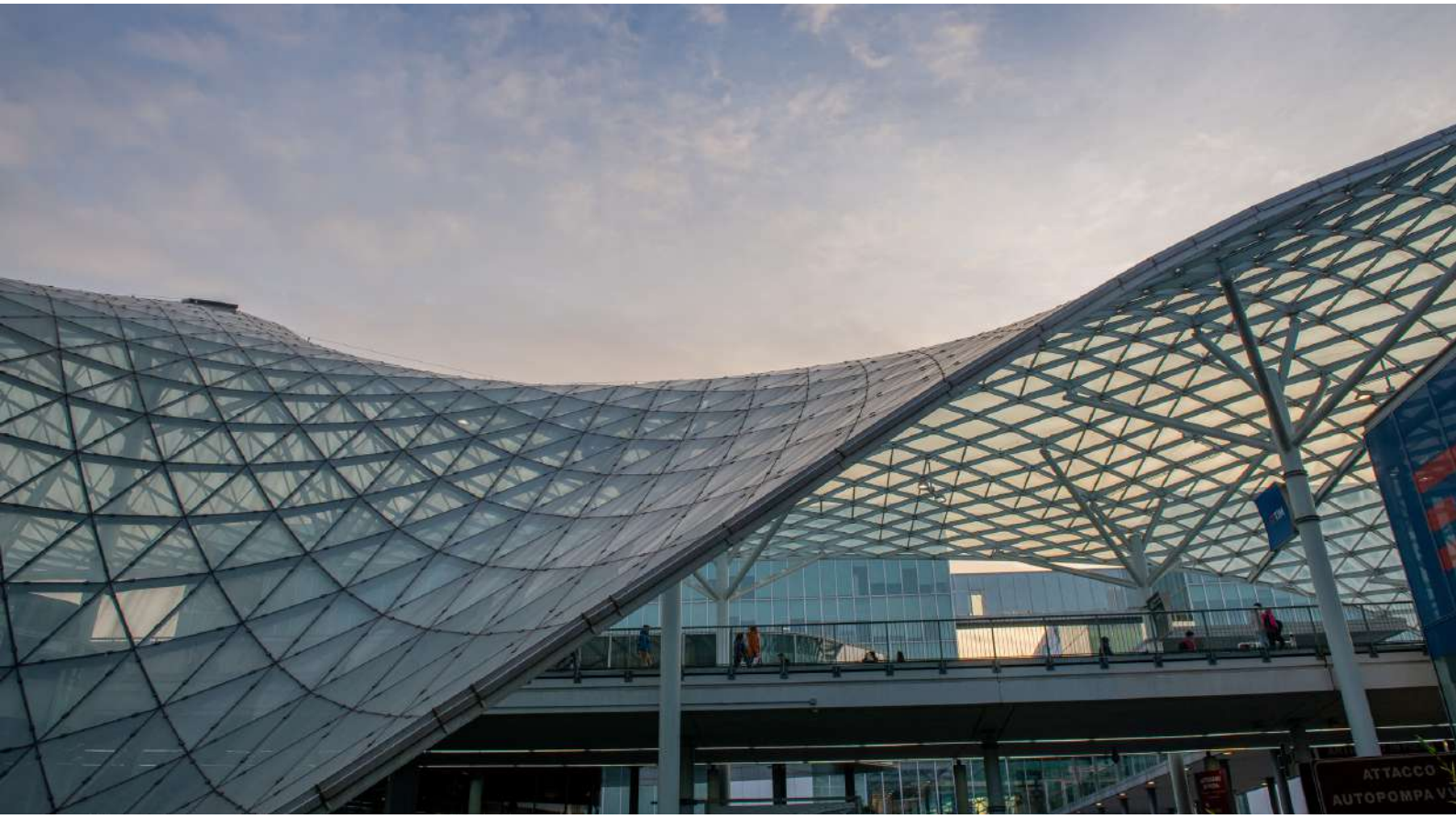
VACCINE/DEATH CORRELATION RATE

The causality assessment with the WHO algorithm was used for 63,4% of the reports with a fatal outcome and it was found that: **59,6% of these are unrelated, 33,6% are indeterminate, 4,2% are unclassifiable for lack of data and 2,6% can be correlated**.

This last figure refers to **7 cases: 4 were already known in the previous months, 3 would therefore be new**. **Two of these refer to a possible lack of vaccine efficacy**, as two patients with immunosuppression who, respectively 45 and 35 days after the vaccination course, tested positive for Coronavirus and were affected by complications of interstitial pneumonia which led to to death. The last case, on the other hand, refers to a fragile condition in the patient who immediately after the first dose of the vaccine suffered from fever and vomiting which led to decompensation in the clinical condition until death after two days.

VACCINE RANKING FOR DEATHS

- Comirnaty **Pfizer: 262, for arate of 0,75** per 100,000 doses administered
- Spikevax **Moderna: 75, for a rate of 1,58** per 100,000 doses administered
- Vaxzevria **Astrazeneca: 72, for arate of 0,84** per 100,000 doses administered
- Janssen **Johnson & Johnson: 14, for a rate of 1,15** per 100,000 doses administered



CPHI: THE BALANCE OF THE 2021 EDITION

THE 30TH EDITION OF ONE OF THE MOST IMPORTANT EVENTS FOR THE PHARMACEUTICAL SECTOR WAS HELD AT FIERA MILANO. WE WERE THERE, HERE'S HOW DID IT GO.

