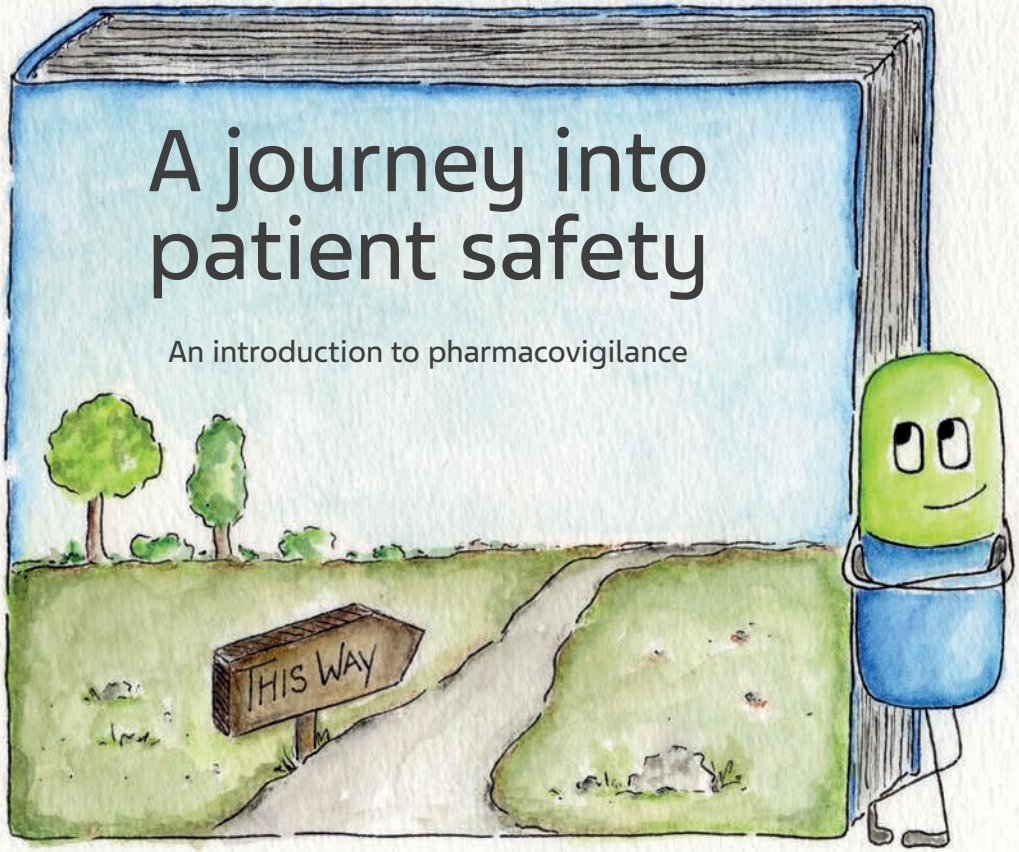
A journey into patient safety

An introduction to pharmacovigilance



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BENEFIT
HEALTH
Pharmaco
Vigilance
Risk!
SIDE EFFECT
SIGNAL

Acknowledgments

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TPC group (including all members, both past and present) – thank you for being our professional and creative perpetuum mobile.

Tamar, thank you for all the effort you've put into this project and for making this dream become a reality.

To our family members and friends, thank you for your support; even in times when instead of dinner, you were served a new chapter of this book.

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Reviewers' comments

I have really enjoyed it. I especially enjoyed the "Did you know..."

Hedva Voliovitch, MD, PhD, MBA

By reading the book one can feel that it was indeed written by a group of PV enthusiasts inspired by patient safety, and I'm very proud of what you created!

Morana Šimundić, MSc med. biochem.

This is excellent and unique book. Examples are vivid and the strongest part of the book. Mateja's illustrations are very original.

Klaudija Marijanović Barać, MD

What a great book - I could not stop reading once started! I really enjoyed the vivid language and enthusiastic, dynamic and sometimes even funny flow of the book.

Nicole Lang, MD, PhD

This is a great book for patients to understand what is done to ensure their safety. Knowing the authors, you can really feel their personal touch in different sections.

Iva Novak, MPharm

Your book "A Journey Into Patient Safety", is an excellent, detailed discussion of PV, for which all the authors should be justifiably proud.

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Contents

Introduction

Dear Reader,

We have probably all been, or will be, a patient at some point in our lives. And we all know, being a patient is never easy. An old Latin proverb says "Salus aegroti suprema lex", meaning "The well-being of the patient is the most important law". Today, as then, patient safety is regarded as one of the world's biggest challenges. But what does it actually mean and what does it involve? This is a book specially designed to answer that question – whether you are a patient or you would just like to find out more about how patient safety is ensured.

Fourteen pharmacists and doctors working in a pharmaceutical company took on the challenge of explaining how patients are kept safe from an industry perspective. We will take you on a journey that will describe when, how, and who takes care of patient safety, share the rationale for these activities, and demonstrate the complex procedures involved. Also, we will describe how pharmaceutical companies work hard to minimize the risks of experiencing side effects and try to provide answers to questions that sound more complicated than they really are, such as "What are the odds of experiencing a side effect when taking a medicine?" and "Is it still worth it to take a medicine even if I might experience a side effect?" But, most importantly, we show how you can contribute to maximizing patient safety – by listening to healthcare professional advice, reading the information provided, taking medications as prescribed, and recognizing and reporting side effects.

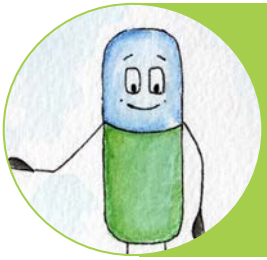
The 20th and 21st century brought discoveries and inventions that have vastly improved our lives, making them easier and safer than a hundred years ago. We can travel whenever and wherever we want, access information twenty-four-seven, and our technical knowledge is growing exponentially, extending both our life span and its quality. The discovery of the antibiotic penicillin enabled us to conquer life-threatening bacterial infections. Similarly, insulin now saves diabetics from severe complications and early mortality, and vaccines protect us from infections such as polio, cholera, or typhus, and save millions of lives every day. However, life has never been so fast-paced and stressful as it is now. We tackle more tasks in one day than our ancestors faced in a month. Our new lifestyle, as well as our greater longevity, has brought forth challenges in medicine that were virtually unknown 100 years ago.

These include a high incidence of cardiovascular and immunological disorders, degenerative neurological diseases (e.g. Alzheimer's disease), and mental health issues. Although advances in diagnostic methods

have uncovered a vast area of genetic disorders, many still remain incurable. Fortunately, our inexhaustible wealth of knowledge and collective experience enable us to continue the discovery and development of new modes of treatment.

It is the mission of pharmaceutical companies to go from understanding a disease to bringing safe and effective new treatments to patients but it is a long and complicated process. Every day, scientists work to piece together the basic causes of diseases and discover "targets" which potential new medicines might be able to affect. It takes about 10 to 15 years to develop a single new medicine from the time it is discovered to when it becomes available for treating patients. **Figure 1-1** illustrates the process of medicine discovery and development and shows the many steps taken before a medicine can be marketed.

Despite these preclinical and clinical investigations, some properties of the medicine may only be revealed after its widespread use. Therefore, the law requires pharmaceutical companies to monitor the life-cycles of their medicines even after their approval, and collect, assess, and report side effects. This process is known as pharmacovigilance.

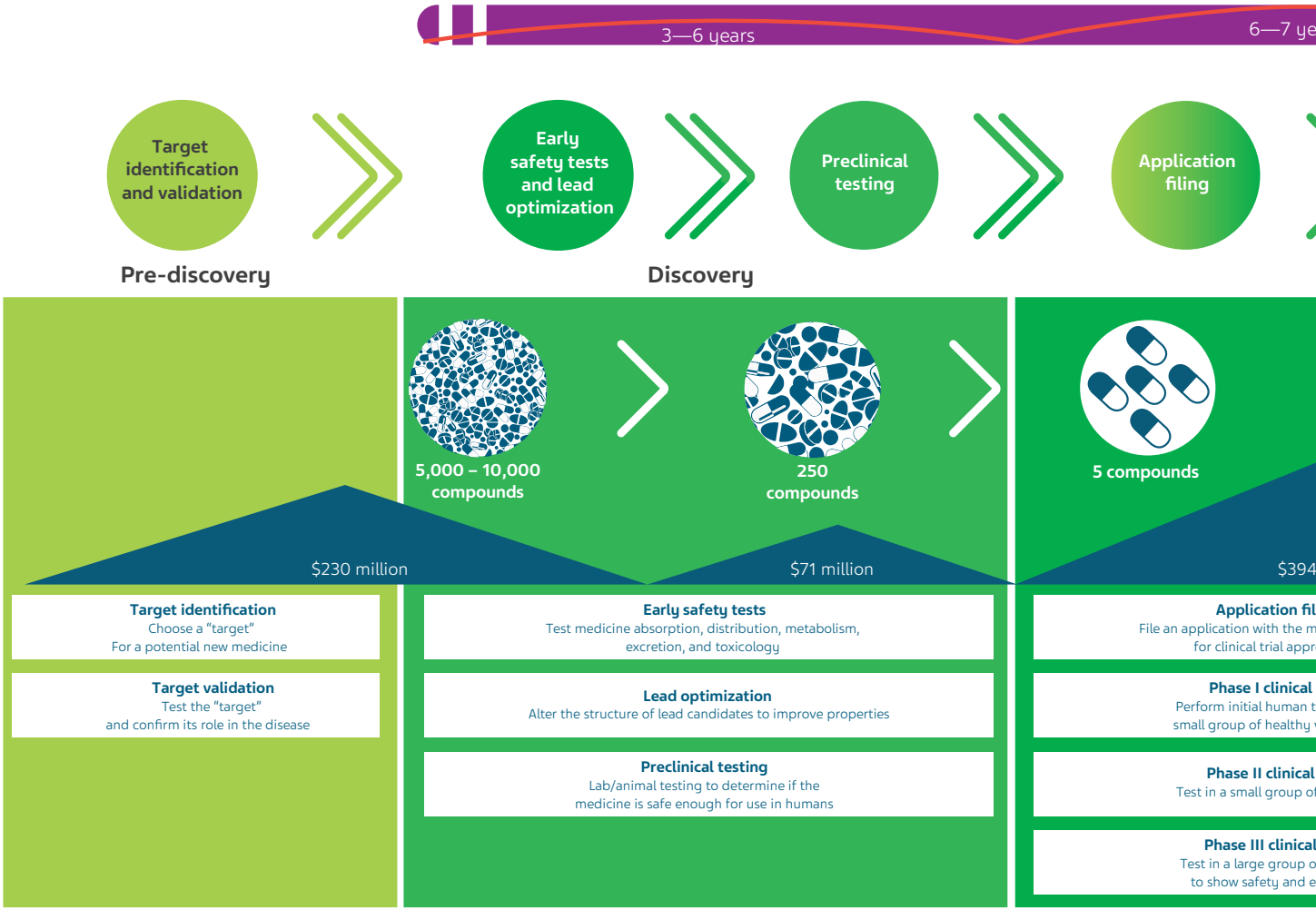


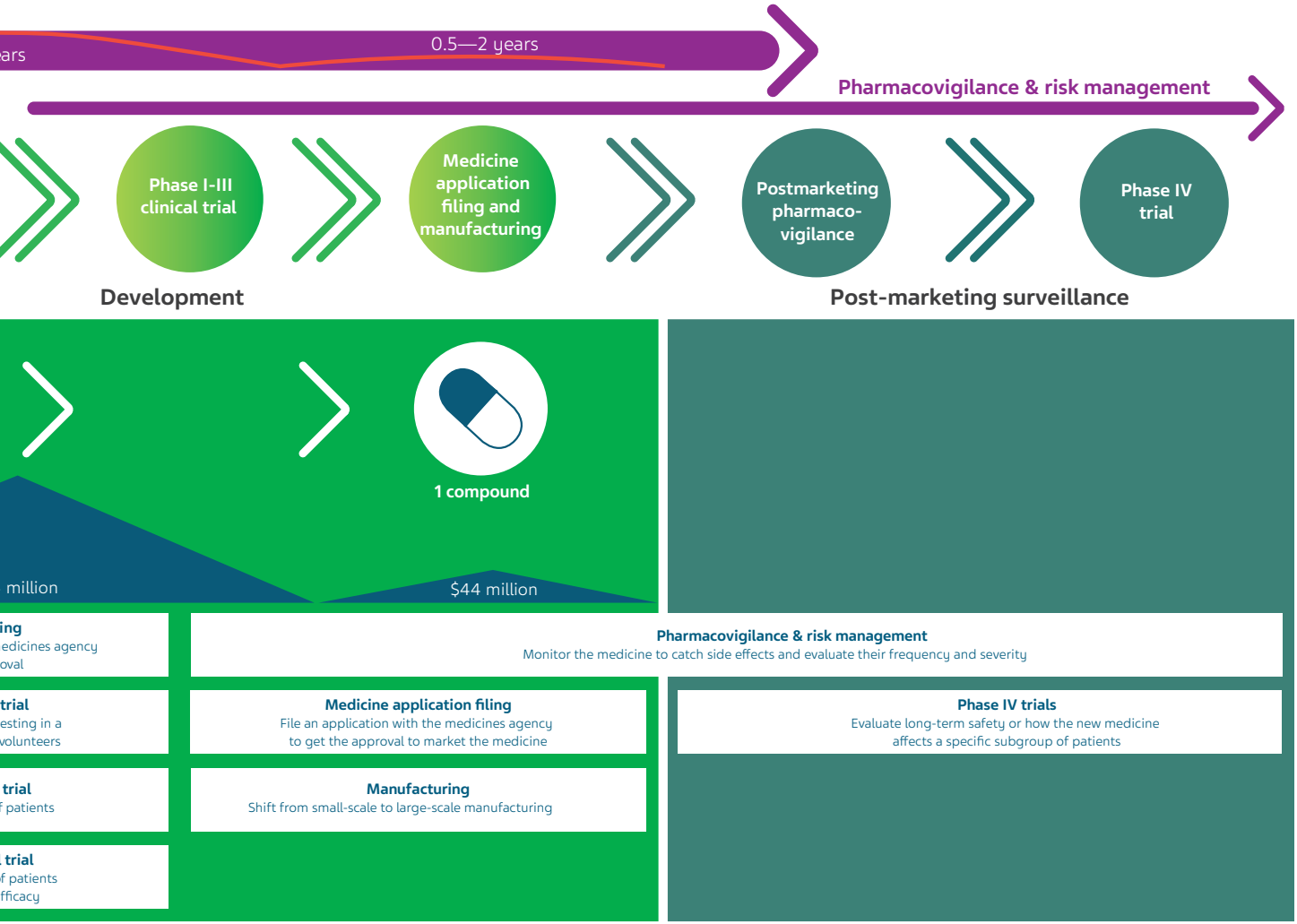
What you might ask yourselves now is:

"OK, I now understand what pharmacovigilance is... but how do I recognize side effects, and who reports them to whom? If a side effect occurs, who is to blame?

Even if I notice a side effect, does it really matter?"

Figure 1-1. The process of drug discovery and development.

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Phase I-III clinical trial
Medicine application filing and manufacturing
Postmarketing pharmaco-vigilance
Phase IV trial
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Pharmacovigilance & risk management
Monitor the medicine to catch side effects and evaluate their frequency and severity
Medicine application filing
File an application with the medicines agency to get the approval to market the medicine
Manufacturing
Shift from small-scale to large-scale manufacturing
Phase IV trials
Evaluate long-term safety or how the new medicine affects a specific subgroup of patients

The following chapters will help you find the answers to these and other questions. By revealing the world of pharmacovigilance in a simple way, you will find out how to report a side effect and what happens as a result; see case examples of the different things that can go wrong with medicines and why they should be taken exactly as prescribed. In a later chapter, we will answer one of the most frequently asked questions about medicines: what is the difference between a generic and an innovator's medicine? We'll also tell you what a safety signal is in pharmacovigilance and what can be done to minimize the risk of experiencing side effects. And last, but not least, you can find out what our youngsters have to say about medicines, side effects, and pharmacovigilance.

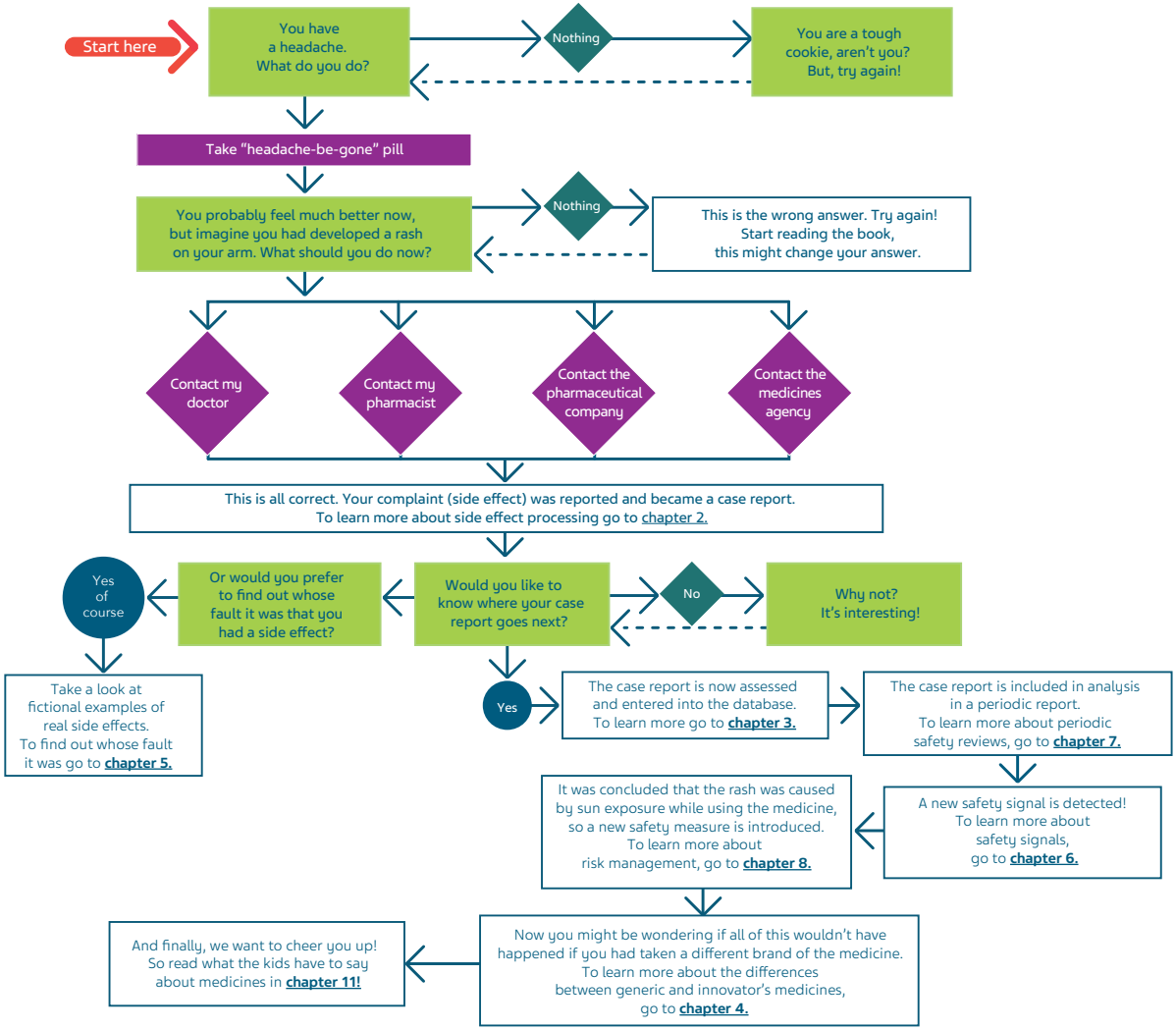
You can also test your knowledge about patient safety and pharmacovigilance by visiting the short quiz at the end of the book. Don't worry – we also provide the answers!

From here, you can choose your own journey. You can simply start reading the book or choose your own adventure in pharmacovigilance by following the steps in this flowchart. We hope you find it educating and entertaining!

The names, characters, and places in case reports presented in the book are products of author's imagination.

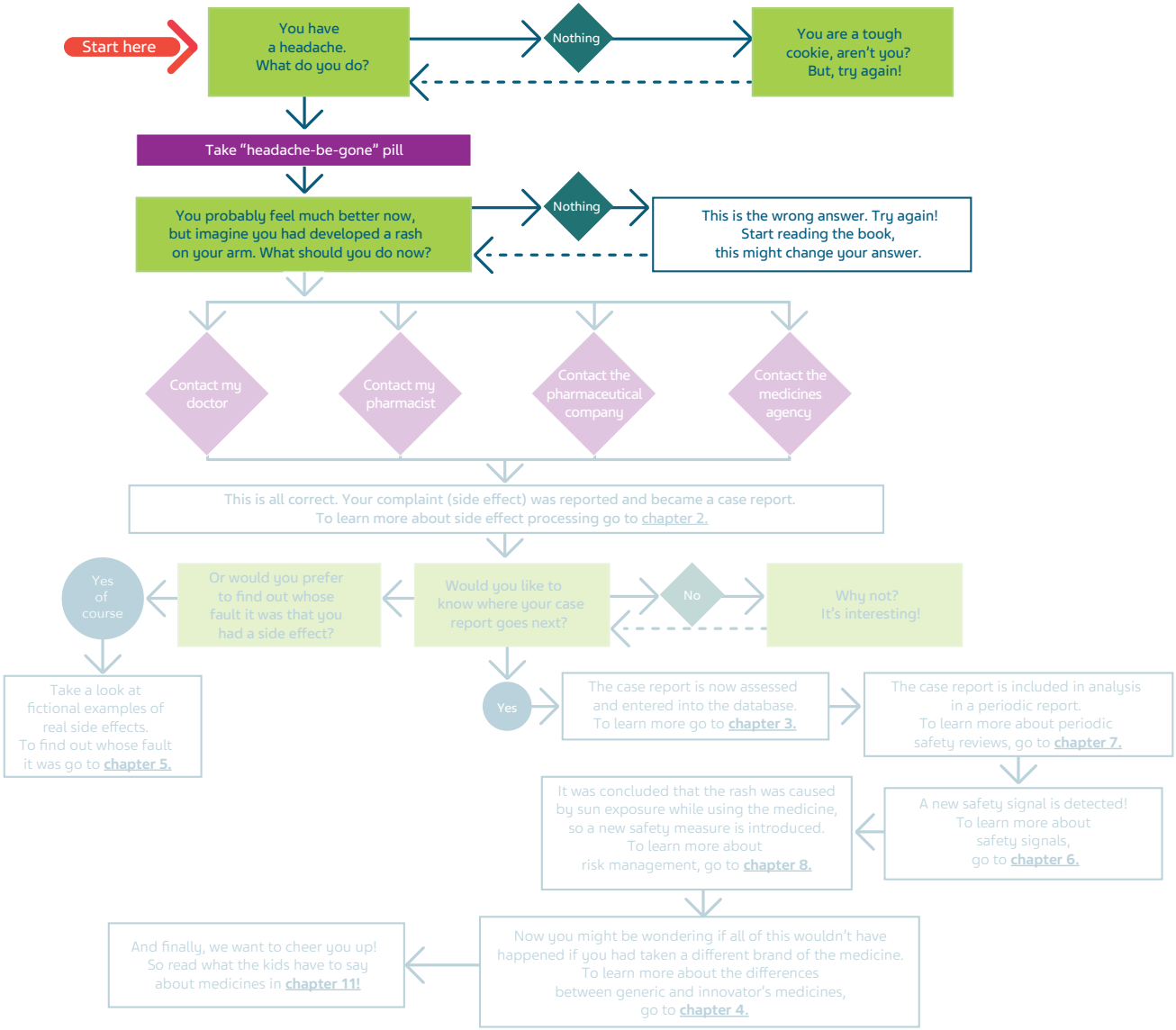
Did you know...

Vincent van Gogh, the great Dutch painter, was not only well-known for his magnificent works of art but also for his troubled life, which ended in suicide in July 1890 at the age of thirty-seven. During his last few years, his paintings were characterized by halos and the color yellow. A striking feature of van Gogh's famous painting "The Starry Night" is the yellow corona surrounding each star. One popular theory is that the Dutch painter had epilepsy and was possibly treated with digitalis, an extract of the foxglove plant, by his physician, Paul-Ferdinand Gachet. This was common practice at the time. Digitalis is also known as digoxin and is now used in the treatment of atrial fibrillation and atrial flutter. In one of van Gogh's three portraits of Gachet, the physician holds a stem of Digitalis purpurea, the purple foxglove from which the medicine is extracted. Large and repeated doses of digitalis can cause the world to be seen with a yellow-green tint, a colour vision deficiency known as xanthopsia. People affected complain of seeing yellow spots surrounded by coronas, much like those in "The Starry Night." A popular theory is that digitalis intoxication and the resulting side effects of xanthopsia and coronas, may have dictated van Gogh's unique and world famous technique.



Any resemblance to actual events, locations, or persons, living or dead, is entirely coincidental.

1.0 Pharmaco....what?? Pharmacovigilance




BENEFIT
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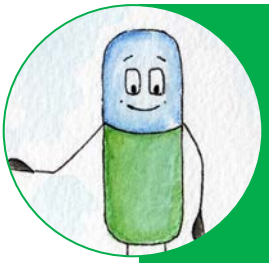


- Before a medicine is made available to patients, pharmaceutical companies spend over a decade in monitoring and improving a medicine's efficacy and safety via rigorous preclinical and clinical investigations.
- Despite preclinical and clinical investigations, there are events which may still be insufficiently described, such as the medicine's interactions with other medicines, the effects on pregnancy (pregnant women do not participate in clinical trials), and the influence of other underlying diseases in humans. The thalidomide tragedy was a catalyst for the establishment of medicine safety requirements: it prompted changes in the monitoring of medicines, namely, the collection, assessment and reporting of side effects – the process we know as pharmacovigilance.
- The word "pharmacovigilance" is a derivative from the Greek word pharmakon which means "drug" and the Latin word vigilare meaning "to keep watch", and it literally means "keep watching the drug".
- In 1968, the World Health Organization started the Pilot Project by pooling side effects from multiple countries, which is nowadays known as side effect reporting or pharmacovigilance.

As it takes 10 to 15 years for a medicine to be developed, you could say that a medicine is a teenager by the time it becomes available to patients. As every parent learns, sooner or later, teenagers can be unpredictable. Despite the fact that a decade is spent in monitoring and improving a medicine's efficacy and safety in various organisms and under various circumstances, there is always a possibility that something may go undetected. Sometimes, only the widespread (or "real-world") use of a medicine in thousands of people (much more than it is possible to achieve in a clinical trial [**Figure 1-1**]) will reveal a side effect that is either rare, affects only a certain genetic population, or arises as a result of many different factors, such as the environment, illness, other treatments or

duration of use. The safety of medicinal products throughout clinical trials and in the post-marketing era (the period following approval for the medicine to be marketed) is monitored through a scientific branch called pharmacovigilance. Rather than quoting complicated definitions to clarify what this means, we'll tell you how it began, a story of a truly unfortunate character named "Thalidomide".

Thalidomide was developed by the German company Chemie Grünenthal in the 1950s as an anticonvulsant; a medicine that prevents or reduces the severity and frequency of seizures. Early trials showed it to be unsuitable for this purpose but they did show that it had sedative properties. Thalidomide was first marketed in Germany in 1957 under the name Contergan. An Australian obstetrician, Dr. William McBride, discovered that thalidomide also alleviated morning sickness in pregnant women. Although it was not approved for use in this way, he started recommending the medicine to his pregnant patients, starting a worldwide trend of off-label use (the use of a medicine for unapproved indications). The only country where thalidomide was never actively marketed was the United States. Dr. Frances Kelsey of the U.S. medicines agency, the U.S. Food and Drug Administration (FDA), denied the approval of thalidomide based on reports of nerve damage in the hands and feet (polyneuropathy) in elderly patients treated with the medicine. Unfortunately, this was only a minor side effect of thalidomide.

In the late 1950s and early 1960s, German pediatricians and geneticists began to notice newborn children with major limb malformations of a most unusual pattern. When two cases were shown at a pediatric meeting, only a few people present had ever seen similar limb defects. In 1961, Dr. Wiedemann described 13 affected infants who had been referred to him over a period of 10 months and noted that such a large number of affected patients amounted to an epidemic. He also drew attention to a number of other malformations in these children, affecting the heart, eyes, intestines, kidneys, ears, and skin. Medical concern regarding the potential teratogenic effect (propensity to cause birth defects) of thalidomide was first raised by Dr. Widukind Lenz, a Hamburg-based physician. On November 17, 1961, Grünenthal received a letter from Dr. Lenz, which summarized his observations and concerns that thalidomide, when taken by pregnant women, may cause malformations in their unborn children. By a remarkable coincidence, the Australian obstetrician, Dr. William McBride, raised the same concern and contacted Grünenthal a week later. Confirmation of their observations and concerns came rapidly from all parts of the world.

