

SD

COLLECTION

2020 SPECIAL

PHARMACOVIGILANCE

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EUDRAVIGILANCE, INSPECTION AND NON-COMPLIANCE: HERE IS WHAT TO PAY ATTENTION TO



THE DIA WAS HELD FROM 5 TO 7 FEBRUARY 2019; THE ANNUAL GLOBAL EVENT ON THE PHARMACEUTICAL SECTOR, HERE'S WHAT EMERGED REGARDING EUDRAVIGILANCE, THE EUROPEAN PHARMACOVIGILANCE DATABASE.

DIA Europe is an annual meeting where conferences around the globe are convened. Thought leaders across all disciplines unite together in a neutral forum to discuss current issues, with the goal of uncovering new ways of working and new solutions for patients, by incorporating representatives from the full life sciences landscape we facilitate open collaboration. Rory Littlebury, Pharmacovigilance Inspector of MHRA, told about the results of his inspection experiences during the session on pharma-

covigilance "The new Eudravigilance one year later". From the implementation of the new EudraVigilance, two major anomalies were found: over-reporting and under-reporting.

The **over-reporting** is mainly attributable to the reporting of cases from literature articles related to a drug for which the company has not obtained the MA yet; to the submission of cases containing only the outcome and to the reporting of ICSR deriving from a secondary source.

The **under-reporting** is instead due to the non-submission of not-serious cases to EudraVigilance within the 90 days required by the regulations and to the trend to exclude the ownership of the drug for cases from literature.

Furthermore, from 22th November 2017, 20 GvP inspections were carried out by the MHRA, which revealed the following non-conformities by pharmaceutical companies:

- lack of documented procedures that describe the data monitoring processes in EudraVigilance
- lack of documented agreements that define the criteria and guidelines for the management of the revision of the eRMRs when outsourced to third parties
- lack of documentation confirming the quarterly revisions of the eRMRs or the implementation of the statements recorded during the monthly meetings of the Safety team.

To counterbalance the anomalies reported by the British inspector, the intervention of MSD UK's Deputy EU QPPV, Margaret Walters, highlighted that the benefits expected from the new implementation of EudraVigilance, such as the simplification of the submission of cases and the signal detection, are, instead, undermined by the massive workload caused by the screening of the numerous cases downloaded.

This led to a boost of time and resources employed, to the revision of internal procedures and to an even more complex handling of cases from literature, as well as to the increase of the duplicates.

In a third speech, Christiane Michel, Novartis Global Head Safety Signal Detection, illustrating the experience gained from the comparison between their internal database and EVDAS for the signal detection management, admitted that even for the Swiss multinational many are the difficulties and the challenges encountered.



MEDICAL DEVICES: WHAT WILL CHANGE WITH THE INTRODUCTION OF THE NEW EUROPEAN REGULATION

THE AFI SYMPOSIUM WAS HELD ON 5-7 JUNE 2019 AT THE RIMINI CONVENTION CENTER. THE TOPIC OF THE NEW REGULATION (EU) 2017/745 WAS DISCUSSED IN THE SESSION DEDICATED TO MEDICAL DEVICES. HERE'S WHAT TRANSPIRED.

On 26th May 2020, the 2017/745 EU regulation on medical devices will come into force. It was discussed at the 59th AFI Symposium, the Italian event dedicated to the pharmaceutical sector, during the workshop entitled "The new regulatory frontiers of medical devices: how to tackle them in a European and international context". Here is what emerged.

One of the aims of the new regulation is to guarantee a higher safety of medical devices. A better clinical evaluation is required, which is currently lacking:

producers will have to fill in the gaps and improve clinical data collection processes, especially for new products, for which it will no longer be possible to use the equivalence approach, but the appropriate clinical investigations must be carried out.

Post-marketing surveillance will also need to be optimized: an active and systematic system that is able to collect and analyse data on the quality, performance and safety of the device will be required.



In this regard, **EUDAMED**, the new European web-database for market surveillance of medical devices and in vitro diagnostic medical devices will play a key role. This will act as a central archive, a system for the exchange of information between the competent National Authorities and the European Commission and support for the uniformity of the application of the new rules.

Data concerning:

- the register of manufacturers, representatives and authorized devices;
- certificates issued, modified, supplemented, suspended, withdrawn or refused according to established procedures;
- the procedure for supervising accidents or near accidents that occur during the use of the medical device.

Clinical evaluation must become an integral part of internal procedures and will be a crucial step in the process of introducing devices on the European market, having to comply with safety standards.

26TH MAY 2020, A LIKELY DATE?

A FEW MONTHS FROM 26TH MAY 2020, THE DATE OF ENTRY INTO FORCE OF THE (EU) 2017/745 REGULATION ON MEDICAL DEVICES, DOUBTS ARISE ABOUT THE REAL POSSIBILITIES OF MEETING THE DEADLINES.

The new regulation will bring several changes, which will involve, in addition to vigilance and safety, also the definition of medical device, of the related risk classes and of the borderline products. The latter, as the name implies, do not fall into a specific sector, it is therefore complex to understand which reference legislation to apply: directives on drugs, biocides, cosmetics, supplements or protection products can be applied individual.

In order to ensure a more coherent classification of these products, the new regulation provides the Member States to decide whether a product falls within the MDR/IVDR application or not. The European Commission can activate itself on a specific product not only upon indication of a Member State but also independently, always subject to the opinion of the Medical Devices Coordination Group.

A **working group** "Borderline and Classification medical devices expert group" was also set up at the European Commission to discuss borderline cases. The decisions taken will be included in a specific Manual, which is not legally binding, but acts as a guide.

However, the changes will not only affect the producers, but also distributors, agents, importers and **Notified Bodies**. Precisely the latter, in fact, in order to evaluate and (re-)certify the conformity of medical devices will have to be re-designated. This process takes at least 18 months.

Furthermore, the number of products to be accredited for by Notified Bodies will be higher, since the **Medical Devices of class I**, such as those substances based, will be **reclassified to a higher risk class**. Consequently, **the surveillance has to be applied to a greater number of devices to which over 35000 IVDs will be added**.

The situation becomes even more complicated with the imminent Brexit, since around **30-40% of medical technologies in the EU are certified by the British Notified Bodies**: the work of these will therefore have to be acquired by the Notified Bodies of other EU states.

Given the amount of changes to be implemented and the approaching of the entry into force of the regulation, it would seem that the date of May 26th, 2020 will hardly be respected.

MEDICAL DEVICE: MARKETING AUTHORIZATION IN USA AND CHINA



THE UNITED STATES AND CHINA ARE THE MAIN MEDICAL DEVICES MARKETS IN THE WORLD. IN THESE COUNTRIES, THE CLASSIFICATION OF THE DEVICES IS DIFFERENT FROM THE EUROPEAN ONE. SO HOW TO PROCEED TO OBTAIN MARKETING AUTHORIZATION? HERE'S WHAT WE REPORT FROM THE AFI SYMPOSIUM ON JUNE 5-7, 2019.