The 30th edition of CPhI Worldwide - Chemical and Pharmaceutical Industry, was held from 9 to 11 November, which returned to Fiera Milano after 14 years.
The choice of location could not have been more appropriate: in recent years a highly innovative international network of excellence has emerged in Italy, made up of pharmaceutical companies. It is worth over 34 billion, with exports growing by 74% between 2015 and 2020: an important value compared to 48% of the EU average. Lombardy is the first region in Italy for investments in research and development - over 400 million euros - and a manufacturing export value of 8.2 billion, 24% of the entire pharmaceutical sector.

Italy is the largest producer and exporter of APIs in Europe. 85% is exported to North America, the EU and Japan. The survey of the 2020 CPhI annual report indicated a growing country: the results showed that Italy was the country with the highest growth in the global ranking of API producers.

The CPhI was already supposed to be held in Milan in 2020, but was postponed due to the Covid-19 pandemic. It took place in hybrid mode, with a live exhibition area and remote conferences: it was possible to return in presence, without however leave the convenience of the online mode to which we have been accustomed in recent months.

From an exhibition point of view, the fair suffered from the doubts and uncertainties brought by Covid-19: 170 countries were represented, with 1400 exhibiting companies (there were over 2500 in 2019). Many companies were missing from China, India and America, usually at the forefront. There was also a decline in attendance, clearly lower than the almost 50,000 recorded in 2019.

As a whole, the event offers space for the entire pharmaceutical world. In addition to CPhI, the area intended for API producers, the complementary sectors are represented:

- ICSE, for service providers
- p-mec, for machinery and equipment manufacturers
- InnoPack, for packaging and packaging manufacturers
- FDF, for producers of finished products
- BioProduction, for producers of molecules from bioprocesses

The event offered Max Application, exhibitor in the ICSE area, the opportunity to present the latest release of SafetyDrugs, the pharmacovigilance database and the connected Business Intelligence module.

DISABILITY AND ACCESSIBLE ROUTES: HERE IS WEGLAD, THE APP TO MOVE FREELY

A FEW MONTHS AGO WE RECEIVED AN UNEXPECTED PHONE CALL: THEY WERE TWO GUYS WITH A BRILLIANT IDEA AND A GREAT DESIRE TO HELP OTHERS. WE IMMEDIATELY BECAME INTERESTED IN THEIR PROJECT AND WE WANT TO TELL YOU ABOUT IT.

The project is called **WeGlad**: : it is an **app developed to help people with motor difficulties or disabilities in their movements through three functions**:

- **Navigator**: by setting the starting point and the destination, WeGlad will show, using Artificial Intelligence, the most suitable route based on the obstacles that the user chooses to avoid according to its abilities. It will also be possible to map the obstacles themselves, fixed or temporary, anywhere, on a map shared with everyone and, to find accessible parking spaces or to identify suitable public transport means and related accessible stops.
- Mapping of structures: on the app it is possible to identify the accessible structures and their relative location and opening times, accompanied by photos of the entrance, of the interiors and of the toilette to verify the accessibility, the manoeuvring spaces

- and the usability. Users will be able to confirm the data or add other information to make the review more objective.
- Social network: the community is the basis of the app, the various users can in fact interact with each other to discuss paths, tell personal experiences, give and ask for help and, why not, make friends.

The founders of the project are two guys from Turin, Paolo Bottiglieri and Petru Capatina, who had the idea following personal experiences in close contact with people in wheelchairs. First in the family and then at work, the boys were able to approach this reality and see with their own eyes how many difficulties these Gladiators had to face every day, because this is how the two boys see them: WeGlad is in fact the contraction of Welcome Gladiators;

"*Gladiators who go down to the Arena of Life and who every day win battles against obstacles that shouldn't exist, having difficulties they haven't chosen. We often don't realize how much 10 centimeters can translate into insurmountable walls* " – explains Capatina.

"Our aim is to get as many people as possible to notice this arena, which is often invisible. Entering it together as a community, which strives for the accessibility of all, is our responsibility!" – adds Bottiglieri.

Tired of seeing people in difficulty or unable to practice certain paths, they decided to make their contribution. Thus began an adventure in which they got information and documented themselves by traveling in Italy and Europe, arriving as far as Brussels, in search of as much information as possible.

In the end, they conceived and developed an Open Social Navigator: yes, because in addition to being a navigator based on the social network, it is also open, meaning anyone can contribute by indicating any architectural barriers, inserting new routes or adding additional accessible places.

WeGlad presents itself as a real innovation to speed up the movements of those people who too often find themselves blocked due to obstacles or inadequate structures, but it is also a project to which we can all contribute.
WeGlad is also the first innovative start-up, with a social and Benefit vocation in Piedmont, and among the first in Italy.

We at **Max Application are proud to have supported this reality from the beginning as lenders and we hope that more and more companies and people will join the Arena.**
And if the altruism and generosity of the initiative weren't enough a **Corporate Social Responsibility project**: was also conceived: the companies that participate can involve employees in an internal challenge that will bring the participants, who have enriched the app with information the most. and mapping, to win a monetary voucher to be donated to non-profit entities of their choice. In short, a gain for everyone.

The WeGlad app is already available for free on the Play Store and App Store. Users can then start downloading it and give their contribution by adding useful information for the community.

Via Bertodano 11, Biella (BI) 13900, Italia
Tel: +39 015 324 68

www.safetydrugs.it

marketing@safetydrugs.it