Based on concerns provided independently by the two physicians, Grünenthal withdrew thalidomide from the market within 24 hours. Some scientists were not convinced that thalidomide was responsible for the epidemic of limb defects. Dr. Josef Warkany, one of the founders of the Teratology Society, expressed doubts in April of 1962, based on two observations: experiments in rats had not produced comparable malformations and malformations in humans were inconsistent (i.e., some mothers exposed to thalidomide had healthy children and some malformations occurred in children whose mothers did not knowingly take thalidomide). It was not until later that year that scientists succeeded in demonstrating the teratogenicity of thalidomide in animal studies in white New Zealand rabbits.

It has been estimated that approximately 10,000 children were born with congenital disorders following thalidomide intake by their mothers during pregnancy. The medicine caused a wide variety of birth defects, not one of which was unique to thalidomide. Nevertheless, the nature and pattern of the defects were, in most cases, characteristic enough to be recognizable by an experienced eye.

The thalidomide disaster is regarded as one of the darkest episodes in pharmaceutical research history. Knowing what we know today, it seems strange that these malformations were not attributed to thalidomide sooner but, looking back, it shouldn't be surprising. If one obstetrician had seen only a few babies with such defects, he would likely have attributed them to other causes, such as genetics or the environment (today, about 3% of babies are born with some birth defect/congenital anomaly). Clearly, only systematically collecting and evaluating family histories, medical histories, and living environments of many pregnant women would have pointed to a common factor – the medicine.

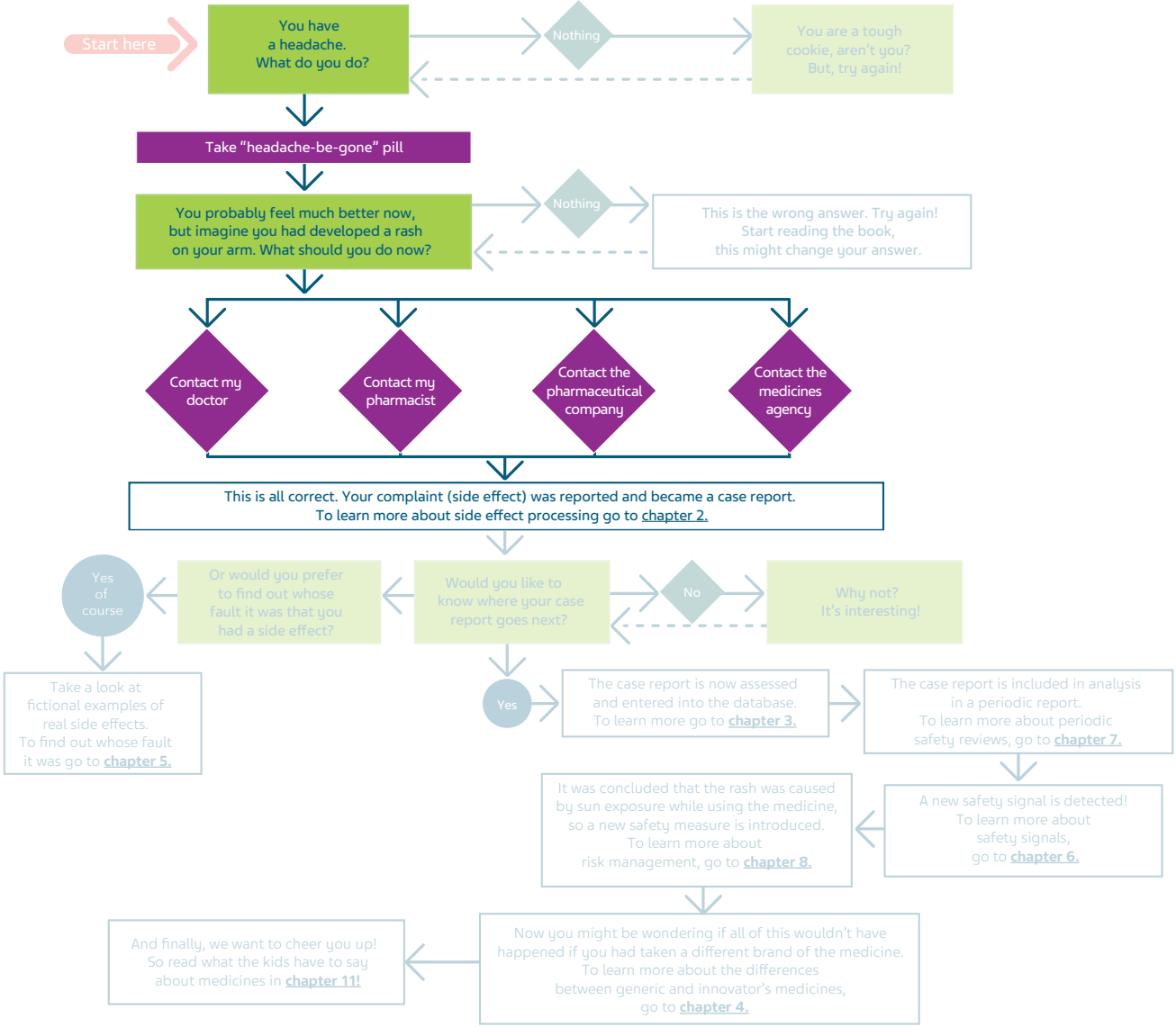
This tragedy was a catalyst for the establishment of medicine safety requirements. These new requirements prompted the introduction of systematic preclinical testing of pharmaceutical products for potential toxic effects on embryo-fetal development. The events around thalidomide generated widespread recognition of the need to consider differences in sensitivity between species. As a consequence, preclinical testing of pharmaceuticals for embryo-fetal developmental toxicity is now conducted in two species, one of which is not a rodent. Another big step was the introduction of medicine safety surveillance in the post-marketing life-cycle of each medicine.

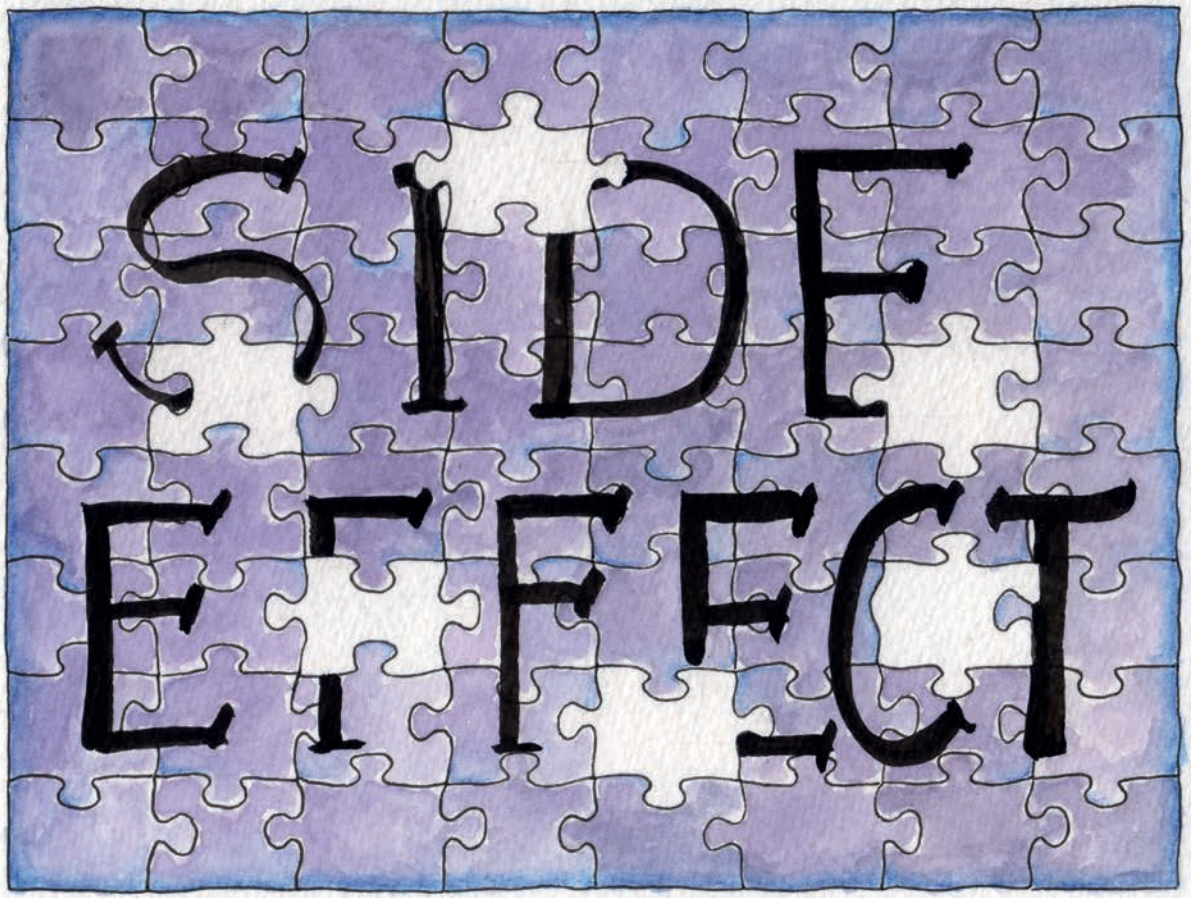
In 1968, the World Health Organization (WHO) started the WHO Pilot Project by pooling side effects from multiple countries, which is nowadays known as side effect reporting or pharmacovigilance. According to WHO, pharmacovigilance is the science related to the detection, assessment, understanding and prevention of adverse effects or any other medicine -related problem. This long word is actually a derivative from the Greek word pharmakon which means "drug" and the Latin word vigilare meaning "to keep watch", and it literally means "keep watching the drug". For the sake of simplicity, we'll call it PV. When a medicine is released on the market, only rarely has it been exposed to more than 5,000 individuals, which is less than 0.0001% of the global population. Despite rigorous preclinical and clinical investigations (see **Figure 1-1**), there are events which may still be insufficiently described. These include the medicine's interactions with other medicines, the effects on pregnancy (pregnant women do not participate in clinical trials), and the influence of other underlying diseases in humans. Some properties of the medicinal product might be revealed only after its widespread use. Therefore, the law requires pharmaceutical companies to monitor the safety of their medicines even after their approval, by collecting, assessing, and reporting side effects.

Did you know...

In 1964, in the wake of the thalidomide disaster, the Yellow Card Scheme was established in the UK to collect suspected adverse drug reactions (ADRs) to provide an early warning of possible hazards. The scheme allows health professionals, patients, parents, and caregivers to report suspected ADRs on a voluntary basis alongside those collected from the pharmaceutical industry. Over 750,000 Yellow Cards have been received since the scheme's inception over 50 years ago.

2.0 Pieces of the puzzle: where do side effect reports come from?

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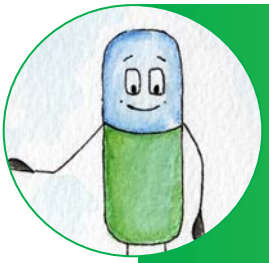


- Reporting a side effect of medication is important. Although you might think that no one is bothered whether you report it or not, the very opposite is true.
- A side effect can be reported to your physician, pharmacist or other healthcare professional, to the pharmaceutical company, or your local medicines agency.
- Once a side effect report reaches a pharmaceutical company, it is sent to its PV department. A pharmaceutical company is obliged to have a PV contact in every country in which it has registered its medicinal product(s).
- These side effects are classified according to their different sources – clinical study cases, solicited cases, spontaneous cases, health authority cases, and literature cases.
- No matter who reports the side effect, or how it was sourced, all cases are entered into the pharmaceutical companies' safety databases and are evaluated to maintain the safe use of medicines.

Why should I report a side effect? Probably no one deals with that, anyway.

This may cross your mind when asking yourself "whether or not to report" a suspected side effect. And you would be completely wrong; once a side effect is reported to a pharmaceutical company, it is sent to its PV department, where all reported side effects from various sources are stored in a database for further analysis. Every country in which a pharmaceutical company has registered its medicinal product(s) is required to have a PV department.

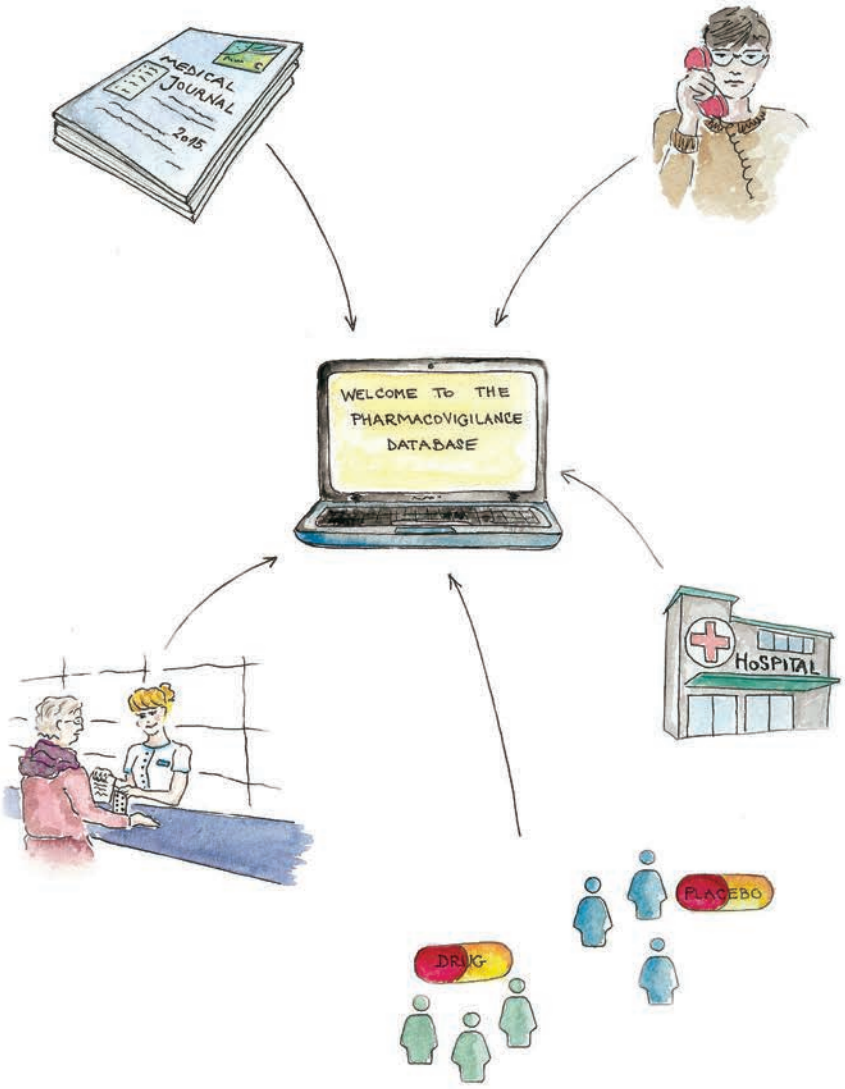
In order to picture the different ways of reporting side effects, take a look at the following example. John, Mary, Leah, Luke, Amy, and Paul are patients with diabetes who occasionally gather at meetings of their local

patient association "Enjoying life with diabetes". At their last meeting, Paul, who was recently diagnosed with type 2 diabetes, shared his story involving his newly-prescribed antidiabetic medication. Ever since he started on this medication, Paul's food began to taste differently. When he complained to his diabetologist, he found out he wasn't the only patient experiencing this problem. In fact, the diabetologist explained that a couple of other newly-diagnosed patients had developed the same reaction. As a result, he planned to write an article for Diabetology Today regarding taste disturbance in newly-diagnosed patients on the antidiabetic medicine (metformin). After Paul's diabetologist published the article, Paul's case and those of the other patients mentioned, were entered into the PV databases of companies that market metformin as **literature case reports.** Screening of published articles in medical journals to identify case reports is an obligation of every pharmaceutical company, and when such publications are identified, they are entered into a company PV database for analysis.

As their conversation continued, Mary said she had also heard about reporting of side effects a few months earlier, when she was enrolled in a clinical trial investigating the efficacy of a recently developed medication for diabetes. A week after starting the trial with investigational medicine, XY113, she started coughing. The physician in the clinical trial made a note of Mary's cough and reported it as a possible side effect to the pharmaceutical company which developed the medicine. Upon investigation, it was discovered that she had atypical pneumonia, the same type as her niece, who visited Mary every day before the clinical trial started. Nevertheless, the case was entered into the company's PV database as a **clinical trial case report** with Mary's medical history and important medical information. Pharmaceutical companies are obliged to collect all side effects occurring in clinical trials. After hearing Paul's and Mary's stories, the rest of the group realized that their side effects were also reported, but in a number of different ways.

Amy explained how she saw an interesting commercial on TV sponsored by the national medicines agency recommending all patients to become more alert regarding their medications and possible side effects. The commercial focused on the importance of reporting side effects, which gave Amy the idea of contacting the medicines agency. When she reached its call center, Amy explained that the dose of her diabetes medication had recently been increased. Shortly afterwards, she started experiencing frequent headaches and wondered whether it might have something to do with the increase in dosage. Amy was asked to provide information regarding the medicine and her medical history, which she happily provided. After the agency's PV department processed Amy's case report, it was forwarded to the PV department of the pharmaceutical company which marketed the medication, where the case was classified as a **health authority case report.**

Figure 2-1. Where do side effect reports come from?



John experienced a similar situation to Amy's and wanted to report bloating. He didn't know he could call the medicines agency, so he called the number provided on the package leaflet of his medication and reached the pharmaceutical company's call center. During the call, John provided the additional information they requested and his case was entered in the company's PV database as a **consumer case report.**

Leah's experience with reporting side effects involved her general practitioner (GP). She experienced a high blood sugar episode when her insulin injection pen jammed and didn't release the required insulin dose. Leah's GP prescribed a new insulin pen and called the pharmaceutical company to report Leah's device issue and side effect. This report was entered into the company's PV database as a **healthcare professional case report.**

Finally, it was Luke who gave the last perspective on reporting side effects. He entered a patient assistance program after starting therapy with a novel antidiabetic medicine only recently developed by a pharmaceutical company. In order to help the patients with the new medication, the program included regular visits and contact with specialized nurses. Luke was feeling very good on the new medication; however, after a couple of weeks, his nurse noticed a widespread rash on his back. As part of the patient assistance program, the nurse reported Luke's case. This was classified as a **solicited case report** in the company's PV database.

To sum up, a side effect can be reported to your physician, pharmacist or other healthcare professional, to the pharmaceutical company, or your local medicines agency and, as you can see, there are different types of case reports classified according to their source **(Figure 2-1).** All these cases are entered into the relevant pharmaceutical company's safety database and evaluated to maintain the safe use of medicines.

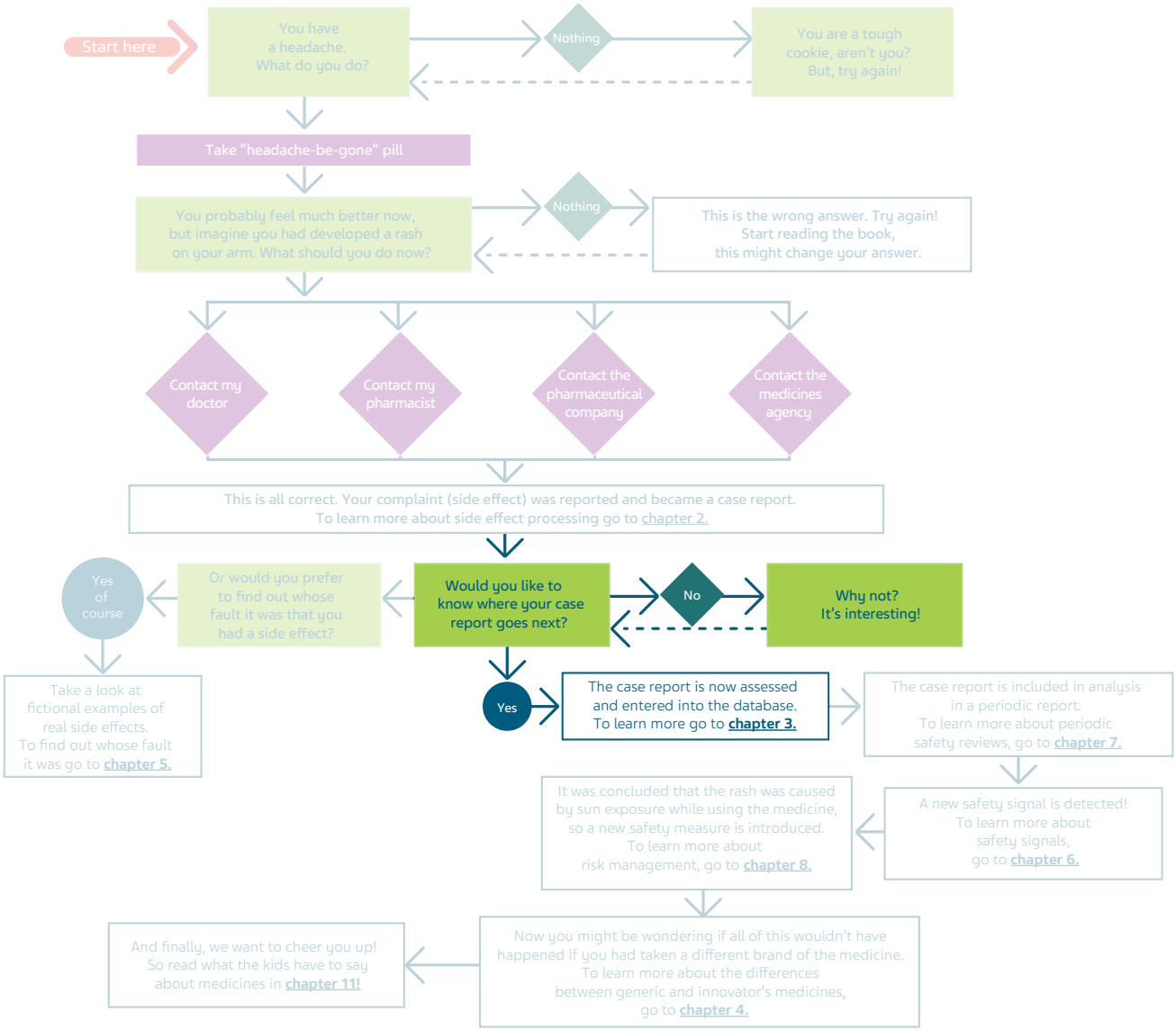
Did you know...

Even Mrs. Mary Todd Lincoln, the wife of US president Mr. Abraham Lincoln, reported that her husband had experienced a side effect! In an interview to the Sacramento Daily Union in August 1865, she stated that she "recalled the fact that her husband had been very ill, for several days, from the effects of a dose of blue pills taken shortly before his second inauguration." The blue pills his wife mentioned, known as "blue mass" were a 19th century staple. They were prescribed for a host of ailments, including apoplexy, worms, child-bearing, tuberculosis, toothaches, and constipation. The key ingredient was mercury; an element we know today to be poisonous. Mercury toxicity most commonly affects the neurologic, gastrointestinal, and renal organ systems.

If you want to test your knowledge go to "Time to Take a Quiz!".

Processing of case reports is described in the following chapter, "Guardians of Patient Safety".

3.0 Guardians of patient safety

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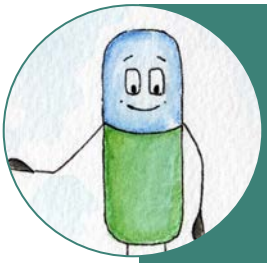
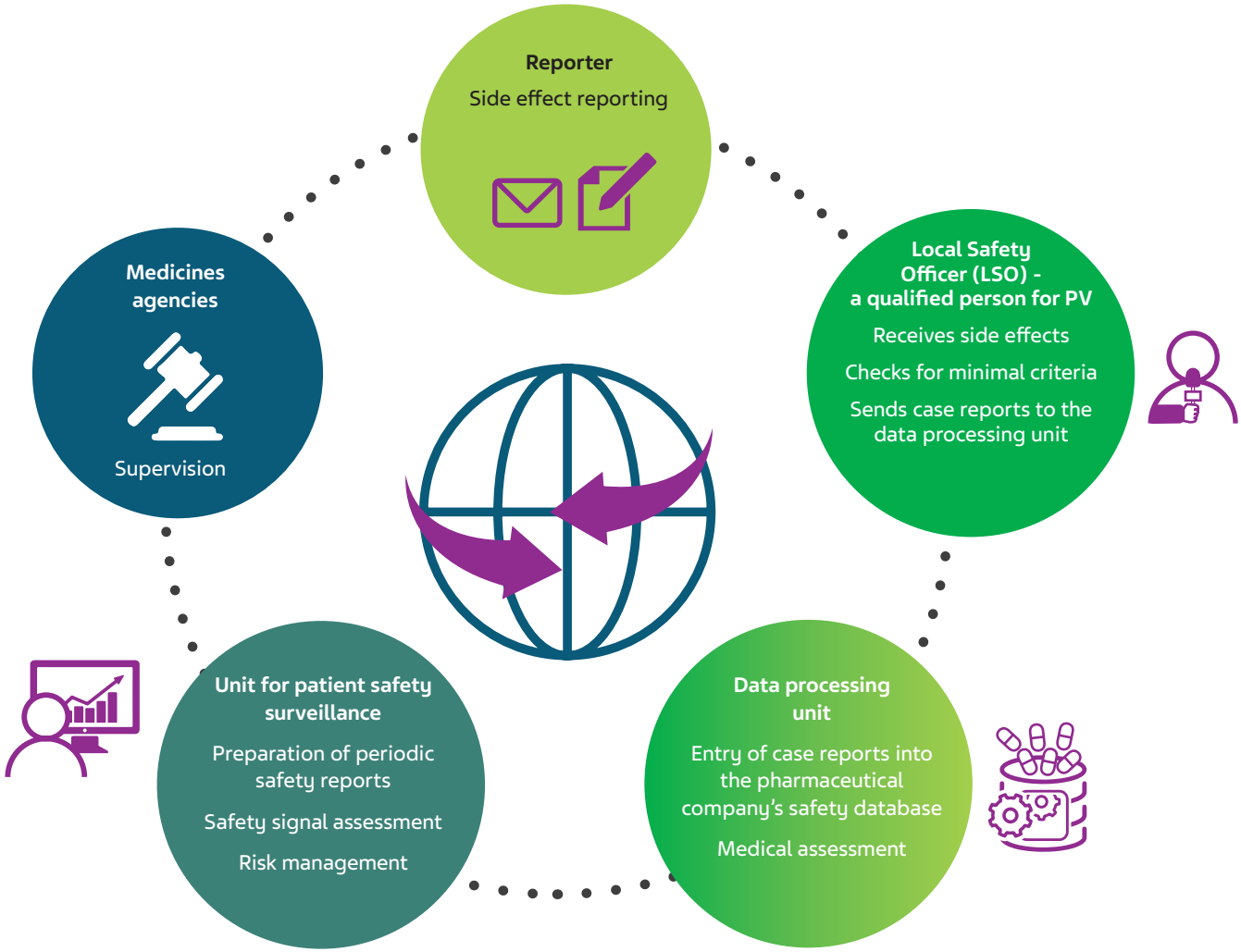


- Pharmacovigilance connects all the parties involved in the monitoring of medicine safety – the reporters of side effects, the pharmaceutical companies who market the medicine, and the medicines agencies responsible for the promotion and protection of public health.
- The process involves the gathering and analysis of reports from the different sources, the preparation of safety reports by pharmaceutical companies, and the monitoring by medicines agencies, including the initiation of procedures to minimize patient risk and withdraw a medicine if needed.
- Reporting a case is not difficult when you know the four minimal criteria that every case requires: reporter details; patient details (gender, age, medical history, all medications taken); side effect; and suspect medicine.
- It is important to know that reporting of events is not limited to side effects: medicine overdose, abuse, or misuse; off-label use; medication errors, occupational exposure to drugs, and notable experience with medicines during pregnancy and breastfeeding are also reported and monitored.
- Following analysis of the collected safety data, the pharmaceutical company and medicines agency have to determine whether there are any new risks for a medicinal product and the appropriate action required.

The PV system is a complex network of closely related interactions between patients, healthcare providers, pharmaceutical industries, and medicines agencies. You can apply the rule "all for one and one for all", as all parties involved in PV have one common mission – patient safety. Circumstances in which side effects are reported and the way they are reported were described in chapter 2.0 **"Pieces of the Puzzle: Where Do Side Effect Reports Come From?"**. This chapter provides an overview of the PV process by describing the responsibilities and tasks taken by those involved in PV. Take a look at the **"Circle of PV Life"** presented in **Figure 3-1** to find out about the journey of each side effect report after it is recorded.

Figure 3-1. Circle of PV Life



3.1 Reporter

Reporter details are important as they may need to be contacted in order to obtain more information. The first step in our journey is with the person who reports a side effect (the reporter). In chapter 2.0 **"Pieces of the Puzzle: Where Do Side Effect Reports Come From?"** we saw that there are different types of case reports based on their source. All reporters are equally important and all information is treated with a high level of privacy. Reporting a case is not difficult when you know the four minimal criteria that every case requires in order to be valid: reporter details; patient details; side effect; and suspect medicine.