MEDICAL DEVICES IN USA

For what concern the USA, to commercialize the medical devices of class II and III and some of class I, the authorization by the Food and Drug Administration (FDA) is necessary.

For the majority of the devices the request occurs through the simplified Pre-Market Notification procedure, provided for by the section 510K of the Federal Food, Drug and Cosmetic Act. This procedure is based on the principle of equivalence: the device requesting the marketing authorization is made equal with one that has the same aim, the same mode of use and that is already legally marketed in the USA.

If, instead, no similarity is found, the Pre-Market Approval (PMA) procedure must be started.

A Request for Designation (RFD), a procedure to request not binding opinion, can be activated in case of doubts about the regulatory identity or about the classification of a product, namely if it is a device or a drug.



MEDICAL DEVICES IN CHINA

Also in China the marketing authorization of the national drug agency, China's Food and Drug Administration – CFDA, is necessary.

All devices must be registered through the regulatory system of the National Medical Product Administration – NMPA.

The devices of Class I must be notified to the Competent Authority; then the NMPA will issue the market authorization.

For the devices of Class II and Class III, instead, the question is more complicated: before the approval, the devices have to obtain the Registration Certificate through the execution of some test in labs located in the Chinese territory. All this, despite the fact that many foreign device manufacturers have already various clinical data to prove the safety and effectiveness.

In addition, the NMPA has recently issued new and significant regulations on classification, registration, inspections and clinical studies:

- “Regulations of the supervision and administration of China Authorized Representative for Imported Medical Device (Exposure Draft)”, which states that the China Authorized Representative, CAR, is the only person in charge of acting as legal intermediary between the MAH and the NMPA abroad.
- “Administrative Regulations of Drug and Medical Device Overseas Inspection”, that is the first regulation that clarifies the procedure and the responsibility for the inspection abroad. The NMPA will begin strict inspections of the manufacturing processes of all imported medical devices.



EUROPEAN PHARMACOVIGILANCE CONGRESS: WHAT WE TAKE HOME FROM THE 3RD EDITION

THE PHARMACOVIGILANCE CONGRESS WAS HELD FROM 28 TO 29 NOVEMBER 2019 IN MILAN. HERE'S WHAT TRANSPIRED.



The European Pharmacovigilance Congress is an annual meeting, held in Milan that offer the possibility to know the news on pharmacovigilance, to compare itself with other PV experts, and to meet targeted audience.

In the third session there were two days of congress rich in topics: 11 discussion sessions, more than 150 participants and more than 30 pharmacovigilance expert speakers from competent authorities and pharmaceutical companies.

The main topics of this third edition were:

- Updates from the main Organizations
- Overview of inspection trends
- Pharmacovigilance systems
- Risk management and risk minimization
- Patient Support Programs (PSP) and Medical Information (MI)
- Special population and rare disease

Here they are in detail.

1. Update from the international pharmacovigilance organization

The ICH is an arrangement bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Since its inception in 1990, it has constantly evolved to respond to the increasingly global face of drug development. Its mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. Harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines.

2. Pharmacovigilance inspections: current and future landscape

The ultimate purpose of the inspection is to ensure that the MAH has a pharmacovigilance system that complies with the regulations, has a qualified person (QPPV) and that the various departments work effectively. On the basis of the size of the pharmaceutical companies, the difficulties change: for small companies the biggest difficulty is to incorporate specific skills for each pharmacovigilance obligation, while for large companies the problems are related to internal communication. However, the inspector focuses on specific areas depending on the type of reality and the asset of the outsourced activities.





3. Updates on EudraVigilance and EVDAS

Starting from 22 November 2017, the new EudraVigilance system (EV) and the EVDAS data analysis system were put online. Exactly 3 months later a pilot phase was launched for MAHs of products containing active substances under additional monitoring, which must use EVDAS for signal search. This pilot phase, which was to end a year later, has been extended.

However, the introduction of these new work tools has led to a different difficulty:

- increase in work
- creation of duplicates set up by multiple submission of cases to the competent authorities
- lack of confidence in the exclusive ICH E2B (R3) download process due to the complexity, to the point that several MAHs still operate an ICH E2B (R2) security database
- lack of harmonization between the European Economic Area and non-EU countries, which leads to a duplication of relations outside the EEC, with the real risk of generating false safety signals

- difficulty in managing the day 0 since no official definition has been provided. The non-EEC regulators are not familiar with the ICSR download specifications and therefore they don't give instructions to the MAHs in CEE for the day 0 in the respective territories or for the obligation, or not, to report the ICSR downloads from EV
- difficulty in identifying false safety signals resulting from duplicate ICSRs submitted to EV. These duplicates must be communicated to the EMA via the service desk by the marketing authorization holders, contributing to the improvement of the contents of the EV database.

Furthermore, due to the relocation of its headquarters in Amsterdam, the EMA has delayed some of the initially established deadlines.

4. Signal management

In order to comply with the requirements of signal detection and management, the MAHs must:

- monitor the safety of their medicines
- monitor the data reported in EudraVigilance
- carry out signal detection through multiple sources
- collaborate with the PRAC providing the additional information requested
- keep their product information up-to-date.

To improve and make all these processes more efficient it is good to use an automated database implemented by signal detection and signal management applications. It is possible to carry out the signal detection even without automations, but in this case the MAH will have to apply not a few precautions such as:

- Implement quantitative metrics such as "Reporting Rate" that can help identify changes in frequency of reporting of a drug-event combination (DEC), which can generate a signal
- use the eRMR downloaded from the EVDAS in a more extensive way, looking for and analysing also the DEC not marked as DSP
- Establish rules to define when a quantitative measure of a DEC should represent a signal
- improve the qualitative review of ICSRs and set rules to define when a DEC observed with qualitative methods should represent a signal and trigger actions to validate or deny it
- Implement "designated medical events" and "product-specific targeted medical events" lists.
- implement a robust tracking system for signal management that allows adequate audit trails and satisfies the pharmacovigilance inspectors.



5. Involvement of patient experts: central role in pharmacovigilance for better and safer use of medicinal products

The work that the PRAC is carrying out in order to make the patient more aware of the importance of reporting adverse events is increasing. In fact, it was found that in 2018 reports from European patients and consumers increased by 91%, a success factor considering the great importance that these reports have: patients, in fact, being the interested parties can provide relevant details that the doctors instead tend to exclude giving it little importance.

The information could come from organized systems, such as surveys by the PRAC, or from digital sources, such as websites or social media. In this case some verifiable problems are the identifiability of the user (fake profiles), the impossibility of carrying out follow-up activities, untrustworthiness of the information.

6. Pharmacovigilance in the special population: geriatrics, paediatrics, pregnancy and breastfeeding

In special populations, drug reactions can be very different compared to the average population.