Reporter details are important as there may be a need to contact them to obtain more information. Patient details include gender and age, medical history, including the condition or disease for which the suspect medicine was prescribed for, and details of any other medicines they may be taking (known as concomitant therapies). The report should describe a clinical event – the side effect which occurred. Finally, details about the medicine which is suspected to have caused the reported side effect are needed. All this information is gathered into one case report.

It is also important for a reporter to know that not only side effects are reported and monitored. Other situations prompting a report include overdose, medicine abuse, medicine misuse, off-label use of medicines, medication errors, occupational exposure to medicines, and a positive or negative experience with a medicine during pregnancy and breastfeeding. **Table 3-1** describes the differences between medication error, medicine misuse or abuse, and off-label use.

Table 3-1. Differences between medication error, off-label use, medicine misuse, and medicine abuse.

Term	Explanation
Medication Error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the healthcare professional, patient, or consumer. Mistakes in prescribing, dispensing, storing, preparing, and administering a medicine are the most common preventable cause of undesired side effects in medication practice and present a major public health burden. For examples of medication error, go to chapter 5.0 **"Medication Errors: Whose Fault are They?"**
Off-label Use	When a medicine is intentionally prescribed (by a healthcare professional) for a medical purpose not in accordance with the authorized product information. **For example:** thalidomide (described in the **"Introduction"** chapter) was prescribed for morning sickness in pregnant women, although it was authorized only for sedation.
Misuse	When a medicine is intentionally and inappropriately used (by a patient) not in accordance with the authorized product information. **For example:** a patient took a medication for a longer period than instructed on the product label since his symptoms were not resolved.
Abuse	Persistent or sporadic, intentional excessive use (by patient/consumer) of a medicinal product, which could be accompanied by harmful physical or psychological effects. **For example:** a patient occasionally uses an opioid product to "get high".

So, maybe you already knew how to report a side effect, but did you ever ask yourself what happens next? Who deals with that report?

Did you know...

- Expected side effects are those which were assessed and recognized as being related to the medicine, either during clinical trials or after the medicine was launched onto the market. They are usually described in the patient information leaflet (PIL).
- Unexpected adverse events are those which are temporally associated with the use of a medicinal product, whether or not considered related to that product. These events either previously went unnoticed or, until now, there was no sufficient evidence linking them to the medicine and they are monitored with great attention.

3.2 Pharmacovigilance unit in a pharmaceutical company

Every pharmaceutical company has a PV function and the people working in this area are involved with different stages of adverse event processing and analysis.

Pharmaceutical companies have a qualified person responsible for receiving and processing case reports – a **Qualified Person for PV or a Local Safety Officer** (LSO) in the country in which they registered their medicinal product(s). The LSOs need to be aware of all products registered in the country under their responsibility and have to fulfill duties regarding these medicines required by national law, such as forwarding cases concerning side effects to the local medicines agency within timeframes defined by law. Further processing of a case report depends on its seriousness and is performed by the data processing unit.

The **data processing unit** is a very busy department in any pharmaceutical company as it processes all received case reports. Depending on the size of the company and the number of products it markets, a pharmaceutical company can receive hundreds of individual case reports daily. Case processing consists of entering each case in the company's PV database, assessing it, and reporting it to the appropriate medicines agency(ies), if needed. If, during the assessment, it is decided that more information is needed for clarification or better assessment of the side effects, the reporter will be contacted. This is why it is useful to leave contact details when reporting a side effect.

Every case report is first assessed for seriousness. A serious case is one that fulfils any of the following criteria:

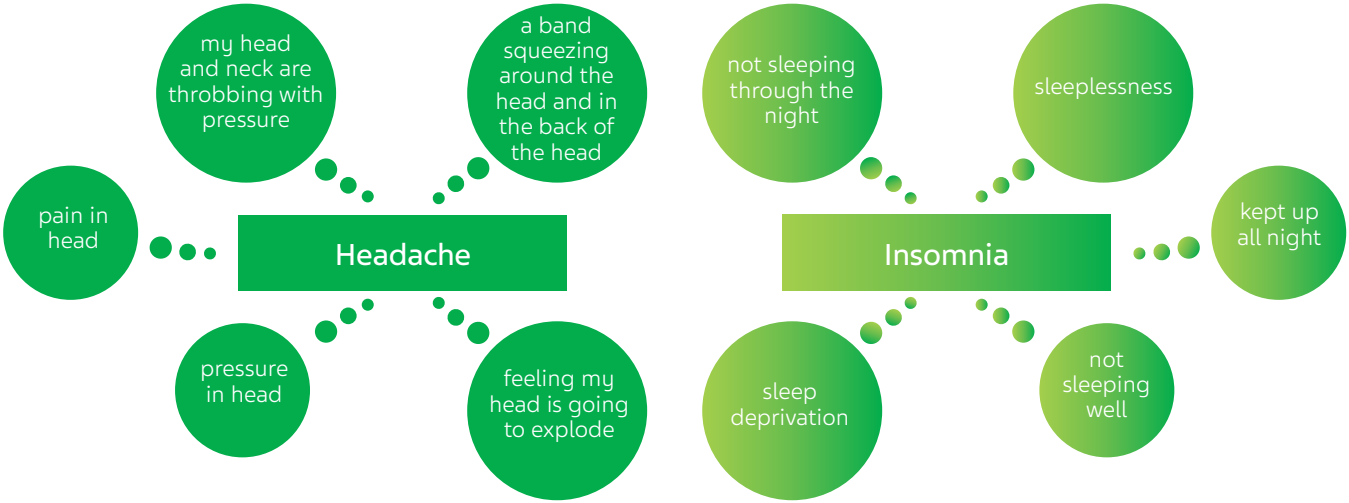
- the suspected side effect resulted in death, was life-threatening, or resulted in persistent or significant disability/incapacity;
- the patient required prolonged inpatient hospitalization;
- it represents a congenital anomaly;
- it represents an important medical event that requires medical intervention.

The seriousness of the case determines the timelines within which the case needs to be forwarded to the medicines agencies. For example, in the European Union (EU) serious side effects for marketed products should be reported within 15 calendar days and non-serious cases no later than 90 days. These harmonized reporting requirements ensure that the medicines agency responsible for medicinal products in each country is informed of any suspected side effects in a timely manner.

The next step involves entering the case in the company's PV database. Every pharmaceutical company has its own PV database. Additionally, there are medicines agency databases (such as the Food and Drug Administration's (FDA) FAERS), as well as international (such as the EU's EudraVigilance) and global databases (such as the World Health Organization's (WHO) VigiBase). VigiBase contains reports of side effects received from member countries' medicines agencies since 1968 and aims to monitor the safety profile of medicines. The medicines agencies notify each pharmaceutical company of all the adverse events they receive for its medicines.

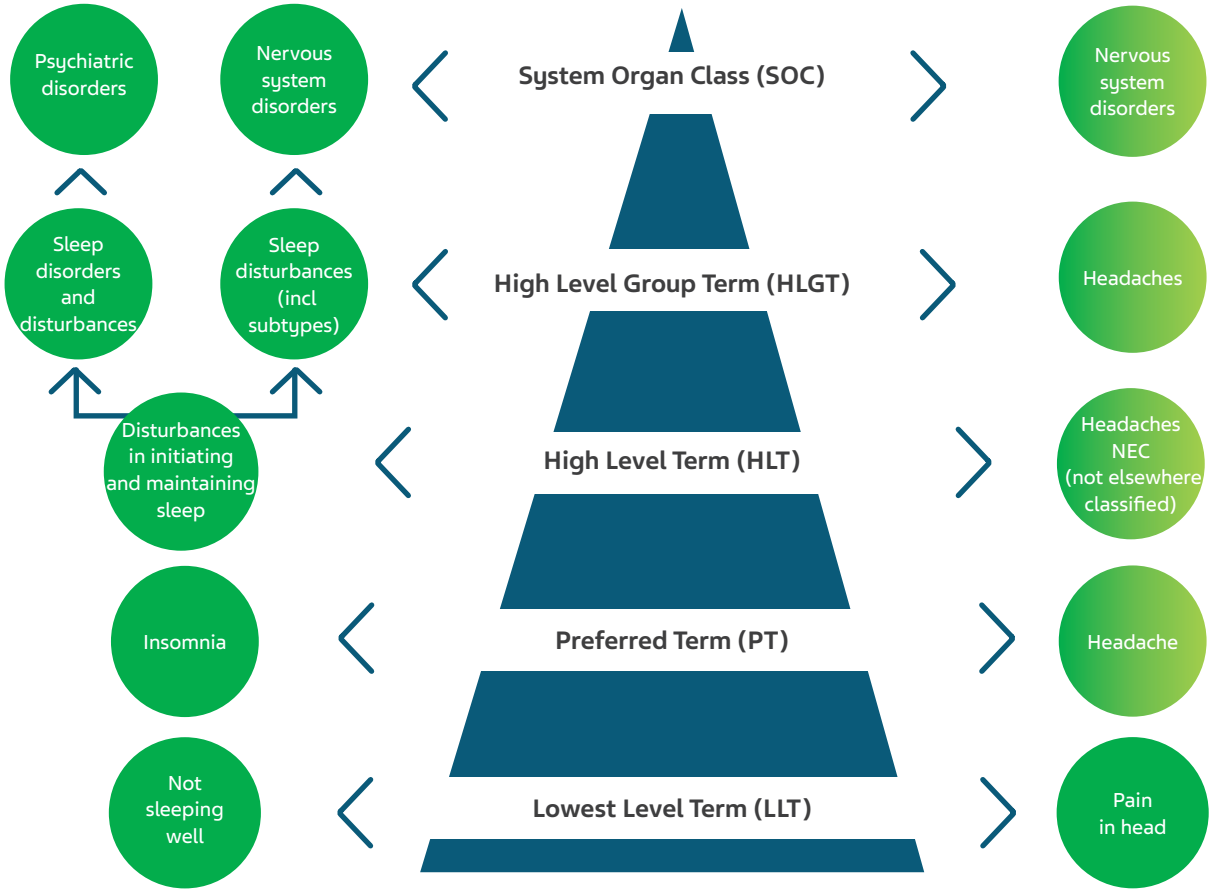
Reported side effects are entered in the PV database using a standardized terminology guided by the Medical Dictionary for Regulatory Activities (MedDRA) – a medical dictionary containing international terminology for biopharmaceutical regulatory purposes. Within MedDRA, for each reported symptom or disease, a term can be found matching the reported event, so that consistency can be achieved when performing database searches, case retrieval, and analysis. It ensures that the same event is always presented with the same name, as you can see from the examples in **Figure 3-2.**

Figure 3-2. Terms reported by patients (presented in the circles) are translated into medical terminology ("headache" and "insomnia"), also named MedDRA Preferred Terms.



The structure of medical terminology within MedDRA is presented in **Figure 3-3.**

Figure 3-3. The terms in the medical dictionary MedDRA are hierarchically organized. The five-level structure of medical terminology provides options for retrieving data by specific or broad groupings, according to the level of specificity required. The Lowest Level Term (LLT) level provides maximum specificity, while System Organ Class (SOC) is the broadest. This facilitates the retrieval and analysis of the case reports and reported side effects.



Case reports were previously received and saved in paper form, but now, electronic databases have made this process much more efficient and secure. The purpose of a company's PV database is to store all safety data and to make it easily accessible and searchable using specific keywords or information. This allows, for example, a search for all case reports involving the same side effect, such as when performing signal detection (see chapter 6.0 **"Discovering New Safety Information: Signal Detection"**).

After the data is collected and entered into a company's PV database, it can be analyzed. Medical writers prepare different types of periodic safety reports, which give an overview of the safety data collected worldwide for a specific medicinal product (see chapter 7.0 **"Periodic Safety Reports or Seeing the Big Picture"**). Completed periodic safety reports are submitted to national and regional medicines agencies in the countries where the product is registered.

Following the analysis of this safety data, the pharmaceutical company determines what, if any, new risks are identified for a medicinal product and if the medicine's benefits remain greater than its risks. If new risks are identified, the pharmaceutical company can take a number of different actions. For example, it can communicate the recognized risks to healthcare professionals and patients via product information, optimize the medicine package size, provide guides and toolkits for patients, or introduce prevention programs (e.g. pregnancy prevention during treatment with a medicine that may harm the unborn child) (see chapter 8.0 **"Understanding the Risks and Keeping our Patients Safe").**

Did you know...

In the USA in 2008, the number of deaths by poisoning (89% of them caused by medicines) exceeded the number of motor vehicle traffic deaths for the first time since at least 1980. There were more than 41,000 deaths due to poisoning, compared with about 38,000 motor vehicle traffic deaths.

3.3 Medicines Agencies

Legally, both the authorities and the pharmaceutical companies are responsible for the safety of medicinal products. Both are obliged to maintain PV systems, to exchange data and, where necessary, to take appropriate action to protect patients. According to WHO, medicines agencies should be established by all national governments.

The main responsibility of all medicines agencies is the protection and promotion of public health. They are responsible for the scientific evaluation of medicinal products developed by pharmaceutical companies. Medicines agencies decide whether a medicine can be authorized for marketing and, after this has happened, they monitor its safety. As already discussed, pharmaceutical companies are obliged to forward received cases and periodic safety reports containing the analyzed safety data gathered in a specific time-period, for all marketed medicinal products to the agencies. If the information indicates that the benefit/risk balance of a medicine has changed since it was authorized (see chapter 7.0 **"Periodic Safety Reports or Seeing the Big Picture")**, medicines agencies are required to take action. This may involve the initiation of risk minimization procedures in order to improve the safety of use of a medicinal product or, if the risk of taking a specific medicinal product considerably outweighs its benefits, it can be withdrawn from the market (see chapter 8.0 **"Understanding the Risks and Keeping Our Patients Safe"**). Pharmaceutical companies are obliged to take any actions recommended by medicines agencies.

Did you know...

Between 1995 and 2015, the European Medicines Agency (EMA) recommended the authorization of a total of 975 human medicines and 188 veterinary medicines.

The two largest medicines agencies are the European Medicines Agency (EMA), a decentralized agency of the European Union, which began operating in 1995, and the Food and Drug Administration (FDA), an agency within the U.S. Department of Health and Human Services with a history dating back to 1927. **Table 3-2** provides some interesting facts about the FDA.

Table 3-2. FDA in numbers

In 1937	107 people died after taking the elixir sulphanilamide, a supposedly healing tonic; the FDA was then authorized to do factory inspections; new medicines were required to be tested on animals and humans for safety before being marketed
$1 trillion	worth of products are annually regulated by the FDA
3,000 products and 30,000 import shipments	are declared to be unacceptable in various ways each year by the FDA
Over 1,000	investigators and inspectors are employed within the FDA
Over 15,000	food-processing, medicine-manufacturing, and other facilities are visited by FDA inspectors each year
2,000 scientists (including 900 chemists and 300 microbiologists)	are employed by the FDA to provide scientific evidence to back up its regulatory and inspection duties

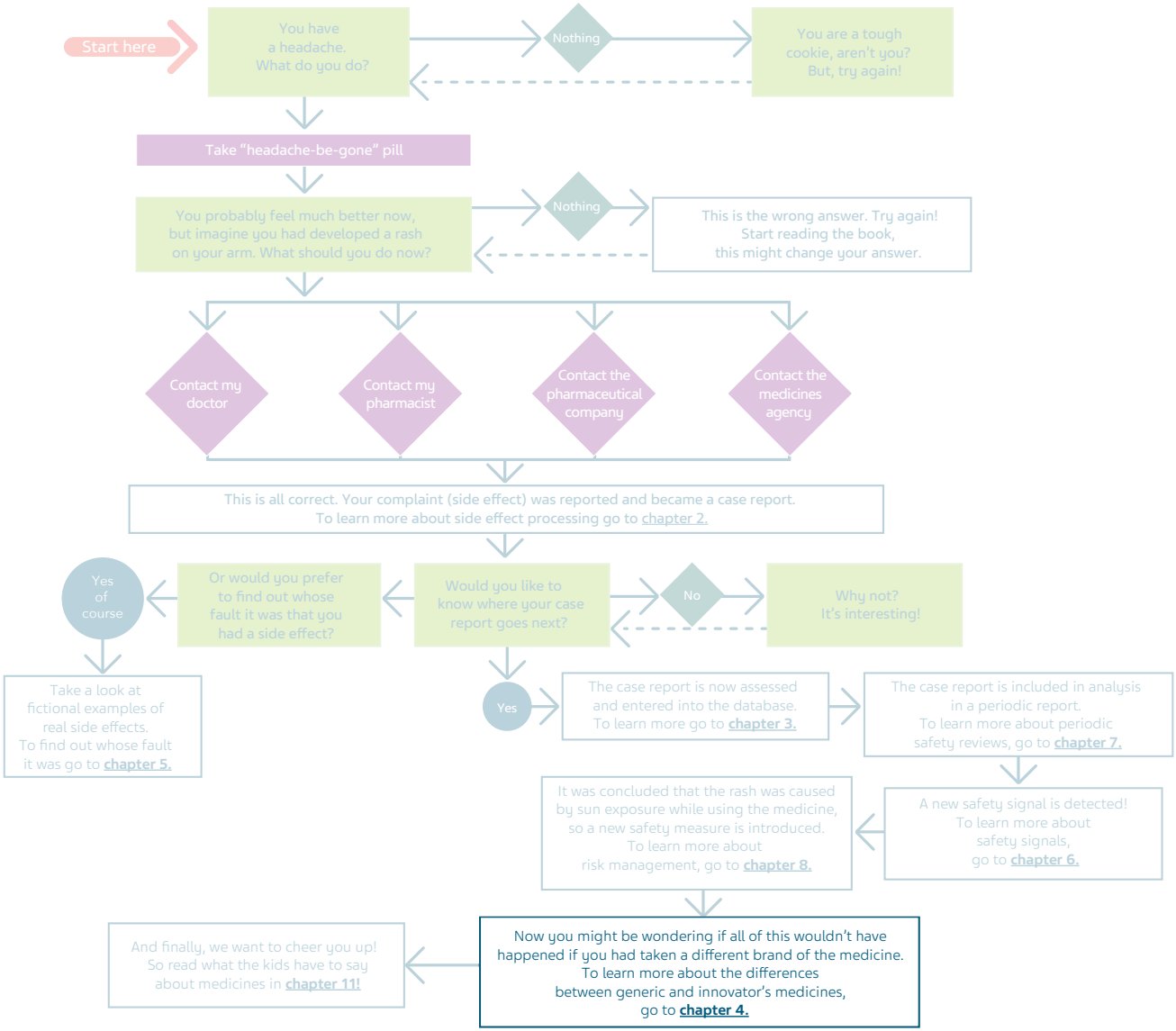
Did you know...

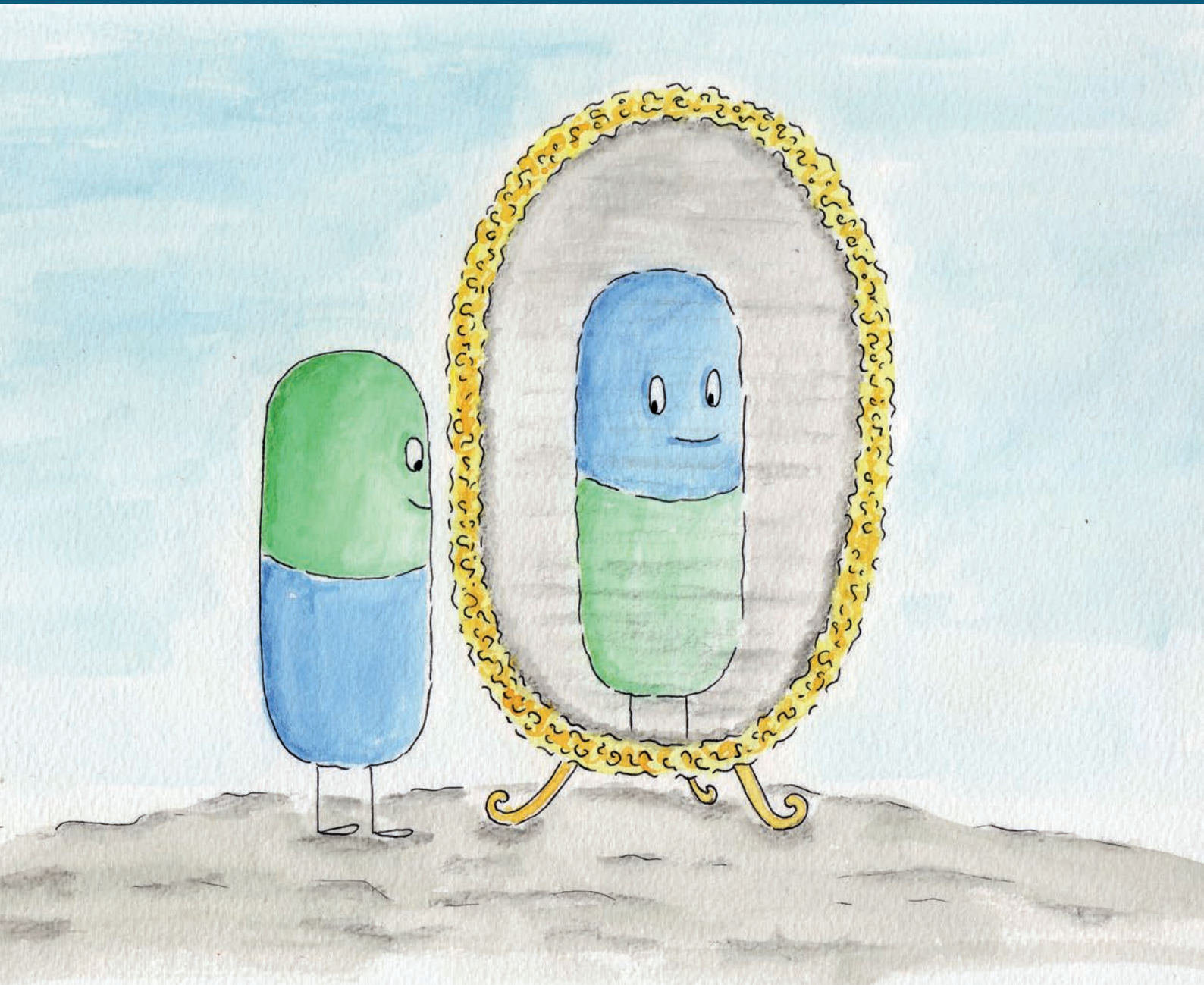
The FDA has longstanding policies allowing the "compassionate use of new medicines" for patients in desperate need, for example, those with cancer. During the 1980s, the FDA came under increasing fire for its slow approval of new medicines. The emergence of AIDS during the 1980s strengthened the public demand for fast delivery of innovative new medicines. In 1987, the agency adopted "expanded access" regulations, which allow for certain medicines to be designated as treatment investigational new drugs (IND). A treatment IND may be administered to patients even while it is still undergoing clinical trials. This program allows patients with no other alternatives to undergo a treatment that may benefit their health.

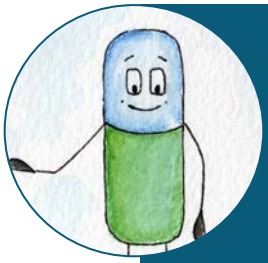
If you want to test your knowledge go to "Time to Take a Quiz!".

Take a look at the following chapter "Generic vs. Innovator Drugs: Understanding the Differences and Similarities".

4.0 Generic vs. innovator's drugs: understanding the differences and similarities







- The first medicine of a kind that is available on the market is called the innovator's or branded medicine.
- Following patent expiry, copies of the same medicine called generic medicines, are manufactured to exactly the same rigid quality and safety standards as innovator's medicines but are sold at lower prices.
- These generic medicines account for almost 80% of the prescription medicines sold.
- Generic medicines may differ in shape, color, expiration date, and packaging, and are allowed to have different inactive ingredients (e.g. flavoring and dye) in comparison to innovator's medicines.
- Generic and innovator's medicines are equivalent in both efficacy and safety and the monitoring of safety for all medicines, both innovator's and generic, is the same after approval.
- Scientific research shows that generic medicines are not inferior to innovator's medicines in any way, confounding the substantial mistrust and lack of confidence in generic medications present in some media and among patients.

Martin (64) has been using the same medicine for his high blood pressure for the last five years. On one of his regular visits to his physician to get a new prescription, the doctor told him that this time she would give him a **generic** medicine, the same medicine but with a different name and different appearance. She assured him that there was no need to worry as the medicines are the same and, moreover, the new medicine would be cheaper.

If you have ever been prescribed a medication, there is a good chance it was a generic medicine just like Martin's, because nearly 80% of the prescription medicines sold are generic medicines. The use of generic medicines helps save billions of dollars to patients and hospitals every year. However, patients are often reluctant to switch to generic medicines because no one wants to skimp when it comes to health, even if it means saving money.

We have included the answers to some common questions about generic medications that will hopefully resolve any concerns you might have over generic medicine use.

What are generic medicines?

When a new medicine is invented it has to go through a large number of laboratory investigations, as well as trials in animals, healthy humans, and patients. Once the safety and efficacy have been proven in these trials, the medicine may receive the approval from the medicines agencies to enter the market. The first medicine of a kind that is available on the market is called the innovator's or branded medicine. Any generic medicine modeled after an innovator's medicine must have the same performance in the body as the innovator's medicine. We say that the generic and innovator's medicines are bioequivalent when their efficacy and safety are essentially the same. Of course, there will always be a slight level of natural variability, just like there is some natural variability between different batches of the same manufacturer's product. This amount of difference is expected and acceptable in both cases: between the batches of the same innovator's medicine, and between a generic and an innovator's medicine. Although generic medicines are chemically identical to their innovator's counterparts, they are typically sold at substantially lower prices than the innovator's medicines.

Are generic medicines equally effective and equally safe as an innovator's medicine?

Approved generic medicines have to meet the same rigid standards in quality as innovator's medicines. To gain medicines agency approval, a generic medicine must be identical in strength, dosage form, and route of administration, have the same indications, and be manufactured under the same strict standards of good manufacturing practice as the innovator's products. One very important point is that monitoring of safety for all medicines, both innovator's and generic, is the same after approval. Therefore, we can say that generic and innovator's medicines are equal in their efficacy and safety.

Why is there a price difference between a generic and an innovator's medicine?

An innovator's branded medicine, like any other new product, is developed under patent protection. The patent protects the investment in the medicine's development. It can take up to 12 years for a company to obtain market approval and the cost of developing a new medicine has been estimated to be more than $1 billion! This is why the company is given the exclusive right to sell the medicine for a certain period, usually about 5-10 years. When the patents or other periods of exclusivity expire, all manufacturers can apply to the medicines agencies for

approval of their generic medicine. However, since they are not required to repeat costly animal and clinical trials, generic medicines are far cheaper than the innovator's ones. In addition, when several medicine manufacturers have the same generic medicine on the market, it creates competition resulting in lower medicine prices.

How are generic medicines different from innovator's medicines?

Some differences between generic and innovator's medicines are allowed. Generic medicines may differ in shape, color, expiration date, and packaging, and are allowed to have different inactive ingredients (e.g. flavoring and dye) in comparison to innovator's medicines. However, all the inactive ingredients in a generic must be safe for human use.

Why do doctors prescribe generic medicines?

In most countries, doctors are encouraged by the government to prescribe generic medicines because they are sold at considerably lower prices than innovator's medicines. On average, the cost of a generic medicine is about 80-85% lower than the innovator's product. In 2010 alone, the use of generics saved $158 billion, an average of $3 billion every week in the United States. Additionally, the use of generic medicines allows wider access to medicines for patients who need them but cannot afford innovator's medicines, especially in less developed countries.

Is switching from an innovator's to a generic medication always the best option?

The effectiveness and safety of generics is equivalent to that of their more expensive counterparts; however, sometimes patients may experience clinical deterioration, decreased tolerability, side effects, and changes in medicine metabolism. This is particularly seen for medicines which are used to treat symptoms of mental disorders such as schizophrenia, depression, anxiety, and epilepsy. Changes in the patient's clinical status may be related to the switch to a generic medicine but also to other factors related to the patient, such as mental and physical factors. In such situations, health care professionals are advised to carefully switch to generic medicines on an individual basis and closely monitor patients throughout the transition.

Research has proven that generic medicines are not inferior to innovator's medicines in any way. There is no scientific background in the substantial mistrust and lack of confidence in generic medications, which is present in some media and among patients. However, if you still have doubts regarding the quality and equivalence of generic medicines, talk to your healthcare provider rather than rely on medical myths.

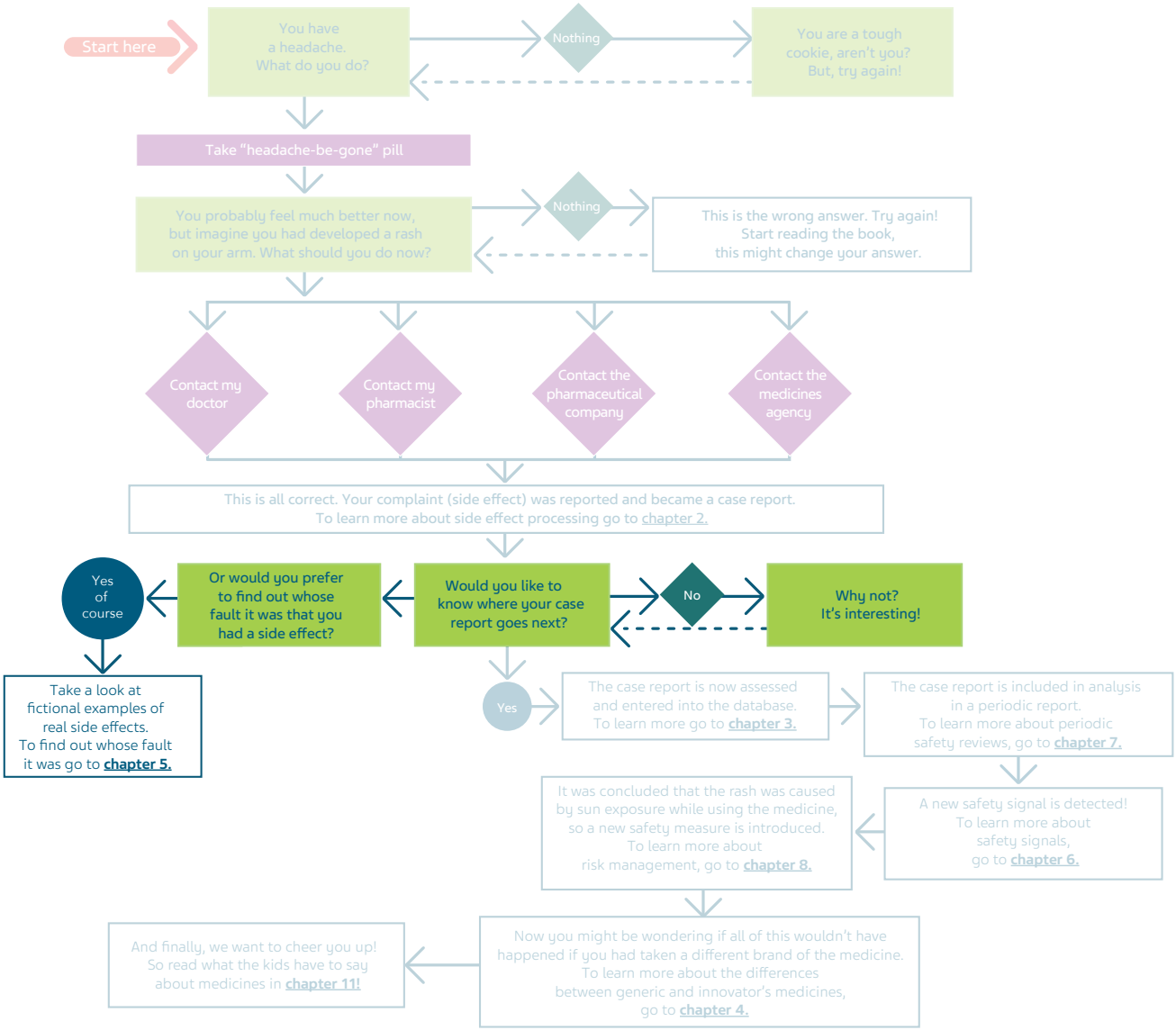
Did you know...

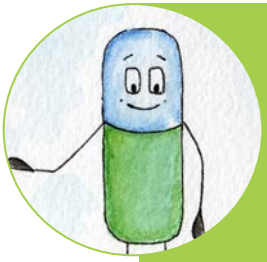
The word "drug", derived from the French word Drogue meaning dry herb, suggests that the earliest medicines were taken from plants. From the beginning of the world's medical history, Chinese Medicine, Ayurveda, and Greek Medicine, despite having wide differences in their principles of treatment, agreed on the fact that disease is a consequence of the imbalance within the constituents of the body and that the aim of treatment is to restore the balance, primarily with the help of herbs. Therefore, herbs played a vital role in the development of pharmacology and pharmacy throughout the history of medicine.

If you want to test your knowledge go to "Time to Take a Quiz!".

Medication errors may occur quite often; find out why and whose fault are they in the following chapter; "Medication Errors: Whose Fault Are They?"

5.0 Medication errors: whose fault are they?





- It is natural to look for someone or something to blame whenever things go wrong as it usually makes us feel better.
- Medications are no exception. If a medicine doesn't work as it should or if something happens whilst taking it that isn't supposed to, one of the first questions is usually: "Whose fault is it?"
- We have seen great improvements in the treatment of many diseases, particularly cancer, and almost a parallel expansion in information available to patients. Unfortunately, not all the sources are reliable, nor is all the information relevant and objective.
- Healthcare providers remain excellent sources of advice for patients on how to stay healthy and take medicines. They should tell you how and when to take it, provide special instructions to avoid unnecessary side effects, and direct you to the patient information leaflet (PIL) for further information.
- In return, patients have a responsibility to listen to and follow these instructions, read the PIL (even if they think they know what to do) and, if they have any questions or doubts about their therapy, over-the-counter (OTC) medications, or even food supplements, ask for advice.
- Patients also have a responsibility to inform their healthcare professionals of any other medications they are taking that might interact with a newly prescribed medicine.

We all have a tendency to look for someone to blame whenever things go wrong. Finding out whose fault it is usually makes us feel better. The same goes with medications. If the medicine doesn't work as it should or if something happens whilst taking it that isn't supposed to, one of the first questions is usually: "Whose fault is it?" In such situations, the usual suspects are the medicine itself and the pharmaceutical company that manufactures the medicine. But is it always the case? Take a look at the following fictional examples to learn more about situations which can compromise medication efficacy and patient safety.

5.1 Antibiotic mystery

Let's look at the example of Ivan, a 28-year-old man living in Zagreb, Croatia. One rainy day he woke up with an intense sore throat. His nose was running and his head felt like it was going to explode. Ivan's muscles were aching, as if he had been boxing all night long, and his body temperature was much higher than usual. But, worst of all, was the prospect of an important business meeting he was supposed to attend that morning. Despite the poor state of his health, Ivan decided that there was not enough time to visit the physician but remembered the three tablets his doctor had prescribed him the last time he experienced similar symptoms. As far as he could remember, it was an excellent medicine. The first tablet wiped out all his symptoms so he felt there was no need to take the other two. "And wasn't that clever of me?" thought Ivan, already feeling better. Ivan found the box labeled "azithromycin" in the drawer and even remembered to check that the two remaining tablets were not past the expiry date. Ivan took one tablet and went to the meeting. However, when he arrived home later that day, his symptoms worsened. The next day he took the last tablet hoping it would finally make him feel better, but it didn't. So, after all, Ivan went to see his physician. Frustrated by the illness and his helplessness, he furiously stated "This medicine isn't working!", thereby reporting a side effect that was marked as lack of efficacy.

Was it really a lack of medicine efficacy and whose fault was it really? Let's first consider the facts. Azithromycin is an antibiotic, one of a number of medicines indicated for the treatment of bacterial infections. Infections may be caused by different microorganisms. Despite the different origins, infections can cause similar symptoms, such as the ones Ivan experienced. Therefore, a proper diagnosis involving the identification of the infectious agent can only be made by a physician. There are many kinds of antibiotics; each of them effective against specific strains of bacteria, hence, they should always be prescribed by the physician after diagnosis. After proper examination, it turned out that Ivan had the flu, which is caused by a virus.

Antibiotics, including azithromycin, are not effective against viruses that cause the flu and should never be used in such situations. Therefore, Ivan was not supposed to take azithromycin without his physician's recommendation. He also made another crucial mistake by not taking the full azithromycin dose prescribed by the physician when experiencing the previous infection. Each medicine comes with a patient information leaflet (PIL); the one for azithromycin states: "Take azithromycin tablets exactly as your healthcare provider tells you to. Do not skip any doses of azithromycin tablets or stop taking them, even if you begin to feel better."

The same applies to other antibiotics. Failing to take the full prescribed dose or taking antibiotics for a wrong indication induces bacterial resistance – although the symptoms of disease are gone, bacteria may still remain in the organism. Those survivors will generate a new generation of bacteria with a potential to resist appropriate antibiotic therapy. Thereby, bacteria that were at one time susceptible to an antibiotic can acquire resistance. Antibiotic resistance is an increasingly serious threat to global public health. Infections caused by resistant bacteria fail to respond to standard antibiotics, resulting in prolonged illness, increased risk of spreading resistant microorganisms to others, and a greater risk of death. Unfortunately, antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and it is putting the ability to treat common infections at risk. On its website, World Health Organization (WHO) reports that "the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill".

In conclusion, Ivan never experienced azithromycin lack of efficacy. On the contrary: he took the medicine for the wrong indication and in an inappropriate way. Healthcare providers are supposed to advise their patients on how to take medicines. Patients are supposed to listen to their doctors and pharmacists as well as read the patient information leaflet for the medications they are taking. The healthcare provider may well have given the correct advice when he first prescribed the antibiotic, but Ivan certainly didn't take it. He did not take the whole azithromycin dose, i.e. all the prescribed tablets and, when he experienced another infection, he took the remaining tablets rather than go to the physician for a proper diagnosis. And last, but not least, Ivan should never have attended the meeting, spreading microorganisms to his colleagues.

Did you know...

Each year in the United States, more than 160 million prescriptions are written for antibiotics. Humans consume 235 million doses of antibiotics annually. It is estimated that 20 to 50% of that use is unnecessary.

5.2 Baking soda - revolution in cancer treatment... or not?

Every scientist or researcher in biomedicine dreams about discovering the cure for a rare or life-threatening disease and cancer is high on the list of targets. There have been huge improvements in cancer treatment, with the discovery of new medications with better efficacy and fewer side effects than those previously available. In parallel, patients today have access to various sources of information. Unfortunately, not all the sources are reliable and not all information they provide is relevant and objective. News about new medicines brings hope to many ill people and makes them more eager to recover. But instead of helping, could it be harmful? Here is one example.

Linda (29) from Philadelphia is a perfectly healthy young woman who wants to stay that way. She wants to be informed about new trends in healthcare and she regularly visits different internet forums and blogs to exchange experiences with other people. Lately, she has read about the many beneficial effects of baking soda, in particular about its "anticancer effect - in therapy and also for prevention, due to its alkaline property". Linda's mother was diagnosed with breast cancer five years ago and Linda knows that she might therefore be at a higher risk of getting the disease. Linda decided to start taking regular baking soda, also known as sodium bicarbonate, as a preventative measure. She went to her local pharmacy, as she usually did when in need of a medicine that can be purchased without a physician's prescription (i.e. an over the counter [OTC] medicine) and asked for three packets. Linda was quite surprised when the pharmacist asked her about stomachache and heartburn. She didn't have any problems with her stomach. Seeing Linda's surprised look, the pharmacist asked if she had "researched" sodium bicarbonate on the internet. When Linda nodded, the pharmacist explained: "Sodium bicarbonate is an antacid, an alkaline salt that has been used for many years in symptomatic therapy of heartburn, hyperacidity, and sour and upset stomach caused by hyperacidity. Antacids are weak bases that react with gastric acid to form a salt and water. Their principal mechanism of action is reduction of acidity in the stomach and they should not be used for more than two weeks. If symptoms last longer, you should visit a physician."

Now, let's consider the effects of sodium bicarbonate. As mentioned above, sodium bicarbonate or sodium hydrogen carbonate is an antacid. In a watery environment it reduces acidity i.e. it increases pH. The blood's normal and optimal pH is between 7.35 and 7.45. pH regulation is an important aspect of homeostasis and every dysregulation, manifested as hyperacidity (low pH) or alkalosis (high pH) creates a problem for the human body. Hypothetically, if we take too much of an alkaline substance like sodium bicarbonate, our kidneys, lungs and other systems have a lot of work to do to bring the pH back to normal.

Even when used as an OTC antacid, long term treatment in high doses is not advisable. This is especially important in patients with renal disease because it may potentially cause a severe condition called "metabolic alkalosis," an acid base disorder with symptoms ranging in severity from mild complaints of nausea, numbness, and muscle twitching, to more severe problems such as dizziness, difficulty in breathing, confusion and even coma. Additionally, due to its high sodium content, sodium bicarbonate may lead to problems in patients with hypertension, renal or heart problems. In medical literature, medicine-medicine interactions with sodium bicarbonate are also well documented because it interferes with the absorption of some medications. What about cancer treatment? To date, there are no clinical trials showing any evidence of sodium bicarbonate as a cure for cancer.

If taking huge amounts of baking soda isn't advisable for Linda, what can she do to stay healthy? Here is some general advice. According to her family history, she should make healthy choices like not smoking, maintaining a healthy weight, eating well, keeping active, and getting the recommended screening tests for prevention or early diagnosis of the disease. With regular visits to her physician, even if something went wrong, she would be in a better position to tackle her illness. To conclude, when you have questions or doubts about your therapy, OTC medications, or even food supplements, ask for advice from your healthcare professional. They know and can check what is evidence based, what can help, and most importantly, what can cause you harm.

Did you know...

- Up to 50% of patients worldwide do not take their prescribed medicines as recommended. Around 4-5% of hospital admissions are due to problems caused by the incorrect use of medicines.
- The concept of "evidence based healthcare" implies the integration of best research evidence with clinical expertise and patient values. It means that the conclusions from clinical trials are being integrated in everyday practice by taking into consideration patients' needs and values.
- To keep up with new discoveries and ongoing research in medicine, a healthcare provider would have to read 17 articles per day, 365 days per year.

5.3 Look before you leap

Bastien is a playful and energetic 4-year-old boy who is always roaming around the house on his bicycle. His mom, Annette, enjoys watching him play and copes well with the odd broken glass or damage to furniture as he speeds between the kitchen and the living room. However, she has a major concern about his health. Annette began noticing Bastien's breathing was getting heavy, he coughed often, and she could hear a wheezing sound from his lungs. After many physician consultations, Bastien was diagnosed with asthma; a condition in which his breathing is hindered by excessive production of mucus in his bronchi and the narrowing of his airways. After trying to manage the condition with a short-term relief medication proved insufficient, Bastien's physician decided it was time to try a different therapy. He prescribed a local corticosteroid, fluticasone, an agent which suppresses the inflammation in the lungs, combined with salmeterol, a bronchodilator, which causes the bronchi to relax and widen, and allows for easier inspiration. Annette was relieved; this new therapy sounded very promising. She stopped by the closest pharmacy with the new prescription and handed it over to the pharmacist. Bastien's new medication was an inhaler, similar to the one he previously used for short-term relief when his breathing was aggravated. The pharmacist asked Annette if she knew how to use the inhaler, to which Annette replied that she had been shown how to handle Bastien's previous inhaler so she was fine.

Once they got home, Annette quickly glanced over the PIL, and noticed that the pictures in the leaflet were almost the same as the ones in the previous inhaler's leaflet. She set the paper aside and helped Bastien with his first dose of the new medication. A couple of days later, the effects of Bastien's new medication were becoming visible, and in the following weeks, Annette realised that the medication was perfect for her son's condition. Unfortunately, soon after Bastien started the new medication, Annette noticed creamy white, slightly raised lesions in Bastien's mouth, on his tongue and the back of his throat. Bastien also started to complain of pain in his mouth. She rushed to the physician to establish what these lesions were and why they had appeared. Once the physician examined Bastien, he quickly diagnosed him with oral candidiasis, commonly known as thrush, a frequent side effect of oral corticosteroid use. He explained that small amounts of the Candida fungus are present in the mouth, digestive tract, and skin of most healthy people. They are normally kept in check by other bacteria and microorganisms in the body. However, certain illnesses, stress, poor hygiene, or medications, like corticosteroids, can disturb the delicate balance of microorganisms. The Candida fungus can then grow out of control and cause thrush. Luckily, oral candidiasis is easily treated with a course of oral antifungal treatment.

However, the most important thing the physician told Annette is that oral candidiasis is also easily preventable. After each application of the inhaler containing corticosteroids, the patient should thoroughly wash their mouth and teeth to avoid medicine build-up and consequent growth of the Candida fungus. When she arrived home, Annette wondered how did she not know that this could have been prevented. Should the physician have warned her? Or the pharmacist maybe? Did she have to find it out by herself? Annette picked up the PIL again, and beneath the familiar pictures showing her how to use the inhaler, she found the following instruction: "After using the inhaler, thoroughly rinse your mouth with water and brush your teeth. This is necessary to avoid getting thrush and becoming hoarse." When she realised that the leaflet might not be the same as the previous inhaler's leaflet after all, Annette closely read through all of the patient information in the document, discovering a couple of other important steps in using the inhaler, like proper cleaning of the device's mouthpiece. In the end, Annette learned to correctly administer the medication to Bastien, who was finally free from his asthma complications and only worried his mother with bruised knees and dents in the walls from his bicycle.

By taking a look at Annette's and Bastien's story, we can see that the problem was everyone's fault. The physician should have emphasized the importance of rinsing the mouth after use when he prescribed the inhaler. Also, it was the pharmacist's duty to inform the patient's mother to complete this step to avoid side effects like thrush. Finally, it was Annette's fault when she overlooked the new patient information leaflet and assumed she already knew everything. The moral of this case is "Look before you leap;" read the PIL carefully before starting a new medication and consult with your physician and pharmacist about any special features of your new medication or device and possible side effects.

Did you know...

The history of using inhaled medications dates back to 2000 BC. It is thought that inhalation therapy for asthma and other lung complaints may have originated from the traditional therapies in Ayurvedic medicine in India around that time. According to WHO estimates, 262 million people currently suffer from asthma.

5.4 Social media craze - paracetamol challenge

Over the course of a few days, Kim, a 14-year-old schoolgirl, started to feel weak and sometimes felt nauseous and vomited. As the symptoms continued, her mother took her to the emergency room. After undergoing laboratory tests, she was found to have severe liver damage – a surprising result for a supposedly healthy girl. Following a long conversation with a young doctor, Kim finally admitted that she and her friends saw the game called "Paracetamol Challenge" on social media and they decided to accept the challenge. As part of this "Paracetamol Challenge", she had taken almost a whole package of paracetamol to become the coolest girl ever.

Paracetamol is a widely used pain medicine which reduces fever, and can be bought as an OTC medicine. It is commonly used to help treat headaches, other minor aches and pains, and is a major ingredient in many cold medications. Kim's blood paracetamol level was very high and her liver function test results showed rapid deterioration. She was treated with an antidote (a medicine which counteracts the effects of another) for paracetamol overdose and transferred to the pediatric intensive care unit. After three days of hospitalisation, her liver function tests improved, but her kidneys started shutting down. Two weeks later, her kidney function tests had finally improved, and 18 months after the overdose, her kidney function finally returned to normal. However, Kim's liver never fully recovered.

What is the "Paracetamol Challenge"?

It is a social media craze spread among teenagers – not unlike "CharlieCharlieChallenge" – a game played by teenagers using pencils and paper to produce yes/no answers to questions they ask – or the "ALS Ice Bucket Challenge" – an activity involving dumping a bucket of ice water on someone's head to promote awareness of the disease amyotrophic lateral sclerosis (ALS) and encourage donations to research. However, the "Paracetamol Challenge" craze is very dangerous, encouraging participants to take large amounts of OTC medication, particularly painkillers and paracetamol. The first cases are believed to have happened in Ayrshire, Scotland, and reportedly led to the hospitalisation of one teenager.

Whose fault was it?

Paracetamol is a medicine which is known to cause serious liver damage in overdose; paracetamol poisoning has even become the most common cause of acute liver failure in the United States. What we have to keep in mind is that it can be bought without a physician's prescription by anyone, including teenagers. The real question is how to stop such online activity and discourage children from engaging in this dangerous "challenge". Police and schools have issued a warning to parents to keep an eye on their children's social media profiles for any sign of them taking part in this harmful "game".

Did you know...

Heroin, a derivative of opium, was promoted in the late 1890s for the use in children suffering from coughs, colds, and "irritation".

5.5 A domino effect of oral thrush

It is early morning and Miriam, a 72-year-old retired accountant, has just woken up. Instead of the smell of fresh coffee that her husband is making in the kitchen, she smells the strong odor of disinfectant soap. After opening her eyes, she realises she is in a hospital and the memory of the day before begins flashing back to her.

Yesterday morning had not started well and, very soon, it got a lot worse. When Miriam tried to put her dentures in, her gums were sore and swollen. Even a few minutes with the dentures in her mouth seemed unbearable and, when she looked at the inside of her mouth in the mirror, she noticed white patches all over her tongue. She picked up the phone and called the doctor who agreed to see her the same day. Miriam immediately drove to the doctor's office. After a couple of minutes looking in her mouth, the doctor diagnosed candidiasis. He explained that candidiasis, or oral thrush, is a yeast infection of the mouth. The fungus Candida albicans is a normal organism in the mouth, but sometimes it can overgrow and cause symptoms. The doctor warned her to be more careful with her dentures, not to sleep with them, to take care of her oral hygiene, and gave her a prescription. "It is not serious", he said, "just apply the prescribed medicine on the infected areas four times a day for seven days and everything should be fine." Miriam thanked him politely, took the prescription and hastily left the office. She was in a hurry when she went to the pharmacy to pick up her medicine. The pharmacist was very attentive; she explained to her that she was prescribed miconazole oral gel, an antifungal medicine that is administered locally. After mentioning that the gel should not be swallowed, but kept in the mouth as long as possible, the pharmacist handed her the medication. The pharmacist also added that all the information about the medication could be found in the patient leaflet inside the box. As soon as Miriam got home she applied the gel, and, a few hours later, she repeated the procedure. The symptoms started to diminish after the first dose and the medicine's box with the leaflet ended up in the trash bin. Late that night, Miriam woke up in intense pain and covered in cold sweat. Her husband insisted on calling an ambulance. The doctor at the emergency room diagnosed Miriam with internal bleeding (blood loss occurring within the body). Because it occurs inside the body, internal bleeding may go unnoticed initially; however, if the bleeding is rapid and severe, it can lead to shock. It is a serious condition that requires immediate treatment. Fortunately, the doctors responded promptly and Miriam recovered successfully.

Now, you may be wondering what triggered this unfortunate event of internal bleeding. In addition to the miconazole oral gel that she had recently been prescribed, Miriam had been taking the medicine warfarin for many years. Warfarin belongs to a group of medicines called anticoagulants, which are used to reduce the clotting ability of the blood. Warfarin is used to prevent and treat blood clots forming in the legs, lungs, brain, and heart. Many medicines, including miconazole, affect the way warfarin works. Although in Miriam's case it wasn't swallowed, miconazole was still absorbed into the blood stream through the mouth's mucosa. It intensified the effects of the warfarin and caused blood thinning and bleeding. This is how harmless oral thrush triggered a domino effect that ended with a hospital stay for Miriam.

After hearing the story, we come back to the question from the start of our chapter "Whose fault was it?" The responsibility in this case is divided between the dentist, who prescribed the medicine without proper inquiry about the patient's medical history or other medicines she was taking; the pharmacist, who did not warn the patient of potential interactions; and the patient, who did not tell the healthcare professionals that she was taking warfarin or read the PIL as instructed by the pharmacist. Although the medication error of the medical personnel in this case is clear, as a patient you are also accountable for your health. The PIL contains all relevant and up-to-date information about the medication and it's written in a clear and comprehensible way for the general population. It is a useful tool to prevent situations like Miriam's. Therefore, always tell your doctor and pharmacist which medicines you are taking and read the patient information leaflet before taking any new medication.

Did you know...

that what you eat and drink can affect the way your medicine works? Food-medicine interactions can produce negative effects in the safety and efficacy of medicines, as well as in the nutritional status of the patient. Generally speaking, food-medicine interactions are to be avoided, due to the possibility of poor or unexpected outcomes. Therefore, as a patient you should learn about the warnings regarding your medications and talk with your healthcare providers about how to lower the risk of interactions.

Table 5-1. Here are some examples of significant food and medicine interactions.

Medicine	Food	Interaction outcome
Lipid-altering agents (atorvastatin, lovastatin, simvastatin) **Antihypertensive medications (felodipine, verapamil, losartan)** **Antihistamines for allergy (fexofenadine)** **Some antibiotics (erythromycin, clarithromycin)**	Grapefruit juice	Chemicals in the fruit can interfere with the enzymes that break down (metabolize) the medication in the digestive system; as a result, the medication may stay in the body for too short or too long a time The interaction between grapefruit juice and statins may cause a serious side effect of muscle degradation called rhabdomyolysis
Antibiotics such as: tetracyclines (doxycycline, minocycline, oxytetracycline) levofloxacin ciprofloxacin	Dairy products (milk, cheese, yogurt, ice cream, etc.) Calcium-fortified juices	Calcium prevents the absorption of some antibiotics and may cause decreased antibiotic efficacy if ingested 1 hour before or 2 hours after taking the medicine

Medicine	Food	Interaction outcome
Monoamine oxidase inhibitors (MAOIs) which treat depression (phenelzine, tranylcypromine) **Medicines used to treat the symptoms of Parkinson's disease (selegiline only in doses above 10 mg/day)**	Foods containing tyramine (an amino acid) such as chocolate, aged and mature cheeses, smoked and aged/fermented meats, hot dogs, some processed lunch meats, fermented soy products, beer, etc.	The medicines can prevent the elimination of tyramine in the digestive tract, resulting in high blood levels of the amino acid and a sudden increase in blood pressure
Theophylline (bronchodilator; a medication for asthma treatment)	Caffeine (chocolate, colas, coffee, tea, etc.)	Increased possibility of adverse events, such as excitability, nervousness, and rapid heartbeat

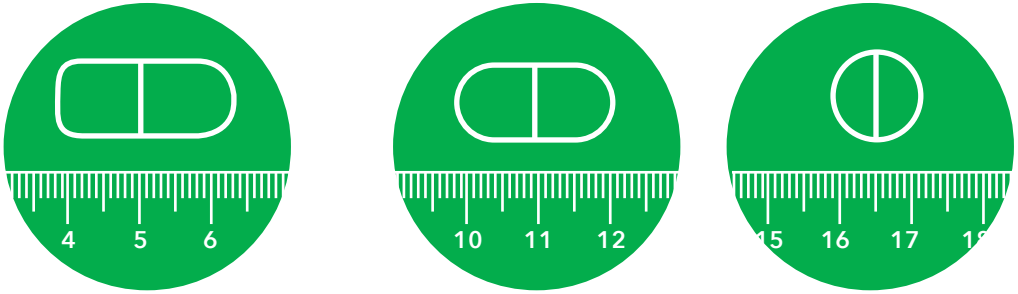
Medicine	Food	Interaction outcome
Anticoagulant medicine (warfarin)	Large amounts of vitamin K (kale, spinach, brussel sprouts, collard greens, green tea, etc.) Note: Eat a normal balanced diet with a steady amount of leafy green vegetables if you are being treated with warfarin. Eating small amounts of foods that are rich in vitamin K shouldn't cause any problems.	Decreased activity of warfarin leading to increased risk of thrombosis
	Cranberry juice and alcohol	Intensified effect of warfarin, leading to bleeding problems

5.6 Lost in translation

Lena is a 19-year-old woman who experienced itching in her genital area. This was the first time she experienced such symptoms. As she was a bit shy, it took her a few days to visit her gynecologist. After the exam, she was told she had a vaginal infection. She was too embarrassed to ask anything except: "Is that serious?" And the doctor responded: "No. You will get your medication and it will be fine in a few days". He asked her if she knew how to use the vaginal tablet, and she said yes. She was relieved, left the doctor's office, and went to the pharmacy to pick up her prescribed medication. She picked up a box containing three tablets. The pharmacist asked her if she knew how to use the medication and she said she did, thinking to herself: "What is there to know about swallowing a pill?" The pharmacist said to take one tablet every night before going to sleep for three consecutive days. On the first evening, she took the tablet from the blister, noticed it was rather big, but remembered that she was once prescribed an antibiotic which had tablets of a similar size (**Figure 5-1**), and tried to swallow it. It took quite a lot of water and was very unpleasant. Lena called the pharmaceutical company and reported that the tablet was too big and that she almost choked on it. It turned out that Lena mistook the prescribed medication for a regular, oral tablet. A vaginal tablet, also called vaginal suppository or pessary, is a medicine formulation indicated for the local treatment of the vagina, and should therefore be applied locally.

Whose fault was it in this case? Was it the physician's or the pharmacist's fault for not explaining in detail

Figure 5-1. Comparison of the shape and size of different pills. Is there a possibility to mistake the first two?



how to use the medication? Or, was it the patient's fault for not reading the PIL or asking the physician or the pharmacist exactly how to use it? All involved parties are responsible in this case. Physicians and pharmacists have an obligation to explain how to use the medication properly and patients have to take responsibility for their health. Although it was clearly stated on the package that these were vaginal tablets and the patient information leaflet explained how should they be used, the pharmaceutical company should have considered if the packaging and tablet form could have been mistaken for another type of medicine formulation and made a more obvious distinction between vaginal tablets and tablets for oral use. All parties involved in the process which starts with medicine development and finishes with medicine application have to continuously work on mutual understanding to protect patients and avoid mistakes.