Whether it's the elderly, children or pregnant women, the data from clinical studies are very limited. These in fact tend to be excluded from the tests thus leading to a gap in important information. Instead, it would be good to include them from the earliest stages of studies or intensify the post-marketing pharmacovigilance in order to better understand the risks and benefits of a specific drug.

7. Pharmacovigilance in the framework of advanced therapies and rare diseases

For advanced therapies and rare diseases, the available data are very limited, in fact the population sample very often does not reach the hundred, or slightly exceeds it.

To take advantage of the few data available, it is good to use all possible sources, from preclinical and clinical data to epidemiological data, from those from relevant class drugs to those from patient support groups.

In the future, "big data" monitoring tools will facilitate the availability of information and the risk/benefit ratio will be easier to optimize.



8. Risk management and risk minimization

The ultimate aim of the risk management plan is to optimize the benefit/risk profile of a medicine through a risk management system, which identifies, characterizes and minimizes risks.

Risk minimization activities are divided into:

- Routine Risk Management, which uses prescribing information to doctors, such as a summary of product characteristics and to patients, as an information leaflet for patients, to inform and guide the best way to avoid or reduce known risks. Effectiveness is usually measured through regular signal detection methods and reviews in periodic safety reports.
- Additional Risk Management, which includes activities beyond those mentioned above and deemed necessary in the EU, usually involve specific professional education for health personnel and patient education, which also includes letters from Dear Healthcare Professional approved by regulatory agencies.

The GVP XVI module divides the measurement of effectiveness into two categories: process indicators and exit indicators.

- The process indicators include the measurement of the effectiveness of the distribution of materials and the proof of the understanding of the materials by the recipients. The distribution of materials can be documented by careful maintenance of material receipt records. Understanding materials is often demonstrated using market research methodologies such as surveys on prescribers and patients.

- Data on result indicators that require a demonstration of risk reduction may be more difficult to obtain.



9. Patient Support Programs and Medical Information

The pharmacovigilance team is responsible for acquiring and analysing information on drug safety and sharing it with healthcare professionals, patients and all stakeholders. A valid help could come from the Medical Information team or better from its collaboration with the pharmacovigilance team: since the MI team is in contact with patients, it should be trained to extrapolate as much information as possible during an episode of adverse reaction and report then to the pharmacovigilance team. The latter, instead, could learn in practice the use of a product.

The medical information team is also "eyes", "ears" and "voice" of the company, as it is often involved in meetings of the brand team, approval of promotional items, advisory committees, preparation of specific websites for companies and diseases and other business activities of which PV cannot be part.

10. Pharmacovigilance systems: organization and quality

The speakers of this session addressed several issues:

- the importance of data integrity and the relative difficulties. The variety of sources and the increase in data to be evaluated does not make it easy to collect and maintain information integrity. More and more companies, in order to maintain a high level of effectiveness, decide to go to third parties or to invest in a more effective management system for the management of pharmacovigilance.

- The relief of the figure of the EU QPPV. This role has become increasingly important in recent years, thanks also to its role as a bridge between Europe and foreign countries. He is the person who, thanks to his skills, can coordinate and monitor all the pharmacovigilance activities necessary even in non-EU territories. In fact, its requirements require knowledge of the pharmacovigilance regulations of other countries, ability to negotiate agreements, prepare and maintain adequate documentation, and supervise the pharmacovigilance system. Currently, his figure can help the Brexit management.
- quality in relations with suppliers. In order to guarantee the quality, during the relationship with the suppliers the procurement process, the determination of the service execution methods and the governance structure to supervise the work must be carefully coordinated and stipulated. Furthermore, the delimitation of operational responsibilities between sponsor/producer and vendor/service provider must be documented and be clear to all parties, so that quality supervision can be adequately demonstrated.



11. Pharmacovigilance in clinical trials

In this session too there are several topics addressed:

- Early Access Program (EAP). These programs allow pre-approval access to medicines for patients who have exhausted all alternative treatment options and do not meet the criteria for access to clinical trials.
- They require detailed plans and implementation times that involve a dedicated multi-functional team and the collection and reporting of adverse events are mandatory: the attending physician must report to the regulatory authorities any serious and unexpected AE / ADRs and must report to the company, or the producer of the drug, any SAE that occurred during treatment.

Furthermore, it is good to have a clear communication strategy relating to the position of the EAP company, e.g. Website, ClinicalTrials.gov, publication of the company policy.

- Pragmatic approaches for PV in clinical trials. The new regulation 536/2014 “The Clinical Trials Regulation” will come into force, which will make changes such as: simplified application procedure through a single access point, single authorization procedure for all clinical studies, authorization by Member State, involvement of ethics committees in the evaluation procedure, simplifies the communication on safety by SUSAR sponsors who are sent directly to the EudraVigilance clinical trial module (EVCTM).

- Challenges of RSI Management: a non-commercial sponsor perspective. The RSI is a key document for conducting pharmacovigilance in clinical trials, as is the related question and answer document which adds clarity to certain aspects such as content, timing for updating, approval and implementation. However, this document was drawn up mainly for commercial sponsors, while for non-commercials it remains unclear. Documentation and alignment of sponsor processes with European legislation is necessary in order to achieve a study result in accordance with the regulations.



PHARMACOVIGILANCE IN SPECIAL POPULATIONS

SPECIAL POPULATIONS ARE CATEGORIES OF PATIENTS THAT DIFFER IN AGE OR IN SPECIFIC DISORDERS. CONSEQUENTLY, THE PHARMACOVIGILANCE ACTIVITY IS MORE COMPLEX IN THEIR CASES. IT WAS DISCUSSED AT THE THIRD EDITION OF THE EUROPEAN PHARMACOVIGILANCE CONGRESS.



GERIATRIC PATIENTS

Geriatric patients, according to Giovanni Furlan, Head of security risk, Director of Pfizer, reported on geriatric patients, especially those aged 75 and over, react differently than patients in the middle age group. This is due to different pharmacokinetics and pharmacodynamics and to the presence of multiple age-related disorders and consequently the greater number of drugs taken that cause an increased risk of adverse reactions caused by interactions.

Furthermore, patients with geriatric conditions, such as, for example, delirium,

falls, syncope or urinary incontinence, have a greater risk of adverse reactions with consequent increased risk of worsening of pre-existing geriatric conditions.

The polypharmacy is associated with poor adherence to drugs which increases the risk of hospitalizations, worsening of illnesses and death. The different expectations that elderly patients have from taking drugs is one of the main reasons for non-compliance. For them it is more important to have a better quality of life, rather than an extension of the same.

However, clinical trials of drugs are present on a sample of mid-range people, tending to exclude the elderly, this due to doubts about the real benefit of the treatment or due to blocking conditions on the part of the patient as difficulty in accessing the centre of evidence due to logistical barriers or physical disability or lack of information on the availability of clinical trials.