So, to conclude, whose fault was it in the described cases?

Sometimes, it was the nature of the disease or medicine; sometimes it was the fault of a healthcare professional or a patient. The question is why does this happen? We all believe that every healthcare provider cares about patients and wants to ensure that his or her patients get all the information they need. But, why are all needs not always met? The answer is quite simple: we all have different expectations. Here is an interesting example. When patients were asked to rank 16 medicine information categories by their importance to them, the most frequently requested information by patients was the one about side effects. The same category was ranked 10th by physicians in terms of what they thought patients wanted to know. Another study, involving 2,500 adults in Kansas, United States, showed that 76.2% of respondents wanted to be told of all possible adverse effects and only 0.4% were not interested in any information regarding adverse effects. Obviously, it is very important that patients obtain the information about medications that they feel are needed. When important information is not provided, patients can wonder if they really need the medication. Today, patients want personalized therapeutic information – they want to know whether the prescribed medication is right for them. In particular, they wonder about side effects for which they are at risk, and about how long they have to take the medication. By improving the delivery of therapeutic information to patients, a huge opportunity arises to prevent medicine-related deaths and to increase the right adherence to medications.

The patient information leaflet (PIL) or package insert provides patients with information about a medicinal product, such as indication, doses, and side effects, and is included in the product package. PILs are written by the manufacturing pharmaceutical company following specific guidelines and are a patient friendly version of the summary of product characteristics (SmPC). The SmPC is a legal document prepared by the pharmaceutical company while applying for marketing authorization. It contains information for healthcare professionals on how to use the medicine. All authorized medicines need to have a PIL and an SmPC. The process of PIL preparation always includes consultations with target patient groups to ensure that the provided information is legible, clear, and easy to use as the PIL must be written and designed to be clear and understandable to patients. The information within the PIL and SmPC is not finite – it changes when new safety information about medicinal product is learnt. Thereby, PILs contribute to risk minimization. (see chapter 6.0 **"Discovering New Safety Information: Signal Detection" and chapter 8.0 "Understanding the Risks and Keeping Our Patients Safe").**

Did you know...

The first patient package insert requirement was issued by the FDA in 1968. It mandated that isoproterenol inhalation medication (primarily used for slow heart rate or heart block) must be accompanied by a short warning that excessive use could cause breathing difficulties. The second patient package insert required by the FDA was in 1970 and specified that combined oral contraceptive pills must contain information about specific risks and benefits for the patient.

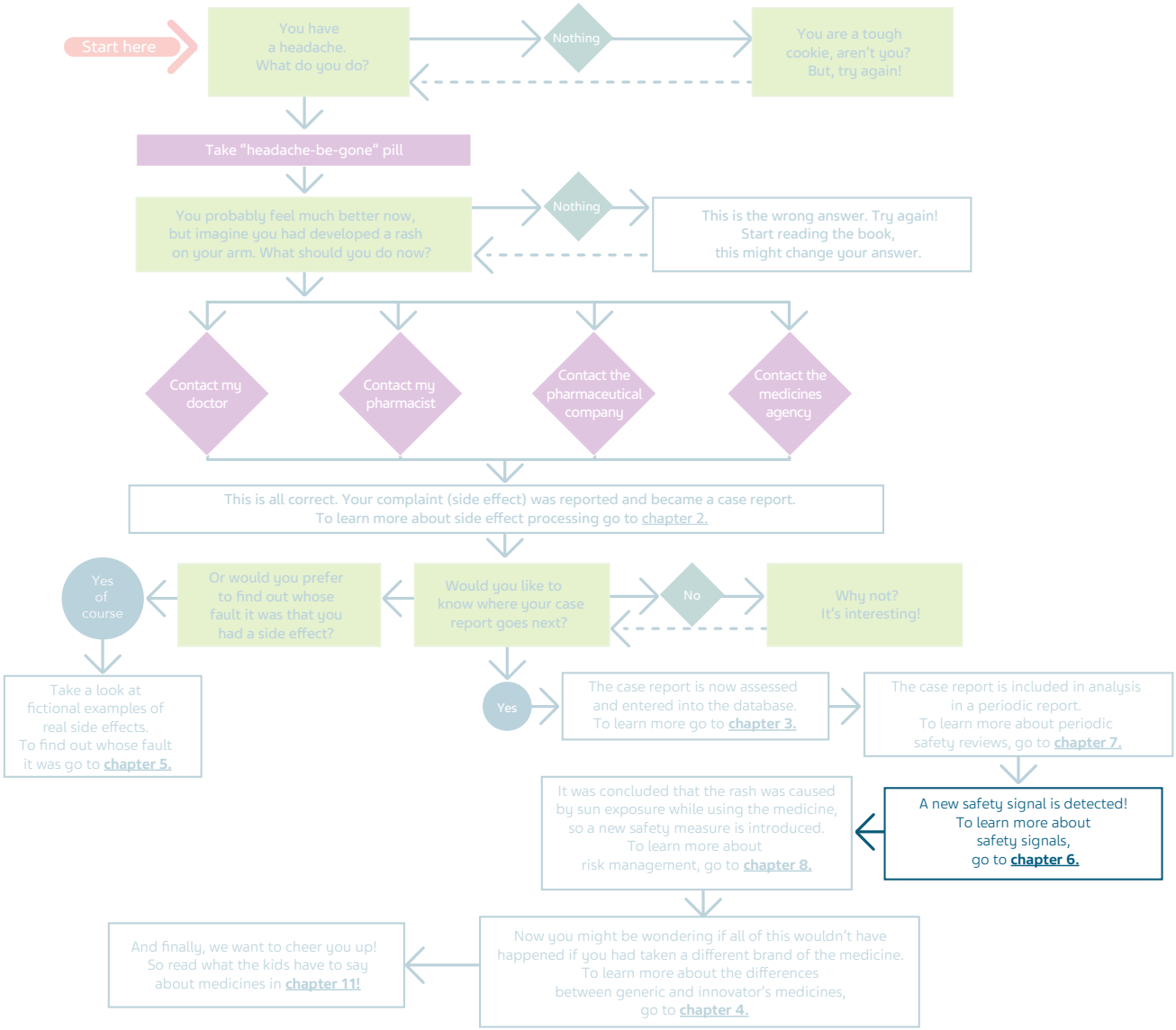
When taking medications, we should be aware that all involved parties may be responsible. Healthcare providers (physicians, pharmacists, dentists, and nurses) are supposed to warn their patients on how to take medication as well as explain their effectiveness and potential side effects. Patients should always read the patient information leaflet for medications they are taking, even if they have taken the same medicine previously, because the PILs change when new safety/efficacy data are discovered. Pharmaceutical companies have the obligation to clearly indicate all information related to medicines, either on the package or in the PIL. Patient safety is everyone's responsibility.

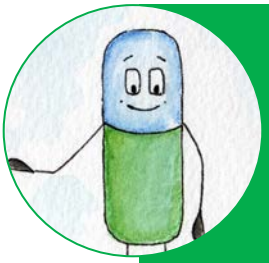
When a medicine is available on the market and widely used by patients, sometimes new safety information may be detected. Whether good or bad, newly discovered safety data is thoroughly analyzed in a process called signal detection.

If you want to test your knowledge go to "Time to Take a Quiz!".

Discover the world of interesting safety signals and their importance to patient safety in the following chapter "Discovering New Safety Information: Signal Detection".

6.0 Discovering new safety information: signal detection





- In PV, any unexpected side effect, or any new information on a previously known side effect potentially caused by a medicine, that warrants further investigation is called a safety signal.
- Every signal has to be thoroughly investigated in order to determine the possible risk factors, mechanisms that lead to its occurrence, and if there is a causal relation to the medicine.
- New information about a medicine may not only enhance what we know about the safety of a product, for example, precautions regarding the use of aspirin in young children, but also, it can open a door for a completely new use of the medicine, such as changes in eyelash growth with use of prostaglandin analogues.
- On occasion, a signal may be refuted due to lack of evidence linking the side effect with the medicine. If new information about this side effect is received, the signal can be reopened and assessed again.
- When a signal is evaluated and confirmed, the new information is usually included in the product information, including the patient information leaflet (PIL) to facilitate better understanding of how to use the medicine safely.
- Medicines agencies collect the data for all products from different pharmaceutical companies and may use it to raise a safety signal or suggest a course of action that will be relevant for all companies.

During the lifetime of a medicine, new and unpredictable effects of its use, good or bad, may come to the surface. You may wonder why these events were not discovered during clinical trials? There are several potential reasons for this.

In previous chapters, we indicated that clinical trials are done on a limited number of patients (up to 5,000) for a limited time period (usually 6-12 months). Also, medicines are not routinely tested in certain patient populations, such as children, elderly, and pregnant women. Once on the market, a huge number of patients become exposed to the medicine. Therefore, an event that occurs rarely with a medicine may be missed in clinical trials and only appear when the medicine is used by a large number of people. Similarly, patients may sometimes use other medicines for their illnesses and, when prescribed a new medicine, a previously unknown interaction between the old medicine and the new one might occur. Such events could not have been seen earlier, because patients in clinical trials usually only take the investigational medicine. In some cases, an undesirable effect, such as nausea, may already have been noted in clinical trials but become more severe and accompanied by vomiting and other symptoms, for example, sensitivity to light, when used more widely.

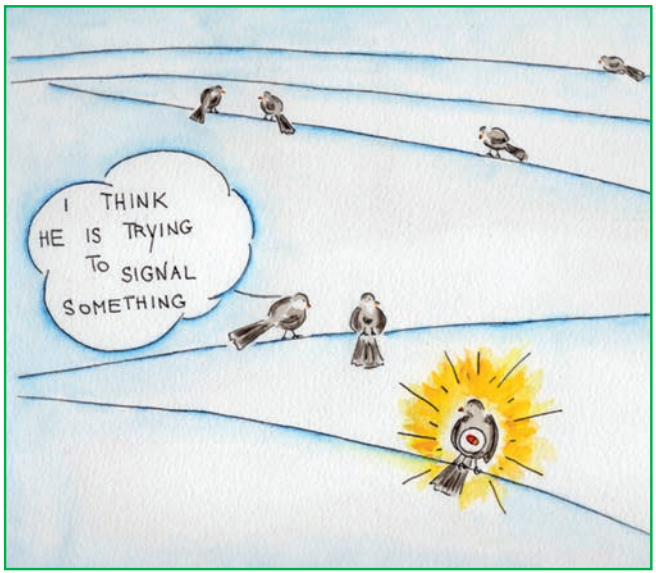
In PV, any unexpected side effect, or any new information on a previously known side effect potentially caused by a medicine, warrants further investigation and is called a safety signal. The presence of a safety signal does not automatically mean that the medicine caused the reported side effect. It could be caused by another medicine taken by the patient or it may be a symptom of the patient's illness. That is why every signal has to be thoroughly investigated. If the analysis of the signal shows that the events are, with a high degree of certainty, caused by the medicine, this new information should be included in the product's information, including the patient information leaflet (PIL).

Sometimes, the signal may indicate that certain precautions are needed to both minimize the risk of experiencing the undesirable event and to enhance the safety of the medication. So, how is this done? Let's look at reports of rash.

If a number of reports of rash have been noticed in patients taking the same medicine, it could lead to the conclusion that there is a connection between the occurrence of rash and the medicine taken. However, it is not that simple. Several points have to be carefully evaluated:

- the characteristics of the patients involved, for example, age, gender, history of similar reactions, other diseases present or other medicines taken at the time the event occurred etc
- the medicine itself, for example, its mechanism of action, route of administration, dose taken by the patient, or any potential for interactions with other medicines or food taken by the patient
- the circumstances in which the adverse events have happened

Now, let's look at a few examples!



6.1 Even old drugs can surprise us

Aspirin (or acetylsalicylic acid) is one of the oldest known drugs; it has been in use for more than 100 years! It reduces fever and inflammation and is effective against pain. It is also used to treat or prevent heart attacks, strokes, and chest pain (angina) under the supervision of a doctor. The most common side effects of aspirin are nausea and vomiting, heartburn, and headache. However, after decades of its use in adults as well as in children, rare cases of nausea and vomiting, lasting for several hours, have been observed in children. Vomiting is usually followed quickly by irritable and aggressive behavior. The children become sick very suddenly and may be unable to stay alert or awake.

These events were mostly seen when aspirin was given to children who had chickenpox or the flu. The specific group of symptoms is called Reye's syndrome; it can manifest as brain damage and liver function problems and have severe consequences. Once the syndrome was discovered and aspirin confirmed as a culprit, a special warning about Reye's syndrome was added to the aspirin PIL. The warning states that aspirin should not be given to a child unless specified by his/her doctor. When a child must take aspirin, care should be taken to reduce the child's risk of catching a viral infection, such as the flu or chickenpox. Aspirin should also be avoided for several weeks after the child receives the varicella (chickenpox) vaccine. After the inclusion of this warning, Reye's syndrome has become a very rare occurrence in the general population.

Did you know...

Ludwig van Beethoven, the famous German composer, is known to have composed his last masterpieces completely deaf. A lesser known fact is that it was his love for wine that led to his hearing loss. Many historians speculated that it was mercury, used as a medication to treat his syphilis, which caused his deafness. However, according to the analysis of Beethoven's bones, it was lead, not mercury, that was found deep in his bone tissue. The finding of shrunken ear nerves at his autopsy is consistent with nerve degeneration due to heavy metals such as lead. Beethoven's physicians thought at the time that he had alcohol dependence, but what they didn't know was that he particularly liked wine that happened to be tainted with lead.

6.2 An unusual side effect

Parkinson's disease is a motor system disorder of the nervous system. It is described as a progressive disorder that affects movement and results in the loss of dopamine-producing brain cells, causing tremor in the hands, arms, legs, jaw, and face, and/or rigidity or stiffness of the limbs and trunk. Dopamine is a neurotransmitter that helps control the brain's reward and pleasure centers; it also helps regulate movement and emotional responses. It enables us to not only see rewards, but to also take action to move towards them. The goal of most medicines used in the treatment of Parkinson's disease, called antiparkinsonian medicines, is to either replace the dopamine levels in the brain, or mimic the actions of dopamine. Without proper and continuous therapy, affected patients can't function normally. Here's an example of how a new signal regarding antiparkinsonian medicines was revealed:

Case 1: A physician reported a case which was received by a patient's wife. Her husband has Parkinson's disease and he handles it very well. A month before her call, she and her husband went on a trip to Las Vegas and she noticed that his excitement and fascination with casinos was huge. When they came back he began staying late in the office and going out for the weekends, so she started to worry that he was cheating on her. She asked his friend to confirm her suspicions, only to find out that her husband had started going to casinos and gambling almost every other day.

Case 2: A neurologist reported that a lot of her patients with Parkinson's disease, who visited her at their regular appointments, complained that they were buying things a lot more than usual and that they couldn't help themselves. Some patients commented that they played computer games like obsessive adolescents; while other patients complained that they were eating much more than normal. The two things all these patients had in common were Parkinson's disease and the same medicine.

While performing their regular signal detection process in the PV department, the pharmaceutical company which manufactures medicines for Parkinson's disease noticed that the number of these cases grew from month to month. Consequently, they raised a safety signal. After thorough investigation, a true relationship between obsessive behavior of all kinds and the suspected antiparkinsonian medicines was confirmed. The reaction "obsessive behavior" was then added to the PIL and other safety documents concerning these products.

6.3 An unexpected therapeutic benefit

Sometimes, a newly found signal can initiate further investigations and lead to the discovery of a previously unknown beneficial effect for the medicinal substance concerned. A medicine originally tested and marketed for the treatment of one disease or condition can become an effective medicine for the treatment of another condition or disease by fortunate coincidence or findings from clinical studies. There are numerous examples of "old medicines" being found useful in completely new indications. One signal that led to further research and use of the medicine in a new therapeutic field was the effect of prostaglandin analogues on eyelash growth. Prostaglandin analogues were originally used for the treatment of increased eye pressure, also known as glaucoma. The first case reports of increased eyelash growth were reported shortly after the introduction of the first medicine from the prostaglandin class for glaucoma in the late 1990s.

One case report concerned a female patient in her 50's who was referred to an ophthalmologist due to glaucoma. The patient had also suffered a total eyelash loss in both of her eyelids after experiencing an allergic reaction five years earlier. She was prescribed a prostaglandin analogue and after just three weeks of therapy, the eyelashes became noticeable to the patient. During her control visit to the ophthalmologist, the change was evident; the patient experienced a complete regrowth of her eyelashes after two months' treatment with prostaglandin analogue eye drops prescribed for glaucoma!

Other similar reports followed for the same medicine. Some of them described more inconvenient effects than the beautifying effect of eyelash growth, like upper cheek hair growth in a patient that excessively used his eye drops, or increased eyebrow growth in a paralyzed patient that was forced to lie down.

Over the next few years, other medicines from the same class of medicines were introduced and the same effect was noted. In one of the cases, a 43-year-old woman reported that she had been using another prostaglandin analogue for treatment of glaucoma in her left eye. After three months of therapy, she noticed that there was a significant difference in hair appearance between the treated and non-treated eye. Eyelashes in her treated eye had increased in number, thickness, length, curvature, and pigmentation.

Following numerous similar reports, it became evident that several prostaglandin medications had the same effect, and there was reasonable suspicion that increased eyelash growth could be expected for the whole prostaglandin analogues class of medicines. Since eyelashes have a protective function against airborne particles and their loss can cause eye irritation, patients who suffered from eyelash loss finally had something to look forward to. In addition, loss of eyelashes can be cosmetically unacceptable to some patients. After additional studies were conducted, this new found effect was used for the development of medicinal treatments for regrowth of eyelashes. Today, further investigations have been made with this class of medicines and there is hope that, some day, there will also be a cure for excessive hair loss. And all of this thanks to a signal!

Did you know...

Aldous Huxley, the famous writer best known for his novel “Brave New World”, documented his experimentation with mescaline in his book “The Doors of Perception”. Mescaline is a hallucinogenic alkaloid isolated from the flowering heads of peyote - Lophophora (formerly Anhalonium) williamsii, a Mexican cactus used in Indian religious rites and as an experimental psychotomimetic. Among its cellular effects are positive effects on serotonin receptors which are known as “the hormone of happiness” receptors. It has no accepted therapeutic use, although it is legal for religious use by members of the Native American Church.

6.4 When will a safety signal be refuted?

Sometimes, potential signals which we come across will be refuted. This is usually because there is not enough information to confirm that the medicine taken by the patient caused the reported side effect, or because it also includes evidence which suggest that another medicine (or any other product the patient is taking at the same time), or the patient's existing disease may have caused the described side effect.

Here's an example: A new antibiotic for the treatment of throat infections was approved. Within a year, hives were reported by 6 patients. No information on this side effect was found in clinical trials, so this was recognized as a potential signal and it was decided to investigate if the medicine caused hives. The analysis of the cases resulted in the following information:

Case 1: A doctor reported that his patient, an adult woman, experienced hives after starting treatment with the antibiotic. The therapy was stopped and the woman started a treatment for hives. Shortly after that, she recovered completely. The woman was not taking other medicines and did not have a history of allergies. Because hives could have been caused by the antibiotic, additional tests were done, however, no causal relationship between the medicine and hives was confirmed.

Case 2: An adult man reported that he experienced hives during treatment with the antibiotic. The therapy was stopped and the patient recovered completely. No testing was done to confirm if the hives were caused by the antibiotic. The patient took two other medicines at the same time, both of which were known to cause hives. Since no tests were done and the role of other medicines could not be excluded, the cause of hives in this case could not be confirmed.

Case 3: A pediatrician reported that a 6-year-old boy experienced hives three days after he started taking the antibiotic. Therapy was stopped and the boy recovered shortly thereafter. The mother stated that he did not take any other medications at the time, but when he was five, he did get hives after eating peanuts. However, the mother claimed that they were very careful about his diet after that, and that he was not exposed to peanuts. After asking for more information, the mother said that the boy got candy from a friend on the day the hives appeared. Apparently, since he was told not to eat candies, he was at first too afraid to admit that he had taken it. The mother checked and confirmed that this type of candy indeed contained peanuts. Therefore, in this case, the antibiotic was unlikely to be the cause of the hives.

Case 4: This case was based on a published scientific article which described an adult patient who took the antibiotic and experienced hives. The complete article was examined carefully. The author of the article focused mainly on the effectiveness of the treatment, providing very little information on the side effects reported. Also, the patient's previous diseases and use of other medicines were not available. It was unknown when the patient recovered from hives. Because of that, it could not be assessed whether the antibiotic caused the hives.

Case 5: An 80-year-old patient told his pharmacist that after taking the antibiotic he experienced terrible hives. After the case was initially reported, more information was requested. The patient could not remember the details but he provided the phone number of his doctor. The doctor confirmed that the patient took the medicine and that the treatment ended about a month earlier. However, the patient never reported hives and looked healthy during the check-up at the end of the therapy. The hives were mentioned in his medical record; however, this had happened 5 years ago. The doctor also added that the patient suffered from dementia, had trouble remembering and often confused events from his past. Additionally, the patient's daughter confirmed that her father did not get hives while he was treated with the antibiotic.

Case 6: A patient (who did not provide any additional information on gender and age) suffered from hives after starting the treatment with the antibiotic. No other information was provided. In order to get more information, the patient was contacted, but he refused to provide more details.

Based on the analysis of these six cases, it could not be confirmed that the medicine in question caused hives. Additional scientific literature searches have not found any other information that could confirm the relationship between the antibiotic and hives. The signal was therefore refuted and it was concluded that no further action was considered necessary, apart from routine PV activities, which include monitoring of similar cases in the future. However, it is important to emphasize that refuting a signal does not mean that the medicine in question cannot cause hives; it means that no sufficient evidence for this association was present at the point of time when the signal was assessed. If new information about this side effect is received, the signal can be reopened and assessed again.

To sum up, when do we find a safety signal?

The examples presented in this chapter illustrate some of the most common situations that can occur after new information on a medicine is received. Sometimes, this new information makes us redefine what we know about the safety of our product and sometimes it may open a door for a completely new use of the medicine. Regardless of whether this unexpected finding will lead to restrictions for use or do just the opposite and open the door for new indications, every piece of newly received information is carefully assessed based on the available evidence.

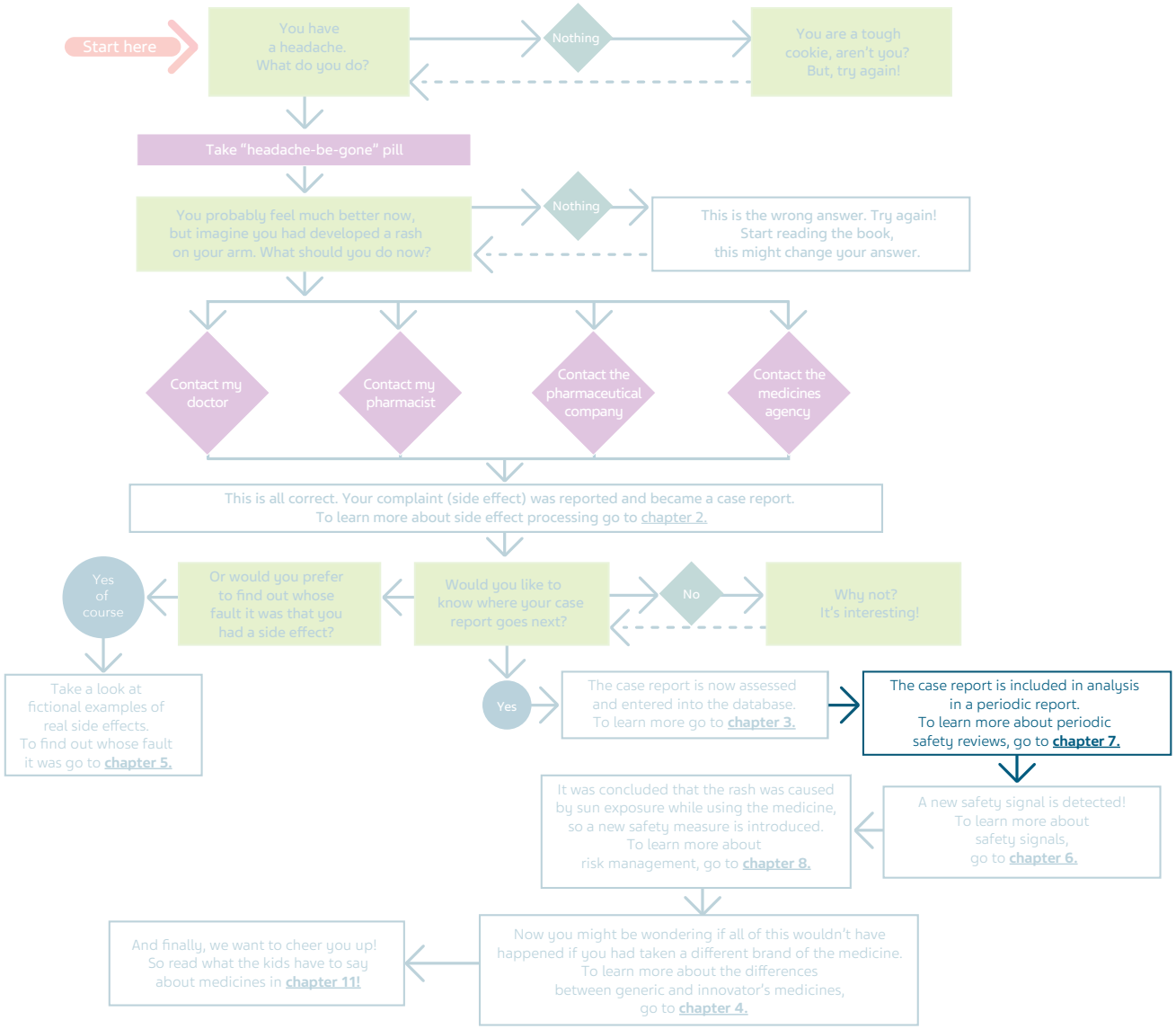
This is why it is very important for pharmaceutical companies to collect as much information from patients and healthcare professionals as possible. It helps to confirm a potential signal and to determine the possible risk factors and mechanisms that lead to its occurrence. So, any company can raise a signal based on the data it collects. Furthermore, different companies may market the same medicine (a product containing the same active ingredient) at the same time. Medicines agencies, which collect the data for all products from different pharmaceutical companies, have access to much more information than an individual pharmaceutical company. Therefore, based on the aggregate data, medicines agencies may also raise a signal or suggest a course of action that will be relevant for all companies.

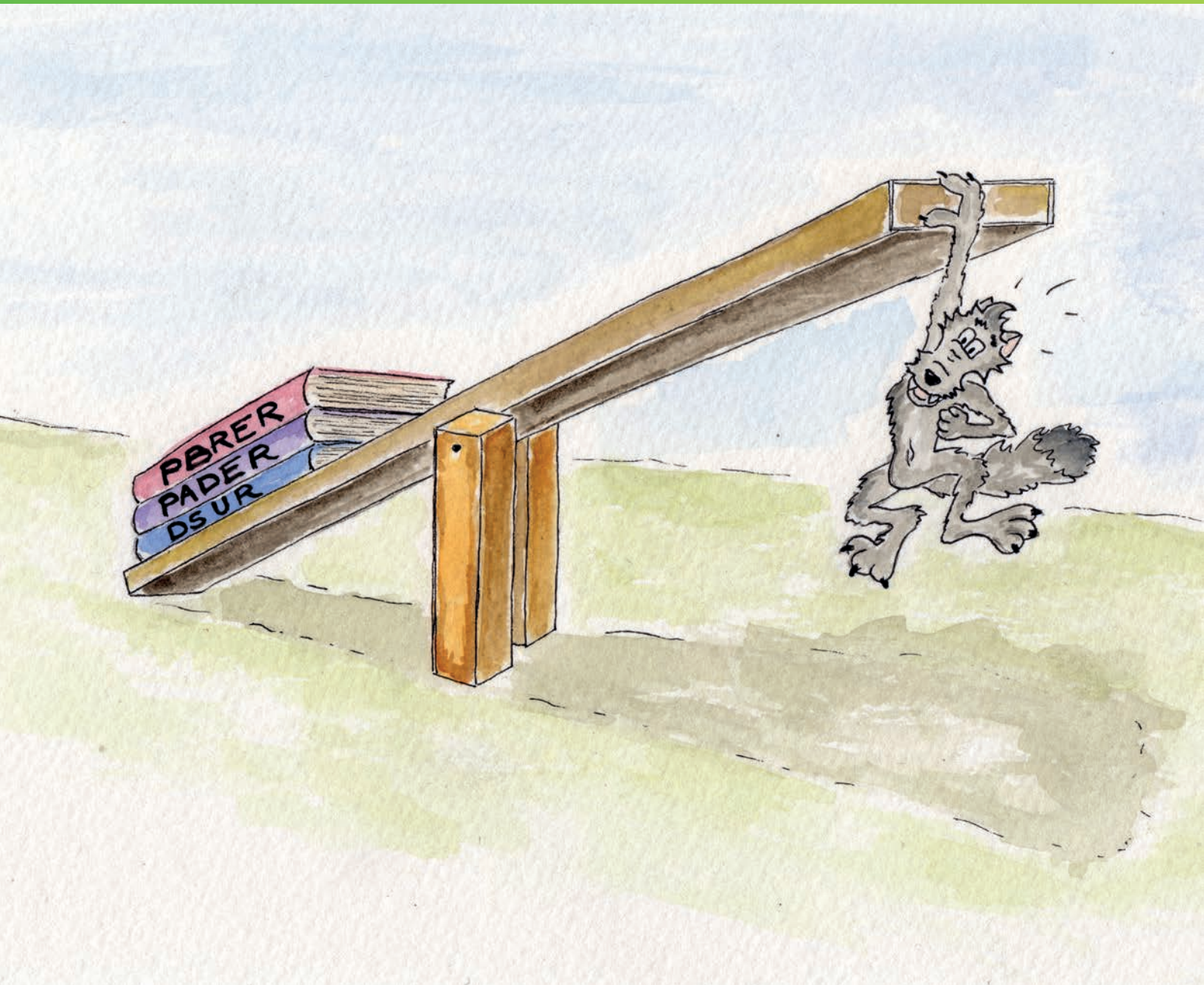
When a signal is evaluated and confirmed, the new information is usually included in the product information, including the PIL. This information helps both patients and healthcare professionals to better understand how to use the medicine safely. It is the responsibility of PV, however, to always be alert, to monitor the unknown versus the known, and to expect the unexpected.

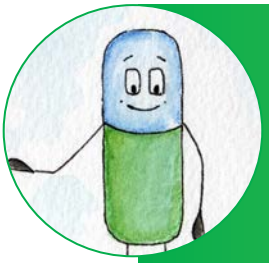
If you want to test your knowledge go to "Time to Take a Quiz!".

Next, our journey takes you to the PV process which will help you understand what happens after all safety data are collected – chapter 7.0 "Periodic Safety Reports or Seeing the Big Picture".

7.0 Periodic safety reports or seeing the big picture




PBRER
PADER
DSUR



- Case reports entered in the database are not forgotten; they are all analyzed as part of the preparation of a periodic safety report. Medical writers working within a pharmaceutical company analyze the data and compile periodic safety reports.
- A periodic safety report provides an overview of the safety data collected worldwide for a marketed medicinal product and provides a complete picture of both the product's safety and efficacy.
- The most important aspect of a periodic safety report is to provide an evaluation of the benefit/risk balance of a medicinal product and detect new adverse medicine reactions.
- Periodic safety reports can be prepared very frequently (every three months) when a product is new and there may still be some unknowns but, for a product that has been used on a widespread basis over a number of years, more time can pass between two periodic reviews (up to five years).
- Medicines agencies use periodic safety reports to decide whether any further investigation or action is needed to protect the public from the identified risks.

By now, you will have seen that reporting any side effect when using a medicine does matter and that each case report is processed in a safety database, but what happens next? A case report entered in the database is not forgotten. After its initial assessment, it is analyzed again and used to make important decisions regarding the future of the medicinal product, for example, when preparing a periodic safety report.

Why do we need periodic safety reports?

A periodic safety report is a document that provides an overview of the safety data collected worldwide for a marketed medicinal product. It indicates whether a product's profile has remained the same or has changed during its time on the market, i.e. since it was first authorized. Its purpose is to "paint" a complete picture of the product's safety and efficacy.

What is included in a periodic safety report?

- Analysis of case reports received in the period covered by the report
- Conclusions on safety signals identified during the relevant period
- Information from published scientific literature
- Information from ongoing or recently completed clinical trials
- Analysis of risks associated with the medicinal product
- Analysis of effectiveness of the medicine
- Analysis of benefit/risk balance
- Description of actions taken by the company to increase benefits and reduce the risks of the medicine

Medicines agencies review periodic safety reports and use them to determine if any new risks have been identified for a medicine and to decide if further investigations are needed or whether certain actions are required to protect the public from the identified risks. This includes updating the information provided for healthcare professionals and patients or initiating a better risk management system (see chapter 8.0 **"Understanding the Risks and Keeping Our Patients Safe"**). On the other hand, if the risks considerably outweigh the benefits, the medicine can be withdrawn from the market. The most important aspect of a periodic safety report is to provide an evaluation of the benefit/risk balance of a medicinal product and detect new adverse medicine reactions.

What is a benefit/risk analysis?

As we probably all know, no medicine is perfect (but we're working on it!), but if it is the best treatment available for a certain illness, possible adverse events are accepted and the medicine can stay on the market. In the treatment of cancer, for example, severe adverse events are accepted because the cancer medicines save lives. However, such events would be unacceptable for an allergy medication. The conclusions of periodic safety reports play a key role weighing the risks and the benefits of a medicinal product and answering the question "Is this medicine worth taking?"

How often is a periodic safety report prepared?

In short, the newer the product, the more often a periodic safety report must be prepared. Time frames are defined by regulatory authorities: they can range from just three months to more than five years between two reports. The rationale behind the changing time frames is that with a new product there may still be some unknowns, so pharmaceutical companies and regulatory agencies need to be alert to anything new that might impact the safety of a medicine. As explained in chapter 6.0 **"Discovering New Safety Information: Signal detection"**, clinical studies are not suitable for detecting very rare adverse medicine reactions (occurring in one in 10,000 patients). Therefore, when a new medicine is marketed, the pharmaceutical industry and medicines agencies closely monitor its safety profile.

The frequency of periodic safety report submissions can be changed by a number of factors:

- new information on risks or benefits that may have an impact on public health;
- following significant amendments to the product, for example, approval of a new indication, pharmaceutical form or route of administration which broadens the exposed patient population;
- a new signal is detected that puts the medicinal product under additional close monitoring.

On the other hand, a medicine that has been in widespread use for decades is not expected to suddenly start "acting out", so a bit more time can pass between two periodic reviews.

How is data analyzed in a periodic safety report?

The most important source of information in a periodic safety report is the company's PV safety database as this is where all the received case reports are entered. After analysis of all the case reports and other relevant data, a periodic safety report may conclude that either new safety information was discovered which might change the benefit/risk profile of the medicine, or that the previously established safety profile is confirmed and no changes are needed.

This all sounds straightforward, right? But consider this: in a single year, a pharmaceutical company can receive anywhere from just a few case reports for a single medicine, to several thousand reports for a newly approved medicine. Searching for significant and new information in thousands of case reports might feel like looking for a needle in a haystack. A very important step, therefore, is to decide if a reported adverse event could possibly be due to a certain medicine. Some good criteria for this assessment are described in **Table 7-1**.

If any new safety information emerges from the data analysis, or even if it seems like it might be new, an ongoing signal is declared and a new evaluation process begins, as previously described in chapter 6.0 **"Discovering New Safety Information: Signal detection".** Special attention is given to cases that report lack of efficacy of the medicine, overdose, inappropriate use, and positive or negative experience during pregnancy and breastfeeding, in order to collect more information about situations that are difficult to investigate in clinical studies.

Periodic safety reports provide an opportunity to put the gathered information in perspective since the medical writer analyzes and compares side effects from all sources of information – consumer, healthcare professional, scientific literature, clinical studies – from around the world and over a prolonged period of time. This is especially important when identifying rare side effects.

Table 7-1. Commonly used criteria for assessing causal relationship (causality) between a suspected medicinal product and an adverse event

Criteria	Causality
The timeline ("latency"): how much time has passed between the medicine intake and the adverse event	More likely if the timeline is compatible: a skin rash will usually appear a few hours after a medicine is taken
Did the same adverse event re-occur in the same person when the medicine was taken again ("re-challenge")	More likely if the adverse event re-occurs: a person takes a medicine and experiences nausea shortly after, but doesn't connect it to the medicine, so he/ she takes it again sometime later with the same effect
Did the adverse event resolve or get better after the medicine was discontinued ("de-challenge")	More likely if the adverse event resolves after the medicine is no longer taken than if it persists: a person takes an antibiotic course lasting 5 days and experiences stomach-ache, but the stomach-ache resolves once the person no longer takes the medicine
How biologically plausible is the adverse event in relation to the pharmacological actions and metabolism of a certain medicine?	This is obviously a very complex question, sometimes requiring a lot of research. A simple example would be someone getting a headache after applying a pain relief gel on skin – causality is less likely since the gel is minimally absorbed and generally acts locally
Other factors	Are there any other medicines that the person was taking at the time (maybe a medicine interaction had occurred), what is important in the patient's medical history (did the patient already experience a similar side effect or does the patient have an underlying disease?)

Who writes periodic safety reports?

Medical writers working within a pharmaceutical company use their scientific and medical knowledge to analyze the data and present it in an organized and succinct way. Writing a periodic safety report can take between a few days to a few weeks depending on the quantity and complexity of the data.

The format of a periodic safety report

While periodic safety reports all have the same objective, the format differs according to when and where they are submitted. These are the most common ones:

- PBRER (Periodic Benefit Risk Evaluation Report), previously known as PSUR (Periodic Safety Update Report) – these reports are submitted to the EMA (European Medicines Agency) and national regulatory agencies within and outside the European Union
- DSUR (Development Safety Update Report) – for medicinal products that are investigated in clinical trials
- PADER (Periodic Adverse Drug Experience Report) – these reports are submitted to the US FDA (Food and Drug Administration)
- ASR (Annual Summary Report) – reports prepared for the Canadian health authority

In conclusion, periodic safety reports are an important part of PV since they provide a summary analysis of all the data available for a medicinal product as well as a critical scientific assessment. Periodic safety reports are where all the hard work done within the PV department is summarized and presented with final conclusions. They play a vital role in keeping patients safe.

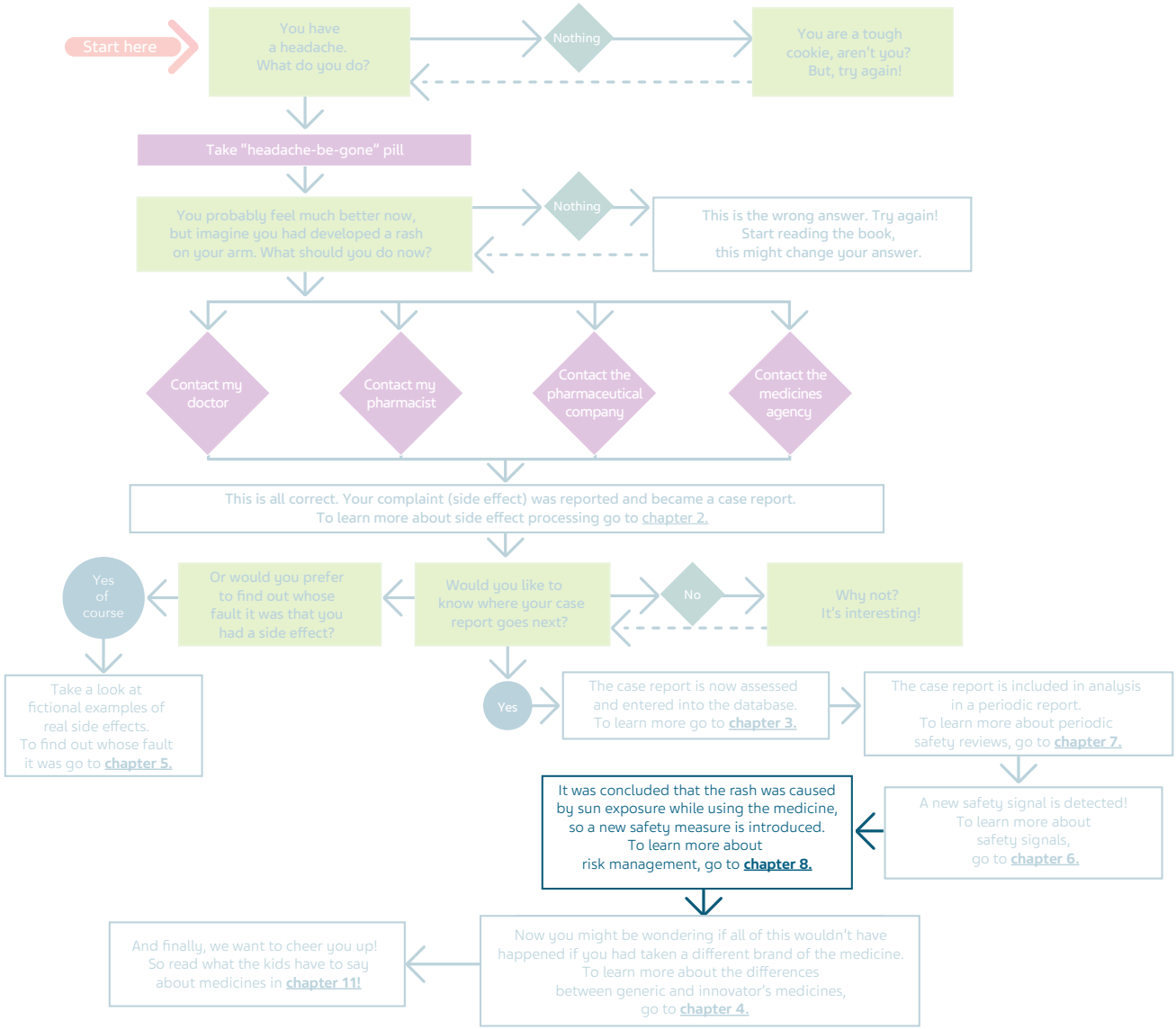
Did you know...

Professor Božidar Vrhovac from Zagreb, Croatia initiated side effect reporting in former Yugoslavia in the early 1980s. His work is respected and admired not only nationally but also around the world. By providing his personal views on how to achieve rational use of medicines when resources are limited, Professor Vrhovac made an important contribution to the Southeast European Pharmaceutical Conference organized by the WHO Regional Office for Europe (WHO/Europe) and the European Union (EU) in Sarajevo, Bosnia and Herzegovina in 2006. He provided a wide overview of the topic "Rational Use of Medicines" and gave the following definition: prescribing pharmaceuticals with proven efficacy, with acceptable risk/benefit ratio and with acceptable cost/benefit ratio (affordability). The term "relative efficacy" was introduced, meaning that when prescribers are considering alternative medicines or treatments, they should look beyond efficacy when selecting the best treatment for an individual patient. A set of measures was suggested to make medicines prescribing more rational and bring costs under control.

If you want to test your knowledge go to "Time to Take a Quiz!".

What happens if new risks regarding medicine use are identified following safety data analysis? Is there someone who actually minimizes potential risks, and how do they do it? The following chapter "Understanding the Risks and Keeping Our Patients Safe" is about to reveal the mysteries of risk minimization measures and procedures.

8.0 Understanding the risks and keeping our patients safe

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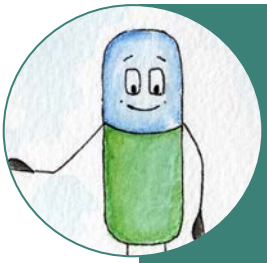


- As new information regarding the positive or negative effects of a medicine when used in the wider population becomes available, the benefit/risk balance for a medicine can change.
- The process of risk management monitors and identifies risks associated with a medicine in order to prevent or minimize them wherever possible.
- A risk management plan foresees the monitoring of safety concerns such as risks proven to be related to the medicine; risks where a relationship with the medicine is suspected, but still not confirmed, and gaps in knowledge that could be important for the medicine's use.
- Various strategies have been developed to advance the safe use of medicines through better communication: updating the basic product information document; optimizing the package size to mitigate the risks of medicine abuse, dependence, or overdose; letters to doctors and pharmacists; guides and toolkits for patients; or pregnancy prevention programs.
- The analysis of effectiveness of risk minimization measures is presented in periodic safety reports and submitted to the medicine agencies that regulate medicines in each country where the medicine is sold.

When a new medicine is released on the market, information about how it is used in real life conditions is often very hard to predict. The decision to approve a medicine depends on various factors. One such factor is how the benefits of the medicine balance against the risks. If the medicine benefits are greater than its risks (which means that the benefit/risk balance of the medicine is positive) the medicine can be approved and made available to patients. However, the benefit/risk balance for a medicine can change over time when used in the wider population as new information regarding its positive or negative effects becomes available.

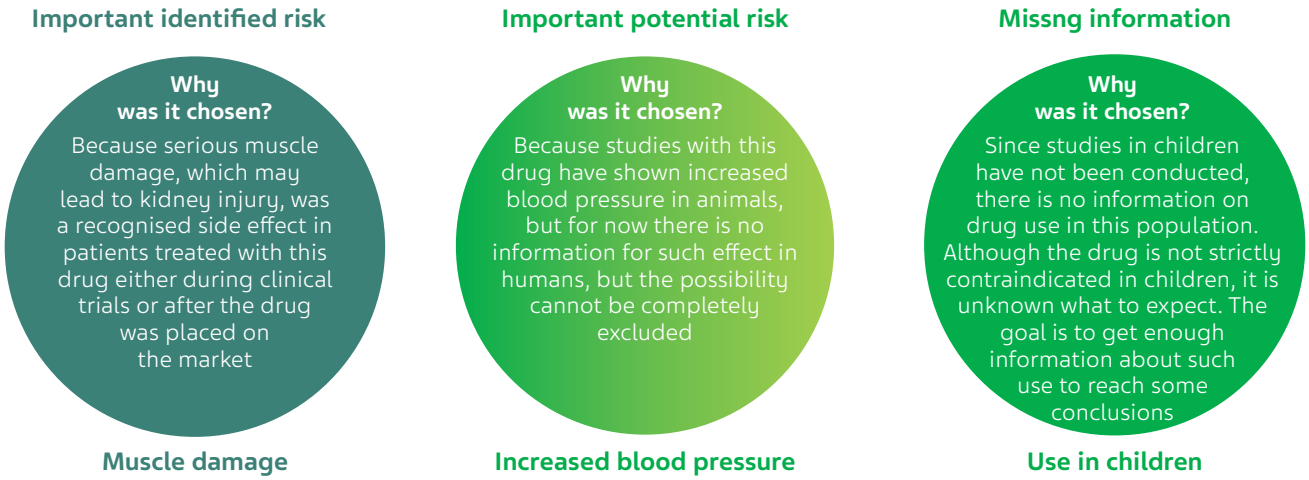
To get closer to what this means, here is one example. A few decades after the approval of ketoconazole, an oral antifungal medicine, the question of an association with liver injury was raised. Although this is a known side effect of antifungals, after reviewing the study data, case reports, and literature, it became clear that this particular medicine may indeed cause serious liver injury. Collection of relevant information confirmed that it occurs more commonly with ketoconazole than with other antifungals and that available alternative treatments are considered safer. Moreover, the benefit of the medicine was also questionable since the data on its effectiveness was limited and did not meet current standards. Therefore, following this review, it was concluded that the benefit/risk balance of this medicine was no longer favorable, and in most countries the medicine was suspended from the market. This example shows the importance of why a medicine's benefit/risk balance needs to be continuously monitored.

The purpose of risk management is to monitor and identify risks associated with a medicine and to prevent or minimize them wherever possible. The severity of risks and the way they are handled and communicated to healthcare professionals and patients (risk minimization measures) may be vital for maintaining a medicine's positive benefit/risk profile. A risk management plan foresees the monitoring of safety concerns and focuses on:

- important identified risks – those undisputedly proven to be related to the medicine
- important potential risks – those for which the relationship with the medicine is suspected, but still not confirmed
- missing information – gaps in knowledge about a medicinal product, which could be important for the medicine's use

Examples of safety concerns that might be associated with a medicine are presented in **Figure 8-1**.

Figure 8-1. Examples of safety concerns



Risk communication tools are important for sharing information. Various strategies have been developed to advance the safe use of medicines through better communication. The basic risk communication tool is the product information document which contains precautions and warnings. For some products, the package size can be optimized to mitigate the risks of medicine abuse, dependence, or overdose. For example, some medicines used for treatment of sleeplessness may only be used for a short period of time to avoid medicine dependence. Therefore, the packaging will only contain a limited number of tablets (e.g. 10) to limit the duration of treatment. Another possible way to reduce risks is to limit availability of a medicine to prescription only. However, for some risks, these routine measures are not enough, and additional risk minimization measures are needed to ensure that patients and doctors are warned about a medicine's specific risks. For example, letters to doctors and pharmacists, guides and toolkits for patients, or pregnancy prevention programs. The purpose of all these initiatives is to positively influence patients' and healthcare professionals' behaviors and, through

these changes, lead to improved patient outcomes. The routes of communication between a pharmaceutical company, healthcare professionals, and patients, are agreed with medicines agencies in advance and are also supervised by them.

Sometimes, pharmaceutical companies conduct additional activities to further investigate a specific risk or to assess the effectiveness of existing risk minimization measures. This can be achieved using different studies or surveys, or the monitoring of treatment by inclusion of patients in registries. The analysis of effectiveness of risk minimization measures is also presented in periodic safety reports and then submitted to the medicine agencies that regulate medicines in each country where the medicine is sold.

In this section, you will find some examples of measures taken to ensure the safety of patients taking various medicines.

Did you know...

Winston Churchill's sleep habits are fairly well documented, as he would regularly wear out those around him with his seemingly tireless work habits. During World War II, Churchill often worked until 3:00 AM and would rise at 8:00 AM, giving him a mere five hours of sleep per night, though it should be noted that the prime minister was also fond of an afternoon nap.
Churchill's tireless work ethic and reduced need for sleep may have been the direct result of his use of amphetamines, a medicine commonly used by enlisted men. He was prescribed the medication to treat his depression and, Anthony Eden, his foreign secretary and successor as prime minister, was also a noted user. Churchill used amphetamines to maintain a sense of alertness during a time when the fate of the world seemed to largely rest in his hands.

8.1 The patient information leaflet (PIL) as a way of minimizing risks

Pietro is a young pharmacist who lives in Napoli with his mother, Adriana, who was recently diagnosed with osteoarthritis. As soon as she got home from her doctor, she called Pietro as she was worried about the medicine the doctor had prescribed. She read the package leaflet that came with the medicine and became concerned because the text was full of possible side effects.

Pietro knew what to do because the patients he saw in the pharmacy came to him almost every day with concerns about side effects of medicines. He explained to his mother that the package leaflet is a way to tell patients how, when and why a medicine should be taken. It also describes the side effects of the medicine. Like all medicines, this medicine can cause side effects, but not everybody gets them. He explained to his mother that it is important for patients to be able to recognize a side effect and contact their doctor or pharmacist if something unexpected occurs. With that knowledge, people taking medicines can be in control of their situation and the doctor can stop or change their treatment regimen if needed. He also pointed out some further information on the leaflet – that the medicine should be taken for no more than 15 days in a single course of treatment. This is because scientific studies have shown that the occurrence of side effects with the particular medicine are more likely if the medicine is used for a long period of time. When scientists discovered this fact, they included the information in the patient leaflet and designed the medicine's packaging to contain a single course of treatment to prevent patients from taking more than the prescribed maximum. This is one of the ways in which doctors and pharmacists keep their patients safe from side effects.

Pietro knew, that for this medicine, there were more ongoing scientific studies which aimed to characterize how the medicine is used in the wider population and observe the occurrence of associated events (either beneficial or adverse). Pietro also knew that by actively participating in the medicine's life-cycle, scientists gather more information every day, thereby helping make medicines safer and more efficient. When he explained everything to his mother, she was finally at ease, because she understood that every medicine has an elaborate risk management system around it which takes care of patients and keeps doctors informed on everything they need to know.

Did you know...

Napoleon Bonaparte, the famous French emperor, was long thought to have died due to arsenic poisoning. Arsenic was a common ingredient in a number of household products in the 19th century, including Salvarsan. This was a widely prescribed drug for the treatment of syphilis, from which Napoleon was said to have suffered. Although plausible, this version of Napoleon's death may only be partially true. Napoleon suffered from intermittent nausea and vomiting for most of the eight months before his death and was frequently given "tartar emetic" (antimony potassium tartrate) to relieve his symptoms. The day before his death the group of English physicians who ultimately controlled the Emperor's care insisted that Napoleon be given a huge dose of calomel (mercury chloride), roughly five times the customary dose, as a purgative. In addition, the Emperor was being treated with a decoction (a concentrated liquor resulting from heating or boiling a substance) containing "bark" - presumably "Jesuit's bark", which contained quinine. With today's knowledge, it is clear that all of these medications should not have been given together because of the possibility of an interaction. Combined, they all affect the heart, inducing a condition we call Torsade de pointes, a kind of irregular heartbeat that can be fatal. It is likely that the immediate cause of the Emperor's death was Torsades de pointes, brought on by chronic exposure to arsenic and a medication error. Physicians of Napoleon's time were blissfully unaware, or at least unconcerned, that these medications may interact and have side effects.

8.2 Avoiding accidental exposures to medicines

Gloria is a 71-year old woman who maintains an active lifestyle, enjoys sports, travelling, and spending time with her family and friends. Throughout her life she remained in remarkably good health. She and her husband Vincent raised two children and they enjoy spending time as a family and trying to keep up with their five grandchildren. In their retirement, they pursued their passion for hiking. When they decided to pursue a big adventure, Gloria and Vincent decided to join a professionally guided expedition to the Rocky Mountains. They were both very excited about it, and they spent a lot of time planning the trip. However, during the last few days prior to the expedition, Gloria didn't feel very well. She felt stomach pain, which was usually provoked by eating, and she had to go to the toilet more often. Since she didn't want to jeopardize their long awaited travel, and thought the pain was due to anxiety before the trip, she tried to ignore them. Unfortunately, the symptoms continued and gradually began to worsen. Eventually, they could no longer be ignored and she sought medical help. By the time she arrived at the hospital, the pain was very severe.

Gloria was admitted to the hospital and, after detailed examinations, diagnosed with bowel cancer. Because she had to start the cancer treatment immediately, she was forced to cancel the trip. Most of the time, Gloria controlled the cancer pain adequately with strong painkillers. However, in spite of ongoing treatment with her regular pain medications, she started experiencing sudden flares of severe pain. The pain was usually triggered by movements such as walking or coughing, but sometimes it occurred without any apparent reason. Since she could not bear such intense pain and didn't want to bother her family with her problems, she increased the dose of her pain medications on her own. The pain went away, but she was frightened when her breathing became shallow and weak. Gloria was experiencing the physical consequences of increasing the medicine dose.

She went back to the hospital where she was referred to Dr. Willson, a pain specialist. She described her recently occurring, troublesome pain, and confessed that she had increased the medicine dose by herself. Dr. Willson explained how important is to take medicine properly and not arbitrarily increase the dose, and then prescribed her a new, strong pain medicine which she had to always use in combination with her regular pain medications. The doctor explained to Gloria that a special program had been set up for this medicine in order to restrict its inappropriate uses and provide guidance and oversight for its safe use. He informed her about the positive (benefit) and negative (risk) sides of using the medicine, and about how to safely use, store, and dispose of it. After Gloria discussed her new therapy with Dr. Willson, she signed a paper confirming that she understood and would follow his instructions. The doctor told her to go to the pharmacy next to the hospital, as it was enrolled in the program and allowed to dispense this particular medicine.

Gloria was very satisfied that someone had taken care of her and she would finally be able to achieve pain relief. At the pharmacy, she was not surprised when the pharmacist started asking her a lot of questions as she knew that the medicine was subject to special monitoring. The pharmacist asked her again... "Do you know how to take the medicine?", "Do you use other medications?" before explaining the precautions, the most likely side effects, how to recognize them and when to alert the doctor or pharmacist. Together with the medicine, Gloria got a small booklet containing detailed information and pictures on how to use the medicine properly. There was a picture of a special container she could get by contacting the pharmaceutical company either by phone or email. Gloria was surprised as she had never had to do this before. The pharmacist explained that the medicine came in the form of a lollipop and that, due to its attractive look, there were reports of children who thought it was a candy and tried it. As the medicine could cause serious harm if accidentally used by a child or by an adult who has not been prescribed the medication, it was essential to dispose of the lollipop immediately after its use. Therefore, the pharmaceutical company developed a kit with child safety locks. After she heard this information, Gloria immediately thought of her youngest, inquisitive granddaughter, three-year-old Susie, who was now exploring the world and loved digging into her stuff and instantly felt secure. Two years later, while standing on the top of the mountain Gloria felt relieved that there was someone who would take care of these things and would also take care of her. She remembered all the people who helped and supported her while struggling with cancer and, with a smile, she sent them a postcard from the Rocky Mountains.

Now, let's see what the pharmaceutical company did to minimize risks in Gloria's situation. Firstly, the medicine was only available via a restricted program in which doctors and pharmacies must enroll, in order to limit access to the medicine by people who did not need it or could abuse it. After she received the medicine, Gloria was informed about its proper use and the most important risks of using it, including disposal, were emphasized. Gloria confirmed that she understood the doctor's advice with her signature.

In situations like this, physicians and pharmacists sometimes receive additional training to make sure they give the correct advice to patients. This might be prompted by new information on the medicine becoming available (e.g. a new side effect has been recognized), or the need to reinforce certain information (e.g. if use of the medicine is complicated or there is evidence that the medicine is not being used as it should be). These training sessions are usually conducted by the pharmaceutical company.