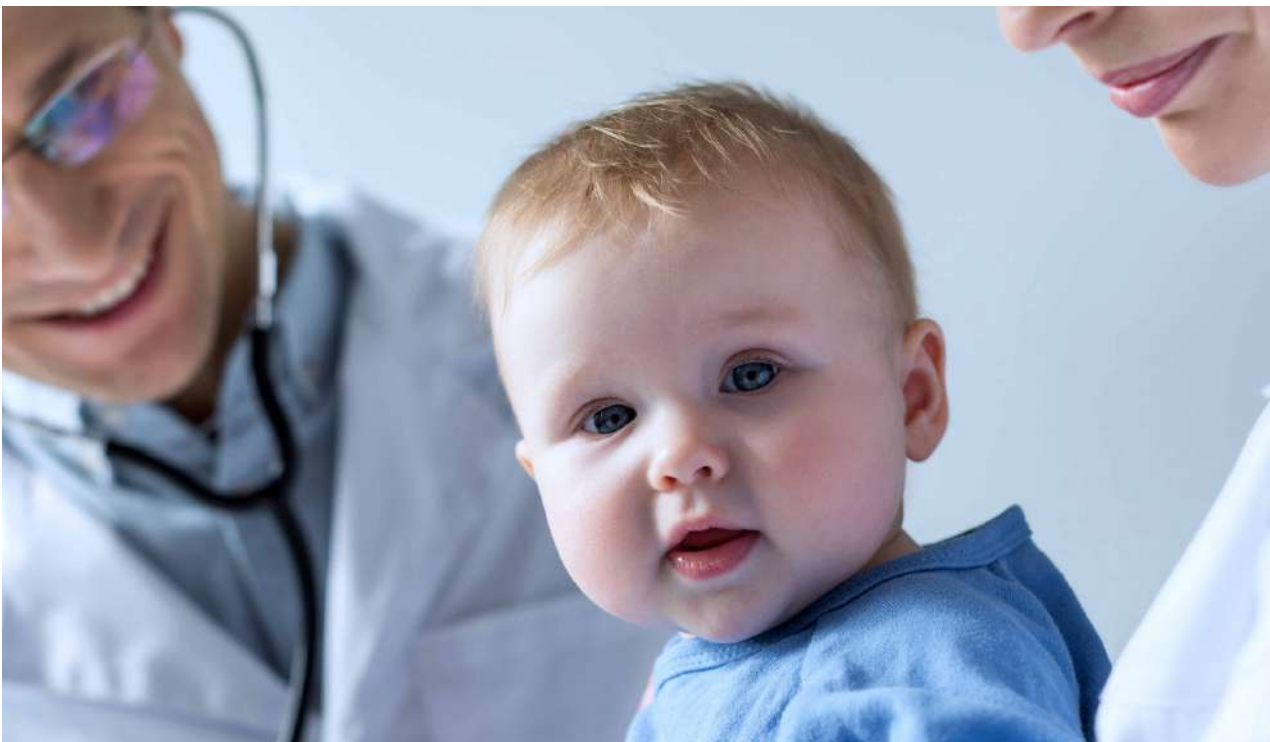
Some proposals to improve adherence to clinical studies could be to provide transport and/or housing, family involvement in the informed consent process, simplification of information consent, implementation of face-to-face communication, abolishing the exclusion criteria that do not allow registration of older people including slow and gradual approach strategies to the drug.

In conclusion it can be said that the adverse reactions and expectations of benefit of a given drug on the elderly, are different compared to the general population, it is a separate tariff benefit for risk/benefit ratio and implement post-marketing pharmacovigilance activities and perform a survey of the separate signal for this precise category.

PEDIATRIC PATIENTS

The physical, metabolic and psychological processes inherent in growth from birth to adulthood, reveal that children cannot be considered small adults and cannot even be considered a homogeneous group in themselves. It is therefore necessary that tailor-made drugs are developed and that the pharmacovigilance activity is more targeted. Here is what Laura Boga, QPPV at Dompè Pharmaceutical, reported during her speech on pediatric patients at the European Pharmacovigilance Congress.

The changes in physiology during growth, the different pharmacodynamic and pharmacokinetic parameters in pediatric subjects compared to adults, the immaturity of some organ systems, the changes in body composition and the greater sensitivity to pharmacologically active excipients cause that pediatric patients have different reactions than adults. Therefore, drugs expressly formulated for this specific age group must be developed.



Moreover, the risk of adverse events can potentially increase in some specific cases:

- long-term exposure: it could have effects on the development of organs, for example on skeletal growth, on sexual maturation or on neurobehavioral development, and can become evident, visible or identifiable only after several years, even in adulthood. It is therefore necessary to perform long-term follow-up to observe the effects in several stages of development-
- off label use: given the lack of specific drugs for children in the past, it was common to administer medicines for adults, thus going beyond the terms and conditions of the marketing authorization and exposing them to additional risks.
- pharmaceutical error: involuntary failure in the pharmacological treatment process that may occur · when a medicine is prescribed, stored, dispensed, prepared or administered. Due to the limited availability of drugs with pediatric indication or appropriate pharmaceutical form, children can be treated at dosages deduced from adult patients or with inadequate pharmaceutical forms.
- insufficient safety data: pediatric clinical studies are limited to a sample that is not sufficiently populated and due to the limited duration, this leads to a lack of knowledge of the real risks.

- erroneousness or lack of clinical presentation of ADR: this may in fact be non-specific or misinterpreted, or worse may not be found and therefore not reported: non-specific symptoms, such as vomiting, drowsiness or crying, are the only ones manifestations observed in new-borns and infants, while symptoms that depend on the patient's ability to communicate, such as nausea, pain, mood changes etc., in younger children may be underestimated or reported incorrectly.

The pharmacovigilance activity must pay attention to different specific aspects in the various phases.

Risk management plan: the methods used to minimize risk in the adult population should be evaluated and adapted to pediatric patients.

ADR management and reporting. ICSRs must include:

- precise information on age by noting day, month, year or indicating the subset of pediatric age (Preterm New-born Neonates, Term and Post-term Neonates, Infants, Children, Adolescents)
- main development parameters such as prematurity, pubertal developmental stage, cognitive or motor development
- indication of use, pharmacological form, dosage and weight and height of patients. The missing information must be followed up to ensure the quality and the integrity of the data.



Periodic safety update report (PSUR).

The PSUR is a tool for the continuous monitoring of the risk-benefit ratio and the cumulative analysis of information on pediatric use, therefore the topics that must be discussed are:

- any new safety problem identified in the pediatric population
- off-label use, including the use of non-age-appropriate formulations or use in pediatric subgroups for which the product is not authorized
- any identified signal of a pediatric adverse reaction
- exposure of pediatric patients during the PSUR signaling interval, exposure per age subgroup
- safety results from ongoing or completed pediatric clinical trials, including those included in the PIP. All sources must be included: clinical studies, post-authorization use, spontaneous reporting, and literature.