The company can also introduce additional equipment or devices, such as the disposal kit in this story, so as to reduce particular risks. For this purpose, Gloria got a pocket book with patient-friendly instructions, created by the pharmaceutical company to reduce the possibility of mistakes. By contacting the company, Gloria could receive a kit for the medicine's storage and disposal to prevent her granddaughter from taking the medication.

Did you know...

In a newspaper article from 1927 titled "Consumers in Wonderland", the author condemns the practice of selling "quack" medicines (with undisclosed ingredients) as miracle cures. Examples include weight-loss pills called "Kellogg's Safe Fat Reducer" and "Marmola". Both contained thyroid gland and thyroid extract, which a physician from the time described as: "while its prolonged administration will sometimes bring about a marked reduction in weight, its use, even under skilled medical supervision, is fraught with danger". The "active ingredient" appears to be porcine or bovine thyroid glands, which contain a mixture of thyroid hormones. Thyroid hormones are still used today, in controlled doses, to treat hypothyroidism. Potential adverse effects include: heart rhythm abnormalities, restlessness, fatigue, weight gain, vomiting, and diarrhea – clearly not acceptable risks for a weight-loss promoter.

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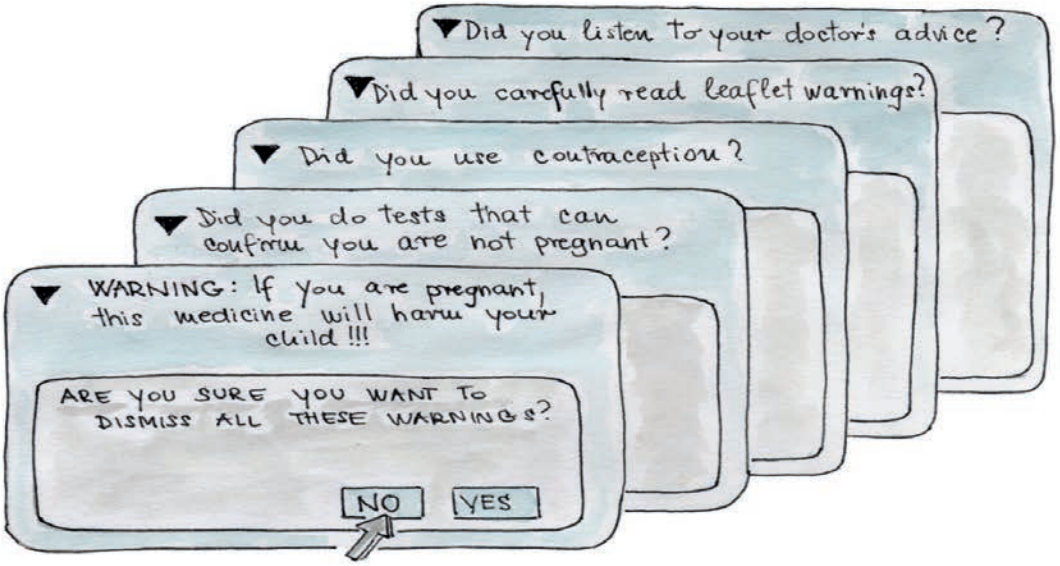
Consumers in Wonderland

III—What We Get for Our Money When We Buy from Quacks and Venders of Cure-Alls

8.3 Minimizing the risks of birth defects

Risk minimization can also include taking steps to reduce the possibility of a medicine causing harm to an unborn child (remember the story of thalidomide from the beginning of this book? – if not, go to "**Pharmaco....what?? Pharmacovigilance**"). As a result, pregnant women are excluded from clinical trials and the PIL usually contains strict precautions relating to use of the medicine during pregnancy. Although extensive preclinical studies are done before a medicine is marketed, the results of these studies cannot confirm that a medicine will be safe for pregnant women or their fetus. Nonetheless, preclinical studies can indicate that harmful effects are possible; and thus use of these medicines in pregnant women will be prohibited. However, while some medication may have devastating effects on the development of an unborn child, they are still marketed because they are safe for use in the rest of the population. Warnings are added for these medicines to notify doctors and patients that they should not be taken during pregnancy. However, in some cases, patients may disregard the warnings and additional measures are needed to make sure that treatment with these medicines is avoided during pregnancy.

For example, isotretinoin is a medicine used for the treatment of severe acne. Acne is a skin condition



characterized by areas of blackheads, whiteheads, pimples, greasy skin, and possible scarring. Various parts of the skin may be affected, including the face, the upper part of the chest, and the back. This may lead to reduced self-esteem in affected patients, as well as anxiety and even more serious psychological problems. Adolescents are the most frequently affected group, followed by young adults. Since a large number of patients are women of childbearing age, it is very important to advise them not to plan pregnancy during treatment in order to avoid harmful effects of the medicine to the unborn child. Most of the patients listen to the doctor's advice and read the warnings on the package leaflet. However, it was noticed that despite the warnings, a significant number of patients become pregnant while using isotretinoin. Because of this, additional measures were implemented to minimize the possibility of treatment with isotretinoin during pregnancy. Measures may vary between countries but generally include:

- Markings on the box indicating that the product is subject to special warnings.
- A warning about the negative effects on child development in the package leaflet.
- Emphasis on the need for women taking isotretinoin to also take contraceptives to make sure that an unplanned pregnancy is avoided (sometimes two forms of birth control are mandatory).
- Regular, sometimes monthly, pregnancy testing before the doctor can prescribe the continuation of acne treatment.
- Provision of educational material explaining the dangers of taking the medicine during pregnancy.

In the USA, for example, a mandatory distribution program for isotretinoin (iPLEDGE) was implemented with the intention of preventing the use of the medicine during pregnancy. The program requires registration of wholesalers, prescribers, pharmacies, and patients, all of whom agree to accept specific responsibilities designed to minimize pregnancy exposures before they distribute, prescribe, dispense, and use isotretinoin respectively. Patients, and their doctors and pharmacists, are required by the Food and Drug Administration (FDA) to register and use a website in order to receive this medication.

In the European Union, a special launch letter was sent to dermatologists and retail pharmacists regarding the indications, application, and precautions to be followed in the context of birth defects caused by isotretinoin. Leaflets for patients are also provided and, in some cases, they are required to sign declarations confirming that they understand the danger involved. Educational packages include information on pregnancy, risk of birth defects, the need for monthly pregnancy tests, and mandatory use of contraceptives.

8.4 Pregnancy registries

Tatjana is a young woman who has been fighting with a mild, but rather persistent form of epilepsy since her childhood. To keep her free from seizures, doctors prescribed her various antiepileptic medication. Currently, she takes three of them, which is finally an effective and well-tolerated combination. But now, she is also thinking about getting pregnant and is concerned about the effect of her condition and the potential effect of antiepileptic medication on her unborn child.

Let's look at her situation. Is her concern justified? Epileptic seizures, which may occur during pregnancy, can endanger both the mother and the child. They can increase the risk of miscarriage or result in falls with possible physical trauma or lack of oxygen, both of which can affect the child's normal development. Because of the unpredictable nature of the illness, cessation of treatment is not recommended. It seems that for a woman with epilepsy, staying on the medication while pregnant presents a smaller risk to her health than stopping treatment.

Tatjana consulted her neurologist for advice. The doctor explained that, in case of pregnancy, her therapy would be maintained, but her condition and concentration of the medication in the blood would be monitored more often and that she could expect changes in the dosing regimen. Her gynecologist would be responsible for monitoring the child's development. The neurologist also suggested that, when pregnancy occurs, if she wants to, she could be enrolled in an antiepileptic medicine pregnancy registry. Just like other women who need to take medicines while they are pregnant for their preexisting chronic diseases (e.g. asthma, diabetes, hepatitis, HIV infection), Tatjana can enroll voluntarily. Pregnancy registries are prospective observational studies; meaning that they monitor and follow up on women who take specific medicines during pregnancy. They focus on future health information, usually collected via interviews, do not interfere in the treatment or medication prescribed and participation is anonymous. These studies aim to enhance understanding of the risks associated with medicines used during pregnancy. The most important information gathered is, of course, about a newborn child. Results are compared to the population of women who do not take medicines during pregnancy.

As seen above, use of some medicines during pregnancy is associated with an increased risk of human birth defects. This does not mean that every medicine will have that effect, but we do not really know for sure.

Therefore, until more data is collected, precautionary measures are necessary. Relevant conclusions can be made only from a large number of patients treated. This is why these registries are started and organized with international collaboration, especially for women who cannot quit their medication during pregnancy.

For example, two big antiepileptic medicine pregnancy registries are present in over 40 countries around the world and have together enrolled over 30,000 pregnancy cases over the last 15 years. With data collected from such a large population, the safety of different antiepileptic medication used during pregnancy with respect to the risk of birth defects can be more easily compared and any specific patterns of abnormalities or dose-effect relationships can be found.

With this new information, a more rational and evidence-based approach to the medical treatment of women of childbearing age can be provided. Thanks to this, a new revised prescription medicine labeling that is under development will have more helpful information about risks to the mother, fetus, and breastfed infant.

To complete our story, several months later, Tatjana got pregnant and gave her consent to participate in such a pregnancy registry. She was willing to share her experience with medicines during pregnancy and, with her contribution, she helped doctors and other pregnant women find out more about the safety of medicines used during pregnancy.

For more information regarding antiepileptic pregnancy registries go to following websites:

http://www.aedpregnancyregistry.org/

http://www.eurapinternational.org/

If you are looking for a pregnancy registry concerning other medicines visit:

https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries

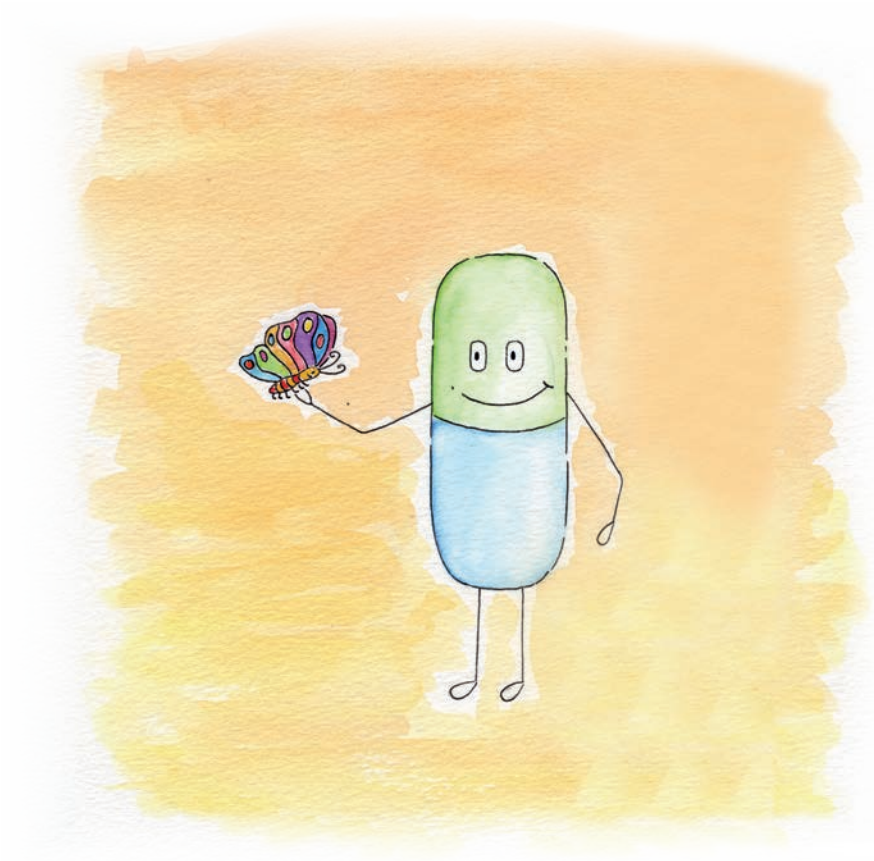
https://www.clinicaltrialsregister.eu/ctr-search/search?query=registry+AND+pregnancy

8.5 Keeping risks at bay

As you can see from the examples described in this chapter, knowing the risks of medication, as well as using successful risk minimization measures to reduce the chance of side effects, is essential to maintaining the positive benefit/risk ratio of medication. This way, we can ensure that everything is done to make medicines as safe as possible for patients. It is also important that patients and doctors understand that risk management plans and risk minimization measures are in place to maintain safety and that ignoring the advice from the doctor or pharmacist and the warnings in the PIL may lead to side effects.

If you want to test your knowledge go to "Time to Take a Quiz!".

9.0 Conclusion

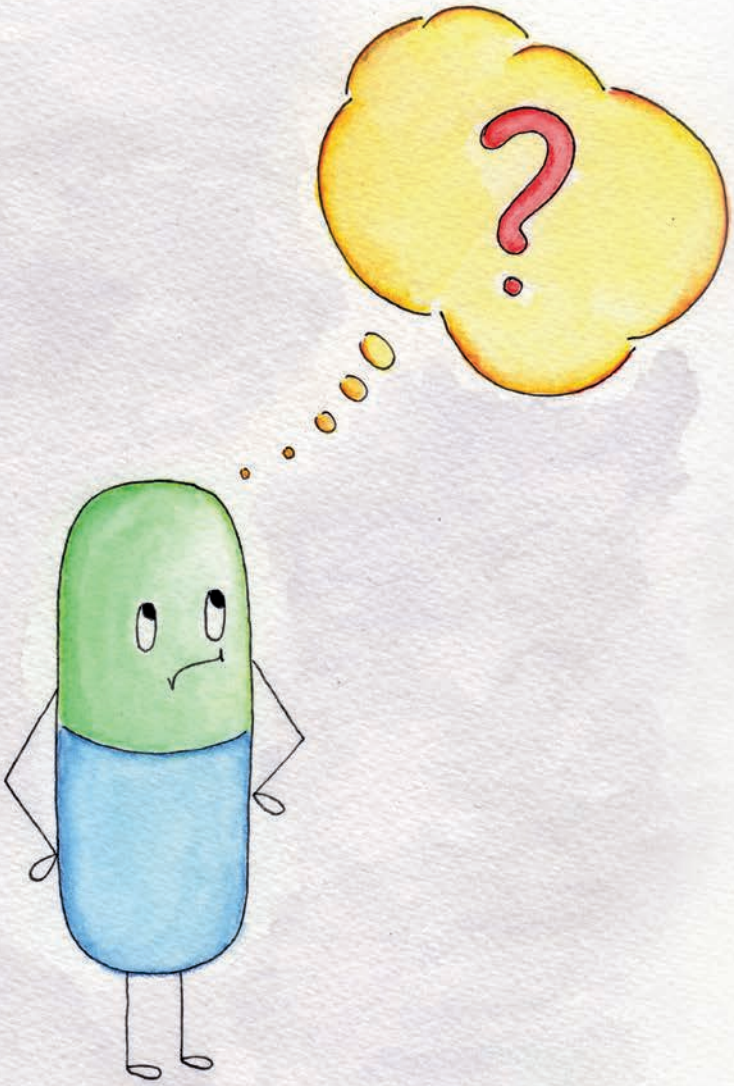


Although it seems as though the journey into patient safety ends here, it actually only begins: we encourage you to practice what you've learnt and use the newly acquired knowledge next time you take a medication. Repetitio est mater studiorum, or repetition is the mother of learning, so let's sum up one more time the most important facts about PV, medicines, and side effects:

- Pharmacovigilance (PV) is the pharmacological science related to the monitoring, detection, collection, assessment, and prevention of side effects caused by medicinal products. It relies on a close interaction between patients, healthcare providers (e.g. physicians, pharmacists, dentists, nurses), pharmaceutical companies, and medicines agencies.

- A side effect is any undesirable experience associated with the use of a medicinal product in a patient.
- If you encounter a side effect you should report it to your healthcare provider, medicines agency, or to the pharmaceutical company.
- When reporting a side effect, always describe what happened in detail, state your age, gender, other medication you are or were taking, your medical history, and other circumstances you might find important as this information will help professionals to assess the side effect and its potential relation to the medicinal product.
- Educate before you medicate! Before you take a medicine, always read the patient information leaflet (PIL). Remember to inform healthcare providers about your medical history and any concomitant medications you are, or were taking. Ask your healthcare provider about the medicine's indication, efficacy, and possible side effects, especially when taking over-the-counter medication (medicinal products that can be bought without a prescription).
- Take the medicine exactly as prescribed by a healthcare provider, or as described in the PIL.
- Remember that your experience matters – it might even save someone's life! Side effects are assessed and described in periodic safety reports prepared by the PV department in pharmaceutical companies and submitted to regulatory medicines agencies. Some side effects have the potential to become a safety signal or to initiate risk minimization procedures. Subsequently, the PIL will be changed to better maintain patient safety.
- Unexpected side effects, or new information on a previously known side effect that is potentially caused by a medicinal product, might raise a safety signal and affect the benefit/risk balance of the medicinal product. If the risk of taking a specific medicinal product considerably outweighs its benefits, it can be withdrawn from the market.
- Pharmaceutical companies take additional steps to monitor and minimize the important identified risks (risks undisputedly proven to be related to the medicine), important potential risks (risks for which the relationship with the medicine is suspected, but not confirmed), and monitor missing information (gaps in knowledge about a medicinal product, which could be important). This process is called risk management.

10.0 Time to take a quiz!



Would you like to test your knowledge about PV? For those who have read the book, this quiz will be "a piece of cake". If, however, you're not sure about one of the answers, go to the end of this chapter where they are provided. Have fun and good luck!

Guardians of patient safety

1. Which of the following about pharmacovigilance (PV) is correct? (only one answer is correct)

a) PV is a pharmacological science related to the monitoring, detection, collection, assessment, and prevention of side effects induced by medicinal products.

b) PV relies on close interaction between patients, healthcare providers (physicians, pharmacists, dentists), the pharmaceutical company, and medicines agencies.

c) Besides authorized medicinal products already on the market, PV also monitors medicinal products used in clinical investigations.

d) All of the above are correct.

2. Are the following statements True or False?

a) A side effect is any undesirable experience associated with the use of a medicinal product in a patient.

❑ True ❑ False

b) Patients can report a side effect by contacting their healthcare provider (physician, pharmacist, dentist), medicines agency, or the pharmaceutical company.

❑ True ❑ False

c) If you are taking part in a clinical study investigating a new medicinal product, you cannot report a side effect.

❑ True ❑ False

d) Published scientific literature is not used as a source of side effects.

❑ True ❑ False

3. To whom can a patient report a side effect?

Generic vs. innovator's medicines: understanding the differences and similarities

Choose the right wording to finish the following sentences.

1. A generic medicine _____ (**is / is not**) identical to an innovator medicine in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.
2. Generic medicines are _____ (**cheaper / more expensive**) than the innovator ones, because generic medicine manufacturers _____ (**are /are not**) required to repeat costly animal and clinical trials.
3. Some differences between generics and innovator medicines are allowed. These differences may change the _____ (**appearance / safety**) of the medicine.
4. Monitoring of side effects for generic and innovator medicines _____ (**is / is not**) the same after approval.

Medication errors: whose fault are they?

1. **Before taking a medicinal product, you should (multiple correct answers):**

   a) Read the patient information leaflet (PIL).

   b) Ask a healthcare provider (physician, pharmacist, dentist, nurse) about possible side effects.

   c) Check your horoscope.

   d) Provide details about your medical history and other medicinal products you are taking to a healthcare provider (physician, pharmacist, dentist, or nurse).

2. **Are the following statements True or False?**

   a) When you are feeling better you can stop taking the medicine; you don't have to take the whole dose prescribed by your healthcare provider.

   ❑ True ❑ False

   b) Over the counter (OTC) medicines can be bought without a prescription and in specific situations can induce side effects. Patients should ask for advice from a healthcare provider if they have questions or doubts about OTC medications.

   ❑ True ❑ False

   c) You should always read the patient information leaflet, even if you have taken the same medicine on a previous occasion.

   ❑ True ❑ False

d) What you eat and drink cannot affect the way your medicines work.

❑ True ❑ False

3. **Who is responsible for patient safety and the prevention of medication errors?**

Discovering new safety information: signal detection

1. **Finish the following sentence.**

   Any unexpected side effect or new information on a previously known side effect that is potentially caused by a medicinal product is called a _____.

2. **Answer the Following Questions with Yes or No.**

   a) Can safety signals be refuted if there is not enough information to confirm that the medicine taken by the patient caused the reported side effect, or there is evidence which suggests that another medication (or any other product the patient is taking at the same time), or the patient's existing disease may have caused the described side effect?

   ❑ Yes ❑ No

   b) Do old medicines that have been in use for several decades also have the potential to induce unexpected side effects?

   ❑ Yes ❑ No

   c) Can a newly found safety signal initiate further investigations and lead to the discovery of a beneficial therapeutic effect previously unknown for the medicinal substance concerned?

   ❑ Yes ❑ No

3. **Which of the following is correct? (multiple correct answers)**

   a) During the lifetime of a medicine, no new and unpredictable effects regarding its use will ever emerge.

   b) If the analysis of a signal shows that the events are, with a high degree of certainty, caused by the medicine, this new information should be included in the PIL to let users know about it; or the signal may indicate that some precautions should be undertaken to minimize the risk of experiencing the event and to enhance the safety of the medication.

   c) Every safety signal has to be thoroughly investigated.

Periodic safety reports or seeing the big picture

1. **Which of the following is correct? (only one answer is correct)**

   a) A Periodic Safety Report gives an overview of the safety data collected worldwide for a marketed medicinal product, indicating whether a product's profile has remained the same or has undergone changes since it was authorized for use.

   b) Medicines agencies review the periodic safety reports and use them to determine if there are new risks identified for a medicine and to decide if further investigations need to be carried out or certain actions taken to protect the public from the identified risks.

   c) The most important aspect of a periodic safety report is to provide an evaluation of the benefit/risk balance of a medicinal product and detect any new patterns in the adverse event profile.

   d) All of the above are correct.

2. Are the following statements True or False?

a) Periodic Safety Reports are more often prepared and submitted for old medicinal products and less frequently for newer medicinal products.

❑ True ❑ False

b) The format of Periodic Safety Reports is the same in all parts of the world.

❑ True ❑ False

c) Special attention in the Periodic Safety Report is given to cases that report lack of efficacy of the medicine, overdose, inappropriate use, and positive or negative experience during pregnancy and breastfeeding in order to collect more information about situations that are difficult to investigate in clinical studies.

❑ True ❑ False

3. What is included in a Periodic Safety Report? (multiple correct answers)

a) Analysis of case reports received in the period of the report.

b) Conclusions on safety signals identified during the period covered in the report.

c) Biography of a Periodic Safety Report writer.

d) Information from published scientific literature.

e) Analysis of benefit/risk balance.

Understanding the risks and keeping our patients safe

1. Are the following statements True or False?

a) The benefit/risk balance for a medicine can change over time when used in the wider population as new information regarding its positive or negative effects becomes available.

❑ True ❑ False

b) A medicine's benefit/risk balance does not need to be continuously monitored.

❑ True ❑ False

c) The purpose of risk management is to monitor and identify the most important risks associated with medicines and to prevent or minimize them wherever possible.

❑ True ❑ False

2. Which of the following are regarded as Risk Minimization Measures (only one answer is correct):

a) Patient information leaflet (PIL).

b) Warnings on the medicinal product's box.

c) Educational material regarding the use and safety of medicinal products.

d) A container with child safety locks provided by a pharmaceutical company.

e) All of the above are correct.

3. Sometimes, pharmaceutical companies conduct additional activities to further investigate a specific risk or to assess whether risk minimization measures are effective or not; can you name one such additional activity?

Are you ready to answer the last question?

You take medicine for a headache and half an hour later you notice a rash on your skin.

a) Whom are you going to contact?

b) Which information will you provide?

c) Why is this important?

Now, when you understand who takes care of patient safety and what pharmacovigilance means, and after you've demonstrated your knowledge by giving the correct answers, let's have fun and see what our youngsters have to say about medicines, side effects, and PV.

Check out the following chapter "What do kids have to say about medicines, side effects, and PV?"

ANSWERS

Guardians of patient safety

1. d); 2. a) True, b) True, c) False, d) False; 3. Healthcare provider (physician, pharmacist, dentist, nurse), medicines agency, pharmaceutical company, lawyer.

Generic vs. innovator's medicines: understanding the differences and similarities

1. is; 2. cheaper / are not; 3. appearance; 4. is

Medication errors: whose fault are they?

1. a), b), d); 2. a) False, b) True, c) True, d) False; 3. All involved parties: healthcare providers are supposed to advise their patients on how to take medication, their efficacy, and potential side effects; patients should always read the patient information leaflet and ask for advice from a healthcare provider when needed; pharmaceutical companies have the obligation to clearly indicate all information related to a medicine on the package or in the patient information leaflet.

Discovering new safety information: signal detection

1. safety signal; 2. a) yes, b) yes, c) yes; 3. b), c)

Periodic safety reports or seeing the big picture

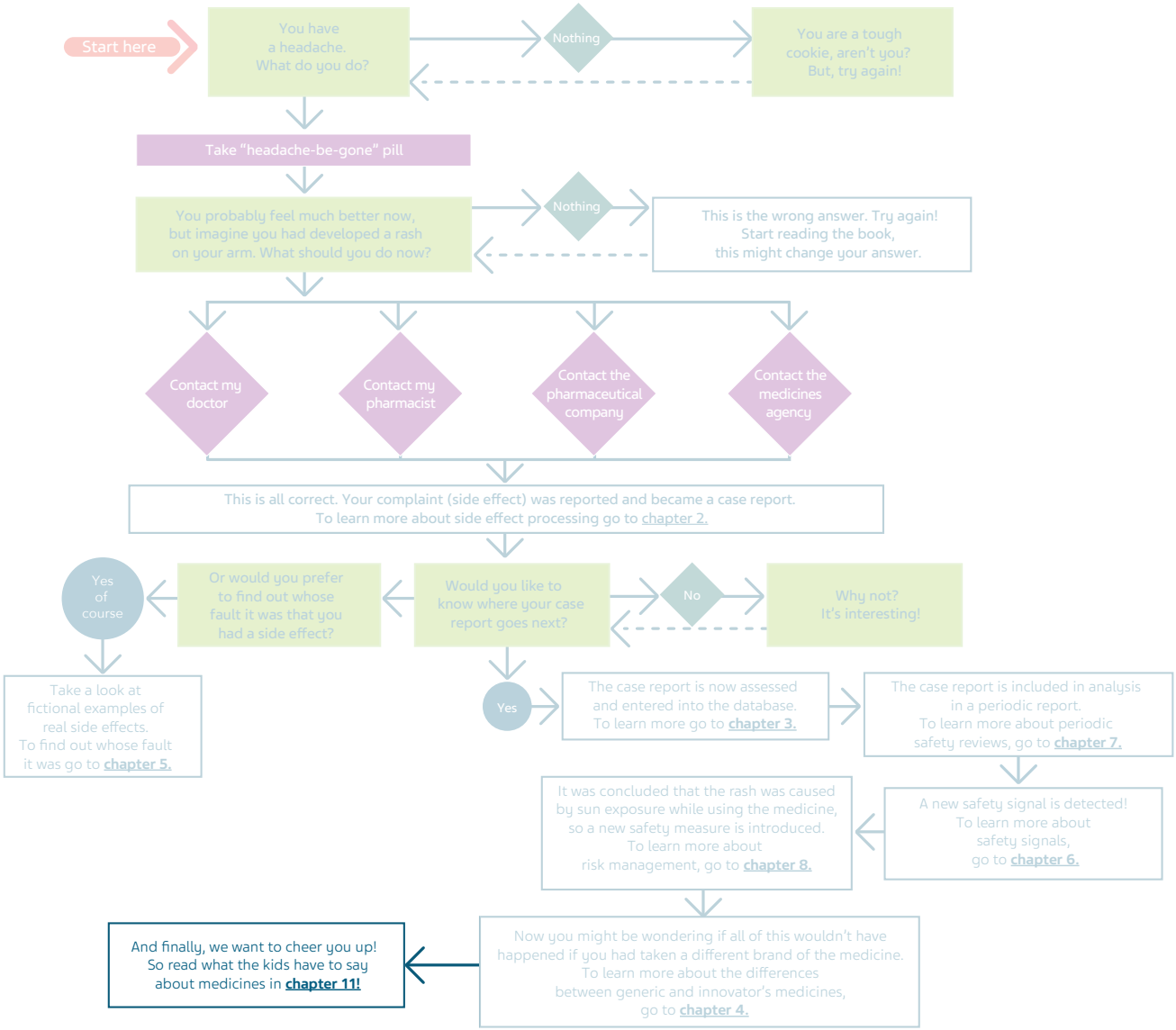
1. d); 2. a) false, b) false, c) true; 3. a), b), d), e)

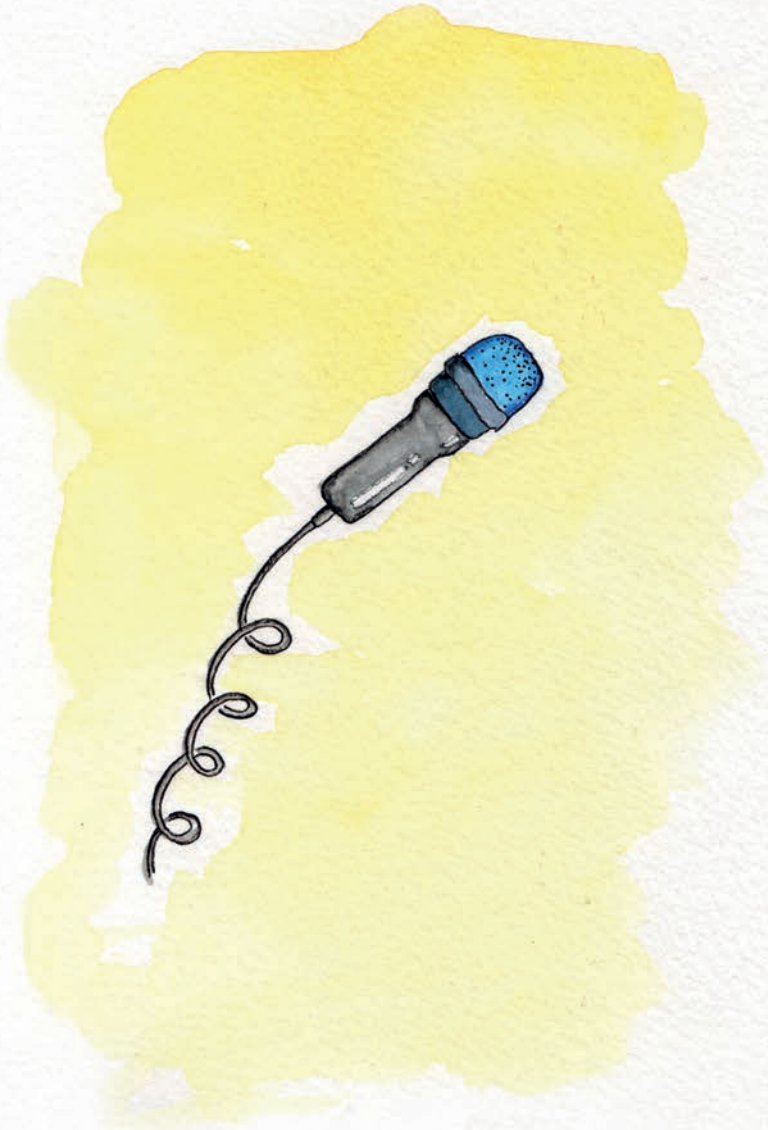
Understanding the risks and keeping our patients safe

1. a) true, b) false, c) true; 2. e); 3. pregnancy registries – they monitor and follow up women who are taking specific medicines during pregnancy

a) healthcare provider (physician, pharmacist, dentist, nurse), medicines agency, or pharmaceutical company; b) information about your age and gender, medical product, side effect, medical history, other medication taken, and other potentially important information; c) your case will be assessed and described in a periodic safety report prepared by the pharmaceutical company and submitted to a medicines agency; it might then become a safety signal or initiate a risk minimization measure.