Post-authorization safety studies

(PASS). For pediatrics, PASS can be of particular value when developmental effects are expected to occur only years after drug exposure when long-term safety data are needed due to chronic use when there is it was an off-label use and a security problem was suspected.

Signal management. For signal detection it is essential to distinguish and analyse the differences in reactions between pediatric and adult patients and to go into the sub-category of belonging, without dwelling on the pediatric range in general.

Safety communication. To ensure that even children can understand the information on the drug, it is good that the communication is personalized and adapted to their age, especially if they are teenagers or children who can use the drug independently, for example infographics, comics and social media.

Despite the progress made in this area, thanks also to the most recent regulations and guidelines, difficulties persist for the pharmacovigilance activities, mostly due to the underestimation of the suspected adverse reactions in children, from the frequent and more serious therapeutic errors in the population to the difficulty of demonstrating the risk minimization efficacy of new drugs available to the pediatric population.



PREGNANCY AND BREASTFEEDING

Pregnant or lactating women fall into the category of special populations. How to manage pharmacovigilance in the event of an adverse event during pregnancy? Margherita D'Antuono, Pharm D, Ph D Corporate Pharmacovigilance Director and EU QPPV at Italfarmaco S.p.a. spoke about this during the European Pharmacovigilance Congress.

Pregnant women are excluded from clinical trials, unless it is about a specially formulated drug for this specific situation. It is therefore difficult to assess the potential risk given the lack of information. However, there are cases in which the woman takes drugs due to particular pre-existing medical conditions: it is in these cases that pharmacovigilance must be even more active.

Cases of congenital anomalies or developmental delay, in the fetus or child, cases of fetal death and spontaneous abortion and cases of suspected adverse reactions in the newborn classified as serious should be given more attention and reported to the authorities.



Cases of exposure to contraindicated drugs during gestation or medicines with a high teratogenic potential may also need to be notified, although with positive pregnancy outcome: often, in fact, pregnant women, or health professionals, contact the MAH to request information on the teratogenic potential of a drug taken before the woman knew about the pregnancy or without realizing the possible effects on the fetus. This is a real opportunity to **collect data on the exposure.**

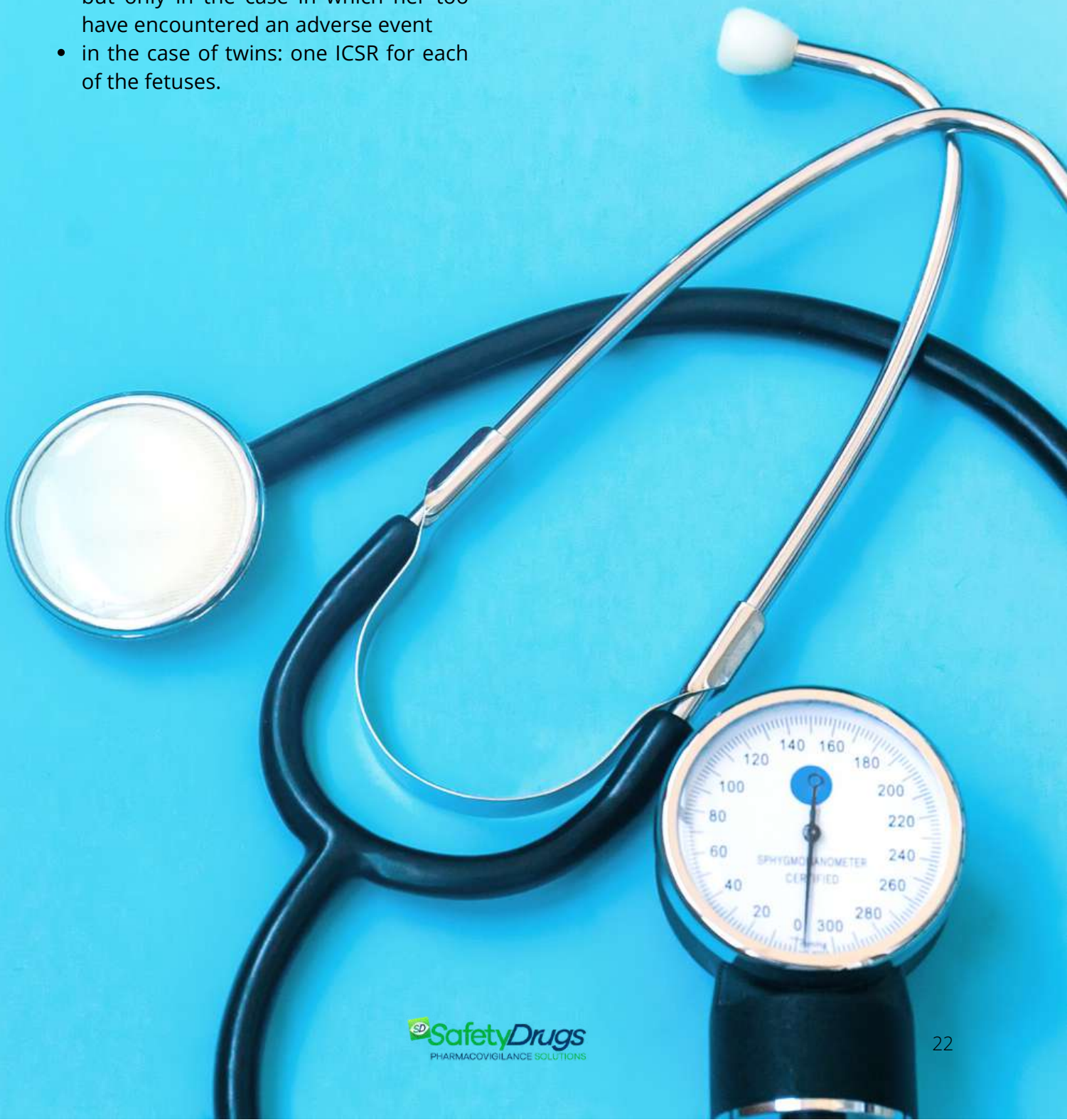
The MAH must implement additional measures in the following situations:

- cases of congenital malformations: provide a complete description of the malformation
- cases of spontaneous abortion: specify the time of occurrence and the history of spontaneous abortion
- cases of termination of pregnancy after the first trimester: obtain and provide the results of fetal autopsy and prenatal tests
- cases of late fetal death: collect prenatal test results, such as ultrasound, amniocentesis, serum markers etc., autopsy results, if available, and other factors that may have had an impact on fetal loss, such as diseases concurrent
- cases of paternal exposure: collecting information also on the father
- cases of taking medicines with teratogenic or fetotoxic effects: provide information on the outcome of the pregnancy.

In case of Adverse Event during the pregnancy, how many ICSRs must be created?

- In cases of abortion or death of the fetus without malformations: only one ICSR for the mother
- in cases of fetal malformations: an ICSR for the fetus and one for the mother, but only in the case in which her too have encountered an adverse event
- in the event of birth defects: an ICSR for the fetus and one for the mother, but only in the case in which her too have encountered an adverse event
- in the case of twins: one ICSR for each of the fetuses.

In conclusion, there are several doctors who prescribe drugs to pregnant or lactating women without knowing the potential risks or actual effectiveness; however, the MAH must ensure that it has done everything possible to collect the information necessary to improve the risk/benefit profile of the product.



ICH R3: WHY AN EXCEL SHEET IS NOT THE BEST CHOICE FOR ADRS MANAGING

MANY ARE THE PHARMACEUTICAL COMPANIES THAT STILL STORE UP PHARMACOVIGILANCE DATA WITH SPREADSHEETS.

AS WE OFTEN SAY TO THOSE WHO CONTACT US, THE ENTRY INTO FORCE OF THE NEW REGULATIONS IS AN OPPORTUNITY TO RETHINK COMPANY PROCEDURES. THERE ARE MANY REASONS TO LEAVE EXCEL AND SWITCH TO A NATIVE ICH R3 SOFTWARE.



1) THE EXCEL DOES NOT HAVE AN INTELLIGENCE DEVELOPED FOR THE ADVERSE EVENTS MANAGEMENT

Spreadsheets are not structured for the treatment of pharmacovigilance as they do not provide by default:

- advanced search for duplicates
- verification of the consistency of the data entered
- complex analyses with aggregated data
- signal detection.

Every action necessary for the treatment of cases must be contemplated, planned and reproduced by juggling the limits of the Excel environment so that the spreadsheet approaches the requirements provided by the regulations.

2) THE SPREADSHEET REQUIRES A MANUAL DATA ENTRY: THE ERROR IS AROUND THE CORNER

An Excel sheet lacks the automatic import function. The user is therefore forced to manually enter adverse cases into the document.

This implies:

- expansion of the processing times of each individual case
- activities with low-added value
- probability of transcription errors

On the contrary, dedicated software speeds up the procedure and safeguards against data-entering mistakes.



3) REPORTS ARE NOT AUTOMATICALLY GENERATED

Reports transmission to the Authorities becomes a laborious action. Since Excel is not a validated database, it does not issue reports that comply with accepted electronic formats. The processed data must then be entered manually in EudraVigilance.

Furthermore, it is not possible to generate all the regulatory reports necessary for carrying out the verification processes or for the external sharing of safety-relevant information.

A dedicated software, instead, integrates the functions necessary both for submission and for pharmacovigilance regulatory activities.

4) SPREADSHEETS ARE NOT A DATABASE

The manual data-entry into an Excel sheet requires a great deal of time and effort; archiving of additional documents (for example RTF or PDF attached to the case) is not possible; large numbers of cases are not easy to manage.

With a database, all processes are automated: storage is simple and straightforward, archiving and searching for adverse events is simplified and the process from the entering to the closing of the case is fully traceable with a digital signature for each change of workflow status.

The database is provided with coding tables containing E2B values and with lists of customizable items (Proprietary Medicinal Products, report receivers and mailing lists), which can be quickly accessible and without error.

5) IL DATABASE IS USER-ORIENTED

A database is not just an object limited to data-entry and storage object, but it is a valid, efficient and helpful tool. All analysis, such as signal detection, are performed without manual calculations thanks to special modules based on complex algorithms.

Another function present in the most advanced software is the message system. This is an articulated notification system via e-mail: it reminds the user of the activities to be carried out and prepares the transmission of specific cases in predefined circumstances.

6) EXCEL IS NOT A WEB APPLICATION

It means that the work environment in Excel contains tools that are not strictly necessary for the management of pharmacovigilance data and constitute a disturbing factor for normal operations.

The interface of a dedicated software is, instead, designed to facilitate the user in carrying out his/her tasks, providing exclusively targeted tools, intuitive

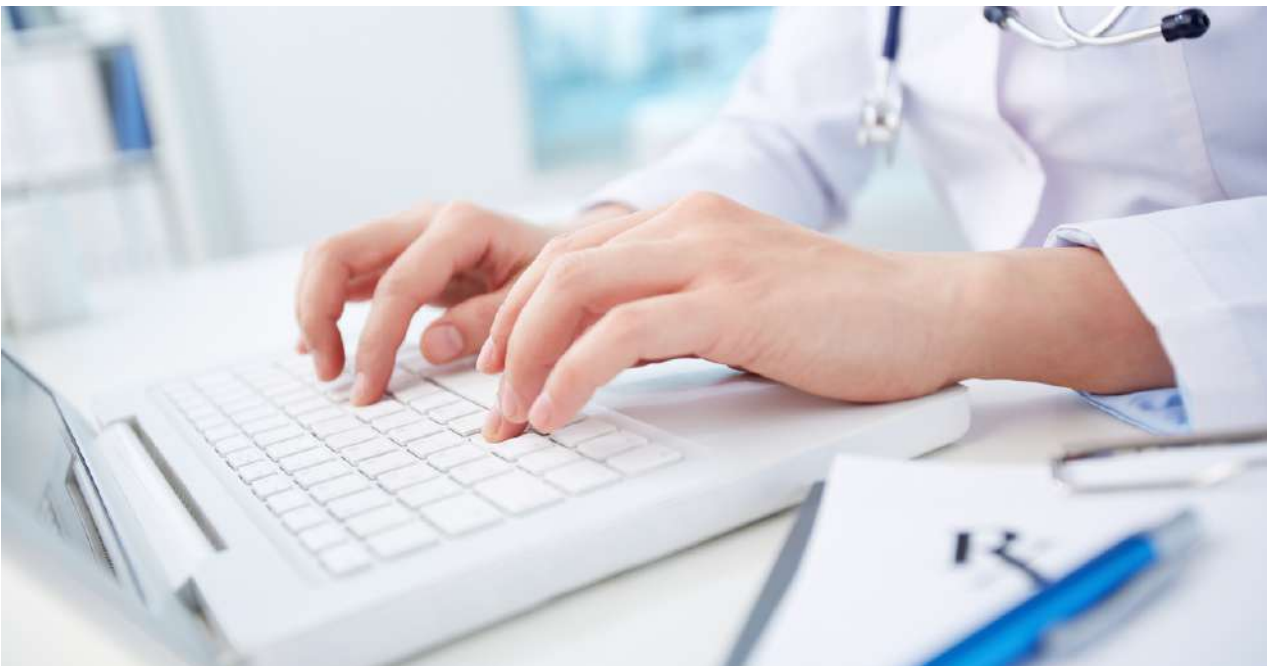
functions and guided paths. The benefit is productivity.

7) EXCEL DOES NOT GUARANTEE DATA INTEGRITY AND PROTECTION

Use of the Excel sheet does not comply with international pharmacovigilance regulations. For example, it cannot integrate an audit trail, on the contrary a compliant software keeps a precise track of the database accesses, of each update and of the case advancement; it also allows the printing of a detailed report with the process history.

Operators could accidentally corrupt the contents of a spreadsheet and the data would be lost if not protected by an appropriate backup.

A safety database, unlike an Excel file, cannot be easily consulted, transferred and used on a USB key. Its higher security level makes easier the integration in company procedures on data protection required by the European regulation (GDPR).



HOW LONG DOES IT TAKE TO INTEGRATE SAFETYDRUGS INTO BUSINESS PROCESS?

THE TRANSITION TO THE SAFETYDRUGS SAFETY DATABASE IS MADE UP OF 5 PHASES AND THE TIMING IS AROUND 6/7 WEEKS, HERE ARE THE DETAILS.



Many software developers have chosen not to adapt to the methods of electronic data exchange envisaged by the new international regulations or in other cases have done so by offering customers expensive or complicated solutions. The consequence is that today many pharmaceutical and service companies are evaluating the critical points and advantages of changing the old pharmacovigilance management software with a native ICH R3 one. Every change raises legitimate doubts and necessary insights.

We understand the state of mind of those who find themselves having to rethink consolidated methods.

The need to acquire procedures that sometimes are very different from the previous ones is undeniable. The leap is even more evident when pharmaceutical companies manage data storage with spreadsheets.

Potential customers always ask us what timeframe is needed to adapt to the new operating mode.

On average it takes 6-7 weeks to migrate to the new platform, to address the software validation and data migration and to train staff to the use of SafetyDrugs, the software for the pharmacovigilance management developed by Max Application.

Validation is often the variable on which the overall timing depends, with time dilation sometimes up to 4 months.

Should the client needs request it, and with the full active cooperation between the parties, a full operation can be achieved even in just 3 weeks.

There are five stages of the transition to new software:

- 1) Initial analysis
- 2) Fine-tuning of conversion strategy and creation of a conversion plan
- 3) Validation
- 4) Training
- 5) Go live

INITIAL ANALYSIS

It is the first phase in which, after the initial contact, a teleconference is usually organized and the companies introduce each other. Max Application analyzes the contractual aspects related to the two types of service provided: SaaS or purchase. In the first case, the cloud structure and the location of the primary and disaster recovery datacentres are detailed and the questions concerning privacy and validation are clarified.

The second part of the teleconference is dedicated to the demo in order to show the main functionalities of the database. Not only those ones strictly related to the process of the case, but also those useful for a comprehensive management of the pharmacovigilance activity: the To-do list helps to plan the activities of each team member, the Alert system sends internal messages and reminders, and the Tracking tool keeps track of follow-up requests, just to quote some examples.

Depending on the kind of customer, in addition to the basic module which manages ICSR from drug, both post-marketing and clinical trials, also the optional modules for the management of cases from devices, vaccines and cosmetics are presented. They can be added to the main database at any time.

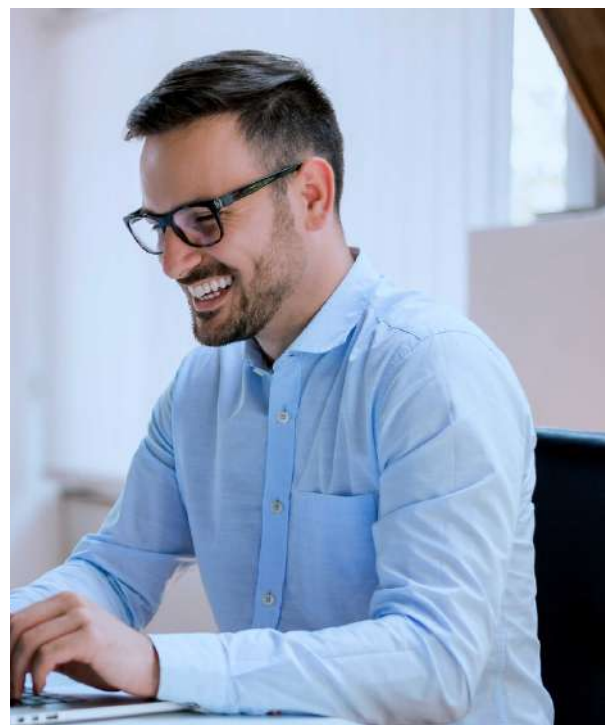


In the presence of a company that manages a fairly high number of cases, it is also useful to consider the Business Intelligence module, which, through flexible tools and intuitive dashboards, allows to carry out in-depth analyses, including the signal detection.

Another topic normally dealt with is that one concerning the migration of cases contained in the old database to SafetyDrugs 6. Depending on the type of original R2 database, Excel or other software, the import modality to be adopted is discussed.

Then, the Quick Start Validation Kit is illustrated. It is a set of validation documents that Max Application provides to all customers.

To conclude the preliminary analysis a tailor-made commercial offer based on the needs that emerged during the teleconference is sent. Following the agreement between the parties, the official Contract will be drafted.



DATA CONVERSION PLAN

After the signing of the Contract, the dates and the timings for the transition to the new software are defined, in order to plan the entire project that will lead to the start up.

Depending on the R2 database of origin, the kind of approach to follow for data conversion is established:

if the client has a database able to extract the ICSRs in XML R2 format, they will be upgraded to the HL7 R3 format using a special conversion tool. After that it will be easy to import the data into the new database, on the contrary, if the cases are stored in an Excel spreadsheet, each single column will have to be analysed in order to normalize the contents and lead them to standard ICH E2B (R3) format. In this way

the information will be aligned to the new requirements making them perfectly acquirable from SafetyDrugs 6.

After this analysis, a conversion map which defines the exact location of each data in the corresponding E2B and not-E2B fields contained in SafetyDrugs 6 will be drawn up. Then, the development of the migration scripts will follow.

After the evaluation of the data transfer modality, the Dry Run tests are performed. These are informal tests which aim is to ensure the successful outcome of the migration process. They are run in the client's test environment, previously configured according to the agreed specifications, to allow its own internal verifications.



VALIDATION

In this phase it is essential to define the installation of SafetyDrugs 6: Max Application will request the compilation of an installation questionnaire in order to provide all the necessary details.

The database is created on the cloud, then the Test environment is configured as defined with the client, who will be able to deepen all topics during the training.

Following the signing of the installation report, as acceptance of the activity performed by our technicians, the formal tests are run and the IQ – Installation Testing is released.

In addition we also offer the Quick Start Validation Kit, a set of documents compliant to the GAMP5® guidelines, containing the Standard Market Requirements, the Quality and Project Plan, the Design Specifications, the Functional Specifications, the Regulatory Compliance, the Traceability Matrix, the Installation Procedure and the Unit and Integration Test performed in our standard environment (OQ – Functional Testing).

Since the Computer System Validation is the most onerous task for the client, Max Application, on specific request, makes its own technical know-how available to provide support during the entire process.



In case of request for a data backlog, the legacy cases are imported in the Test environment and the quantitative and qualitative validations of the conversion are provided:

- the quantitative validation verifies the correspondence of the totals of the cases present in the original database and those contained in SafetyDrugs 6. Moreover, a check is also performed on some subtotals, such as the subtotals by SERIOUS/NOT SERIOUS cases, of the cases by PRIMARY SOURCE COUNTRY, of the cases by REPORT TYPE, of events by MedDRA SOC, of events by OUTCOME and of the subtotals by DRUG.
- the qualitative validation compares data between the old and the new database, of every single field migrated on a sample of random cases.

At this point the Production environment is created as an exact copy of the previously validated Test environment. Now everything is ready for the go-live.



TRAINING

For the training we recommend at least two days of coaching to the operator at the customer's site and the rest divided into multiple webinar sessions.

Day 1

The user will be formed on the logic of general parameter settings, logins, menus, lists of values, product dictionary and MedDRA.

We then proceed with the creation of a new case starting from the function of searching for duplicates. We continue by inserting the information of the case in the respective sections provided by the ICH and by making it advance through the chosen workflow. In all this process the automatic functions which calculate the durations and those which create the correlation matrix and the narrative are of great help.

The day ends with an in-depth analysis of the possible receivers of the case, of the related deadlines calculation function and of the reports, such as CIOMS, Audit Trail, Quality Check for the validity check of the case and the Cover Case, where are registered all the data of the status change, comments included.

During the day there will be practical exercises for all users.

Day 2

The chapter on case management ends by facing the creation of XML files in the new R3 format, the mask to query the ICSRs present in the safety database and the one to manage the activities linked to them such as the follow-up requests. The training then moves on to the creation of a new version of the case itself and to the related history. It concludes with the

explanation of the automatic function which updates the MedDRA terms to the latest version in force.

At this point the following topics will be related to import and export: the Converter (XML-HL7 and HL7-XML) and the Selective Import, the function that allows to display the main data of the case, before importing, are presented. In order to be able to select and acquire only those deemed relevant. The Message System will also be explained, the internal messaging function to SafetyDrugs for sending cases or reports to a list of receivers.

Day 3

The day is mainly devoted to reports, in particular to line listings and summary tabulation that will be part of PSURs and DSURs, to the SMQs and finally to the control reports on the cases processed, submitted, sent to partners, etc.

The training for the operator user concludes with full-field exercises to shed light on any doubts.



Day 4

The last day of training is exclusively dedicated to the administrator user, who in addition to having acquired the skills of the operative user, will also be trained about the general parameterization, the parameters of the search for duplicate, the dictionaries, the coding tables, the products tables and those of devoted to clinical studies, the Message System and the Audit Trail.

At the end of the training the relative Training Certificate will be provided to all participants.

For those clients who have signed up for the Business Intelligence module, a further day of training is planned dedicated to examining the various dashboards for detailed analysis, including the Signal Detection.

THE GO-LIVE AND THE ASSISTANCE SERVICE

Once all the previous steps have been completed, the customer can finally start working with SafetyDrugs 6.

Users who attended the training, are able to work independently on the database, but in case of need they can use our after-sales service, it is possible to directly access the "ACU" portal, dedicated to assistance requests, by simply clicking on the icon installed on the desktop of the user's PC or via the SafetyDrugs website. The user will need to log in with his/her login credentials, open the ticket add the necessary details and then will be able to monitor the progress of the request, to interact with the technician and to be notified at the end of the resolution.

An internal team will be ready to intervene quickly on every request, according to the Max Application SLA (System Level Agreement) that foresees taking charge within the next 4 working hours. Furthermore, for the first few weeks after the departure, the customer will receive particular attention and will benefit from a specially reserved channel with the assistance team to receive priority support.



HOW MUCH DOES SAFETYDRUGS COST?

MORE AND MORE PHARMACEUTICAL COMPANIES OR PROVIDERS OF PHARMACOVIGILANCE SERVICES ARE LOOKING FOR A DATABASE THAT ENSURES COMPLIANCE WITH THE NEW ICH R3 REGULATIONS. IN THE EVALUATION PHASE, COST IS A CENTRAL ELEMENT AND IN FACT THE MOST FREQUENT QUESTION IS: HOW MUCH DOES SAFETYDRUGS COST?



There are many variables that affect the software economic impact in a company's budget: a one-time start-up cost and a monthly fee.

1) START-UP

There are two types of contracts:

- On-Premises, solution with installation at the client's server
- SaaS, Software as a Service, cloud solution with data centre installation.

In both cases the start-up includes:

- **Installation** of test, production and eventual business intelligence environments on the server;
- **Parameterization** of the entire database;
- **Configuration** of the client on each location;
- **Upload** of MedDRA and WHO **dictionaries**;
- Supply of **project technical documentation** and results of functional tests.

Other items that contribute to the definition of the start-up cost:

- **Training.** To acquire the concepts of database use, we recommend four days, two of which in the client's offices and two via internet with a dedicated webinar.
- **Import of legacy data.** The cost of import varies based on the quantity and quality of the data. It also depends on the original source: Excel sheet or database.
- **Support for validation.** It is an optional service for an operational contribution in the functional testing phase in the customer's environment.

2) MONTHLY FEE

Companies big and small have different needs, the modularity of SafetyDrugs satisfies everyone. The architecture of the functions, and consequently the monthly fee, is mouldable on the various business realities.

The fee is the combination of three parameters:

- **Number of users.** It means the quantity of physical users with personal access to the database. To comply with the regulations must be at least three, one for each phase of the case process: data entry, quality check and medical assessment. Two profiles can be configured for each user - administrator and operator - each with customized read and write privileges.

- **Number of sites.** Quantity of separate and independent virtual spaces intended, for example, to branches or business units, to specific customers of a service company or to clinical studies of a Contract Research Organization (CRO).
- **Number of cases.** The annual number of cases entered into the database determines an environment with more or less large memory space.

Each of the parameters and the resulting fee can be reconsidered as needs change. The basic module manages the entire pharmacovigilance cycle for drugs and clinical studies. Includes the Selective Import function for the massive acquisition of HL7 files with relative triage mask prior to import.

Among the optional modules there are:

- Device with MEDDEV and MedWatch reports
- Cosmetics
- Vaccines
- HL7-XML and XML-HL7 converters
- Business Intelligence

The fee also includes the license to use the database, disaster recovery, maintenance-assistance and all updates.

In conclusion, to determine the costs of configuring the safety database that best adheres to company quality processes, it is necessary to weigh each variable and balance the best cost/benefit ratio.





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