11.0 What do kids have to say about medicines, side effects, and PV?





Children are a gift, and each one of them is unique, just like snowflakes. The way they experience the world around them is sometimes delightful, and sometimes it simply makes us laugh. Thus, at the very end of our journey we present you something unique and special, something that will brighten your day – the thoughts and contemplations of children from around the world about medicines, side effects, and PV. Take a look at the journey through PV that children's imaginations created after we asked them the following questions:

1. What is a medicine and why do people use them?

Maxence (13), **Raphael** (7) and **Mika** (9): To get better when they are ill.

Yonatan (5): If you're sick then you need to take medicine because it will make you healthy. Also, because if you don't take medicines you'll never get better.

Yael (7.5), **Matej** (7): Medicines are used to help people to feel better.

Mia (4): A medicine is a syrup but there is also a medicine for legs.

Helena (4): A medicine is something you have to take when you are sick.

Jakša (5): I don't know what a medicine is, but people use them to get better when they are sick.

Nola (9): A medicine is a compound that helps you overcome the disease.

Maša (6): A medicine is "the thing" you have to swallow, or mummy puts it into your nose or eyes or butt, to make you feel better when you're sick.

2. Are medicines “good” or “bad”? What do you think?

Maxence (13): Good. Some medicines save lives.

Raphael (7): Bad because sometimes you can get more ill from it.

Mika (9): Good because they help people, bad because they can cause side effects.

Yonatan (5): Medicines are good because you can be healthy if you take them.

Helena (4): They are good. But they do not taste good. I once saw orange and red tablets.

Jana (6): I think they are bad, since you can get really sick if you take too much of the medicine. Or you get some additional disease!

Fran (6): It is very bad that they are tested on poor animals. Other than that, medicines are good; they help you when you are sick.

Ida (6): Oh, you don’t know anything; the medicines are tested on humans. Or maybe on animals that are close to dying. So, if the medicines are good, animals will live, and if they are bad, they will die. And you will know.

Ida (6): I think medicines are generally good. I always feel better after taking the medicine, for instance, if I have high temperature or have a cough, and I take a medicine, I always feel better.

Fran (6): You have to eat something before taking the medicine or else your belly will hurt. General conclusion: MEDICINES ARE GOOD FOR YOU!!!

Jakša (5): They are good because they make you feel better, but some people can get diarrhea or they can get... how is it called what you once told me about? I forgot (I once told him about adverse reactions).

3. What do you think a side effect is?

Maxence (13): An effect that is unexpected and that you don't want or like.

Raphael (7): I don't really know but I think it is something you don't like.

Mika (9): A bad feeling caused after you took a medicine.

Yael (7.5): It's something that you don't know if it will happen but if it does, it'll happen in the future.

Matej (7): A side effect is when you get a rash or vomit because of the medicine.

Helena (4): I don't know... A side effect? I have never heard of it. Can you tell me what this is? Pleeeaseee!!!

Fran (6): I think this is some kind of disease that still has no name.

Ida (6): It sounds like some sort of very soothing song or music.

Nola (9): I know that! That's when you get a stomachache from a medicine indicated for headache.

Maša (6): Well, that doesn't sound good...that's a medicine acting badly.

4. What does your mommy/daddy do? What is their job?

Maxence (13): Hmmm ... I don't exactly know. It has something to do with checking the adverse events of medicines. She needs to take the phone whenever someone is calling.

Raphael (7): She decides what should be written on the paper that is inside the box of the medicine.

Mika (9): To read the reports of adverse event, and help the people :).

Yonatan (5): My mommy helps make sure that medicines are safe and help people.

Yael (7.5): My mommy is making medicines and making sure that everything goes to the right places.

Ella (6): My mother is studying the "diseases of Drug".

Nola (9): My mum collects adverse events and writes about them to warn people and improve medicines and earn money so she can buy me cool stuff.

5. What does signal stand for? What is the first association that comes up?

Maxence (13): It is a warning.

Raphael (7): Ring Ring! Like the school bell.

Mika (9): A sign to do something.

Yonatan (5): Being a detective.

Helena (4): Signal? Oh... I don't know... Is maybe side effect a signal? I don't know!!! Can you tell me a story about a signal?

Ida (6): I think it has something to do with mobile phones, TV and tablets. Am I right?

Jana (6): Hm... a bad signal... I think a bad signal would be when your head starts to hurt and then your brain sends you the signal that you will probably get sick. And that is bad.

Fran (6): Signal is definitely something related to electricity. And then again... Signal is also a type of toothpaste!

Jakša (5): Signal is when you have power for the mobile phone, so you can watch cartoons on it.

Maša (6): There's probably some kind of TV that tells you when something goes wrong with a medicine.

Nola (9): There's no such TV, Maša, don't be ridiculous. I think that doctors sometimes give their patients a bracelet which signals when something goes wrong with the medicine.

6. What is pharmacovigilance if pharma means “medicine” and vigilance means “to see”?

Maxence (13): Protecting people who are taking medicines.

Raphael (7): Hmmm! Difficult words ... Protecting the people taking medicines.

Mika (9): To take care of people’s health.

Yonatan (5): Keeping medicines safe.

Yael (7.5): It means watching out for what medicines do and making sure they don’t hurt people.

Helena (4): Why are you asking me all these questions?

Nola (9) and **Maša** (6): That’s easy! It’s a medicine that sees what’s wrong with you!

7. What do you think, how are medicines made?

Fran (6): First of all, there are scientists behind it all. They constantly have to think and come to an idea of how a medicine should look, and they make them and test if they are good or bad. To make a medicine you have to take some medicinal plants, plants that are good for you, put them in a flask with water and then you have to have a press which squeezes all the good stuff from this plant.

Jana (6): And then this liquid drips into the bottle, and then you have to add some other stuff to it. And then you stir it and send it off to pharmacy where it can be sold.

Ida (6): I think they make medicines in factories and then put them in trucks and drive them to pharmacies.

Fran (6): You can buy medicines only in pharmacies, all but magnesium. Magnesium can be bought in supermarket. My grandmother takes magnesium. She says it is good for your brain. It makes you think better.

8. What do you think RMP stands for?

Nola (9) and **Maša** (6): It has something to do with medicines... R – Robotic M – Multi P – Production ... of medicines.

9. Will you draw us a picture of a medicine or an adverse event?

Maša (6) drew a medicine for children with a nice flavour.

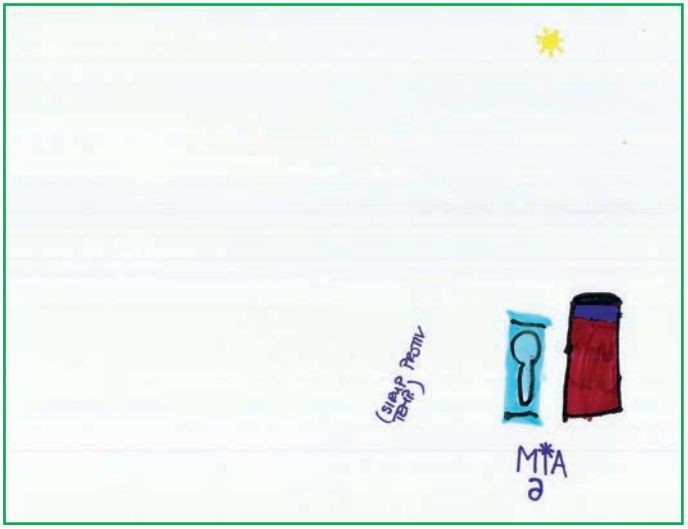
When we asked **Nola** (9) to draw an adverse event, she drew a girl who broke a medicine bottle after she experienced an unusual adverse reaction which is explained in the text box "Senseless drug! I have taken the drug and now one of my legs got bigger and the other one smaller!"

Tara (9) drew a boy who experienced several adverse events after he took a medicine – vertigo, nausea, stomach-ache, rash, and sweating.

Maša (6) drew a medicine advertisement for children.

Filip (5) drew a patient with a spoon and his intention to take syrup.

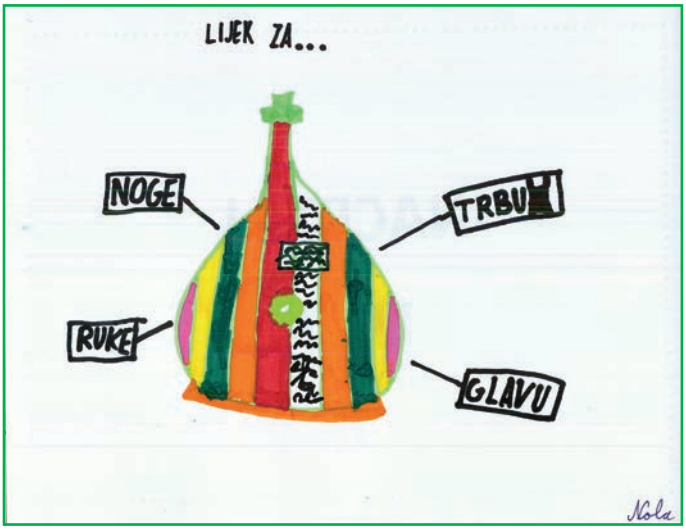
Nola (9) showed us what happens to a tablet in a patient's body.



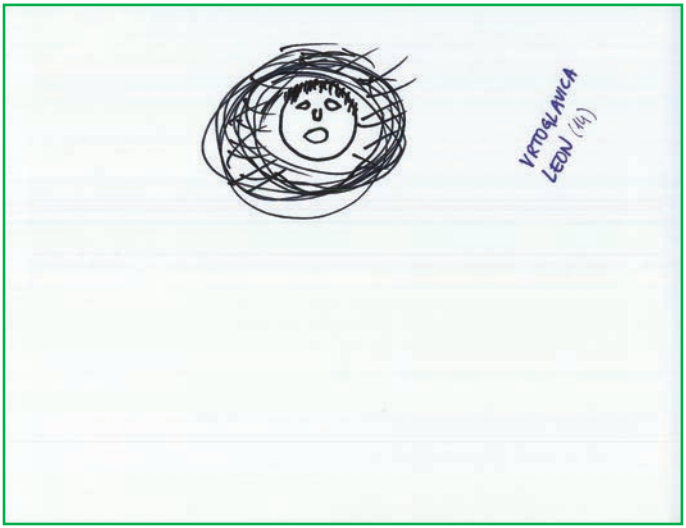
A)

B)

A) **Mia** (6) and B) her sister **Nika** (4) drew a girl who took fever and cold syrup. We are not sure if we are watching beautiful long-haired Rapunzel or the girl who experienced an adverse reaction where her hair grows very fast. ☺



Nola (9) took her "job" very seriously so she presented us panacea - a remedy that cures all diseases! She wrote that this medicine is for legs, arms, belly, and head.



Leon (14) drew a patient who experienced dizziness and vertigo.

In the end **Maša** (6) decided to draw a forest and a path...maybe she was thinking about a journey...a journey into patient safety...

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If you want to know more about the authors, their biographies can be found on the next pages

12.1 Author biographies

Vanesa Ivetić Tkalčević was born on 16 December 1975, in Zagreb, Croatia, and obtained a degree in Veterinary Medicine from the University of Zagreb in 2001, and a PhD degree in Molecular Biology from the Faculty of Science, University of Zagreb in 2010. She joined the pharmacology department at PLIVA Research Institute in 2001 as a Scientist-Pharmacologist, subsequently moving to the GlaxoSmithKline (GSK) Research Centre in 2006 as a Senior Scientist-Pharmacologist, Galapagos Research Centre Ltd. in 2010, and Fidelta Ltd. in 2013, and to Teva Pharmaceutical Industries Ltd. in 2014. Until 2014, she participated in the establishment of dozens of pharmacodynamic and pharmacokinetic in vivo models, transgenesis, microsurgery, and stereotaxic surgery. In 2014, she joined Teva Periodic Reports & Risk Management Center at the Global Patient Safety & Pharmacovigilance department as a Pharmacovigilance Professional. In 2016, she was promoted to a Senior Pharmacovigilance Professional and in 2019 to a Lead Pharmacovigilance Professional. Her work included the preparation, medical review, and quality control of periodic adverse drug experience reports (PADERs) for the US Food and Drug Administration (FDA), safety signal evaluation and medical review, the implementation of changes to Company Core Safety Information (CCSI) documents requested by medicines agencies, mentoring, and testing of newly implemented databases. In November 2021, she became a Team Leader responsible for the process of preparation of PADERs. She has won two scientific awards: Rector's Prize Award in 2000 and PLIVA's Annual Award for scientific contribution and teamwork in 2005, and is a senior research associate at the Veterinary Faculty, University of Zagreb. She is the author and editor of a scientific book "Laboratory Mice and Rats in Biomedical Research – Rationale and Principles of Use", the author of more than 20 scientific papers and congress abstracts, and the co-author of one international patent. She is married, has two kids, and likes books, movies, animals, travelling, mountaineering, and cycling.

Ina Novak was born on 12 August 1987 in Čakovec, Croatia. She obtained the degree Doctor of Medicine (MD) from the University of Zagreb School of Medicine. Her thesis "Incidence and mortality trends of leukemia and lymphoma in Croatia, 1988-2009" was published in the Croatian Medical Journal. After a one-year internship at the 'Merkur' clinical hospital in Zagreb and passing the State license exam, she joined Teva Periodic Reports & Risk Management Center at the Global Patient Safety & Pharmacovigilance department as a Drug Safety Associate. Her present work includes the preparation of periodic adverse drug experience reports, the implementation of changes to company`s reference safety information documents, medical review of the reports, and the review of scientific literature. She has participated in the Annual Pharmacovigilance, Drug Safety, and Risk Management conference in Brussels and is a member of the Croatian Medical Chamber.

Ana Babić Perhoč from Poreč, Croatia, was born on August 22, 1988. She graduated from the Faculty of Pharmacy and Biochemistry of the University in Zagreb in 2012. During her college education, she worked on experimental animal studies investigating the antinociceptive effect of botulinum toxin A, which became the theme of her Master thesis. In addition, she was highly involved in the work of national and the international students' associations of pharmacy students. She volunteered in a community pharmacy and in PLIVA Croatia Ltd. After graduation, she worked as a pharmacist in a community pharmacy in Zagreb and obtained the license for independent work from the Croatian Chamber of Pharmacists. She joined PLIVA Croatia Ltd., a member of the Teva Group, in February 2014 as a Pharmacovigilance professional in Teva's Periodic Reports & Risk Management Center in Zagreb. Her job focused on preparing safety reports for submission to the FDA and signal management. In 2015, she obtained a Postgraduate Certificate in Pharmacovigilance and Pharmacoepidemiology from the European Programme in Pharmacovigilance and Pharmacoepidemiology, with a focus on medicines risk identification and quantification. In 2017, she returned to science and teaching at the University of Zagreb School of Medicine, where in 2021, she obtained a PhD in pharmacology based on her research of experimental Alzheimer disease. As an author and co-author, she published numerous conference abstracts, 11 scientific papers in respected journals and chapters in 2 textbooks of pharmacology. She is a member of the Croatian Pharmacological Society, the Croatian Society of Neuroscience and the Croatian Society of Biochemistry and Molecular Biology. She works as a freelance translator of life science content and as a doping control officer with the Croatian Institute of Public Health.

Mirna Pogačić is a third generation pharmacist in her family. She obtained her Master's degree from the University of Zagreb in 2010. She then completed a one-year internship working in a pharmacy and successfully passed the state professional exam in the Croatian Ministry of Health to become a licensed pharmacist and member of the Croatian Chamber of Pharmacists. She first started working in pharmacovigilance in PrimeVigilance in 2013 as a Pharmacovigilance Associate, before coming to work for PLIVA/ Teva in 2014. Currently, she is a Senior Pharmacovigilance Professional, and her main responsibility is preparing safety reports for submissions to the FDA (such as PBRERs, RMPs, PADERs) and signal evaluations. Mirna is fluent in German (in addition to Croatian and English), and she speaks French. She loves to travel and has spent short periods of time in schools in Canada and Germany. She plays the piano and loves art. She has actively competed in rowing and skiing as a junior, and currently likes running, bicycling and yoga.

Gabriella Letinić Klier was born on 9 October 1968 in Pula, Croatia and obtained a degree in Medicine from the University of Zagreb in 1993. After 5 years of practice in the medical field, she started working in pharmaceutical industry in 1998 (PLIVA Ltd.), first as a Medical Advisor, than as a Medical Representative for four years. In 2004 she started working in pharmacovigilance, first as a Local Safety Officer, and in 2006, she joined the Global Pharmacovigilance department as a Senior Drug Safety Assessor, responsible for writing and reviewing Global Periodic Safety Reports (PSURs), Company Core Safety Information (CCSI), signal detection and evaluation, and medical review of case reports. In 2009, PLIVA became a part of Teva Group and, from 2011, as a pharmacovigilance expert, she has been responsible for reviewing PSURs, CCSIs, addressing questions raised from Regulatory authorities, contributing to the Risk Management Plans (RMPs) and Risk-Benefit Assessments within PSURs. Since 2013, she has also been a Safety Physician for a branded oncology product with the responsibility for continuous assessment of the product's benefit/ risk by analyzing case reports from studies and postmarketing, signals, literature, and protocols for clinical studies. Since 2014, she's been the Team Leader responsible for the process of preparation of Periodic Adverse Drug Experience Reports (PADERs) submitted to the USA Regulatory Agency (FDA) for registered products. As of 2018, she joined IQVIA as an Associate Medical Safety Director, working as a Global Safety Physician. She is a member of the Croatian Medical Chamber and the Croatian Society for Clinical Pharmacology and Therapy. She is married, has two kids, likes classical music, piano playing, hiking and sailing.

Jelena Žanetić was born on 06 May 1989 in Dubrovnik, Croatia. She graduated from the Faculty of Pharmacy and Biochemistry of the University in Zagreb in 2012. In 2011 she won a University of Zagreb Rector's Award for the best student scientific paper in the field of medicinal chemistry. The results of her work on synthesis of novel semicarbazide derivatives of primaquine were published in the "Chemical Biology and Drug Design", 2011. After graduation, she worked as a pharmacist in a community pharmacy in Zagreb. In January 2014, she joined Teva Periodic Reports & Risk Management Center at the Global Patient Safety & Pharmacovigilance department as a Drug Safety Associate. Her present work includes the preparation and quality control of Periodic Adverse Drug Experience Reports (PADERs) for the US Food and Drug Administration (FDA), signal evaluation, and the implementation of changes to Company Core Safety Information (CCSI) documents. In 2015, she enrolled in a Postgraduate Specialist Study of Clinical Pharmacy at the Faculty of Pharmacy and Biochemistry of the University in Zagreb. She loves travelling, theater, and spending summers in her hometown, on the island of Korčula in the Adriatic Sea.

Ana Sakoman was born on 24 November 1988 in Osijek, Croatia. She obtained a degree of Master of Pharmacy in 2013 at the Faculty of pharmacy and biochemistry in Zagreb as a diligent student with a scholarship from the Ministry of Science, Education and Sports of the Republic of Croatia. Being an ambitious pharmacy student, she joined PLIVA Croatia Ltd., a member of the Teva Group, in the Pharmacovigilance department in 2012. It was one of her best decisions as she continued to work in Teva Periodic Reports & Risk Management Center at the Global Patient Safety and Pharmacovigilance department in Zagreb as a Drug Safety Associate after graduation. As a Master of Pharmacy who volunteered in a community pharmacy, she was granted a license for independent work from the Ministry of Health in 2014. She is a member of Croatian Chamber of Pharmacists and Croatian Pharmaceutical Society. In 2015, she became Senior Drug Safety Associate. Her main responsibilities are preparation of periodic reports, signal evaluations, responding to questions raised by the regulatory agencies, and mentoring newcomers. She has participated in several pharmaceutical congresses in Europe and pharmacovigilance training course in London. After more than four years being part of the pharmacovigilance team, in 2016. she turned a new page in her life and joined PLIVA's Marketing and Sales team, becoming a medical representative for neurology and psychiatry. By 2021, she has been promoted to Product Specialist for Neurology and Psychiatry. She is a mother of two who enjoys traveling with her family, music and exploring features of the gastronomy, wines and cuisines of different countries, as she believes this to be one of the best ways to meet people and expand her horizons.

Mateja Raguž born in July 1979 in Koprivnica, Croatia, obtained a degree in Dental Medicine from the University of Zagreb in 2007, and a University Master of Dental Medicine degree, with thesis in Paediatric Dentistry field, from the University of Zagreb in 2011. After working as a general dentist for 4 years, in October 2011 she joined Teva Periodic Reports and Risk Management Centre in Zagreb, where, during the last 10 years her work included preparation of aggregate reports and risk management plans, signal detection, and medical assessment and review. Currently, she is working as a medical reviewer in aggregate reports department. She is passionate about music, photography and fine arts, and enjoys writing poetry and children stories. She is a member of Croatian Chamber of Dental Medicine.

Josipa Migić was born on November 11, 1981, in Derventa, Bosnia and Herzegovina, and obtained a degree in Veterinary Medicine from the University of Zagreb (Croatia) in 2009. While studying veterinary medicine, she was actively involved in international veterinary student's association and participated in the organisation of the activities and event for students. She was also a member of national veterinary organization for veterinarians (Croatian Veterinary Society) and is a member of Croatian Veterinary Chamber. As a student, she wrote two scientific student manuscripts for which she received Rector's and Dean's Prize, and is also a co-author on a book on haematology. After graduation, she worked for one year as a veterinarian in a veterinary clinic for small animals in Zagreb. From 2011 till 2013 she worked as a Regulatory Affairs Associate for veterinary drugs in Genera Inc. In May 2013 she joined Teva Periodic Reports Centre at the Global Patient Safety & Pharmacovigilance department in Zagreb, where she started working as a Drug Safety Associate within the Periodic Reports department and her scope of work included preparation of periodic reports, writing risk management plans, search of scientific literature, signal detection, medical assessment, evaluation of signals, coding the indications for drugs (for regulatory database), and implementation of changes to Company Core Safety Information (CCSI) documents requested by drug agencies. Her current scope of work includes preparation of periodic reports, search of scientific literature, and medical assessment. In her free time, she enjoys movies, reading books, music, hanging out with her friends, badminton, and swimming.

Valentina Galkowski was born on February 21, 1988, in Bjelovar, Croatia, and obtained a degree in Medicine from the University of Zagreb in 2012. In 2013 she enrolled in a PhD program in Neuroscience at Medical College, at the University of Zagreb, with thesis "Influence of hypoxic-ischemic encephalopathy on thalamocortical development in premature infants". Whilst a student, she won a Dean's Award for the best student science paper 2011/2012, "Postnatal changes of brain tissue and endocranial volume ratio". She was a student associate at science projects "Development of human cortical pathways" and "Neuroimaging, neurogenomics and pharmacogenomics of frontal lobe connectivity: normal development and abnormalities in developmental cognitive disorders" with Professor Ivica Kostović as a mentor. As a PhD student, she is an associate at the science project "Subplate zone of the human brain: unsolved problems" with academician Ivica Kostović as a mentor. She was an active participant of international neuroscience congresses: 8th FENS Forum of neuroscience, Barcelona, Spain, active

attendant (first author) with poster presentation, "Postnatal Changes In The Ratio Of Human Brain Volume To Endocranial Volume", 4th Croatian neuroscience congress, active attendant with poster presentation "Volumetric analysis of cerebrospinal fluid and brain parenchyma in patient with hydranencephaly and macrocephaly" and 9th FENS Forum of Neuroscience, Milano, Italy, active attendant (first author) with poster presentation "Volumetric parameters of thalamocortical development in preterm and term born children". After an internship at the Clinical Center, Zagreb and passing her State license exam, she worked in General Practice. In November 2014 she started to work as a Drug Safety Associate and a Safety physician in PLIVA, part of Teva Group. Her present work includes the preparation of Periodic Safety Update Report (PSURs), signal management, review of changes to Company Core Safety Information (CCSI) documents requested by medicines agencies, writing Health Hazard Assessments (HHAs), health authority requests, and medical review.

Andrea Martinović was born in 1979 in Zagreb, Croatia and obtained a degree of Master of Pharmacy in 2004 and postgraduate degree in Clinical Pharmacy in 2015 from the Faculty of Pharmacy and Biochemistry, University of Zagreb. After a one-year internship in a pharmacy she was granted a license for independent work from the Ministry of Health in 2005. That same year, she started working in Medoka Ltd. as a Regulatory Affairs Officer and Pharmacovigilance Deputy. She was responsible for specific vaccines manufactured by Sanofi Pasteur, aloe vera skin care products, and medical devices for diabetes management. When she joined PLIVA's Global Pharmacovigilance department in 2007, as a Drug Safety Associate, she was responsible for case processing and medical assessment, signal detection and evaluation, writing of periodic reports and Company Core Safety Information (CCSI). In 2012, Andrea became a Drug Safety Specialist within the TEVA group (following PLIVA's move to the Teva Group in 2009). She was also involved in the coordination process for CCSIs, to ensure that they are up to date, CCSI review, and responding to questions raised by the regulatory authorities. In 2014, she joined the Risk Management group, and as Risk Management Plan (RMP) Coordinator she started writing RMPs. In 2015, she became a Pharmacovigilance Expert, and started reviewing periodic reports. Since 2017, she's been the Team Leader responsible for the process of preparation of PBRERs and other periodic reports for Teva's registered products which are submitted to Regulatory Agencies. She is a member of the Croatian Chamber of Pharmacists. She is married with one kid, and enjoys travelling, hiking with her friends, reading graphic novels, and going to theatre and concerts.

Mateja Cesarec born on 30 May 1988 in Zabok, Croatia, obtained a degree of Master of Pharmacy in 2012 at Faculty of pharmacy and biochemistry in Zagreb. She started carrier in a community pharmacy in Zagreb, first as an intern and then as a pharmacist after she granted Pharmacy licence from the Ministry of Health. She joined Pliva Croatia in 2015 as a Drug Safety Associate, responsible for preparation of Periodic Benefit-Risk Assessment Reports (PBRERs), in Pharmacovigilance department. Her main responsibilities as Lead Pharmacovigilance Professional are preparation of Risk Management Plans (RMPs), implementation of additional risk minimization measures and evaluation of effectiveness of additional risk minimization measures. She obtained a postgraduate degree in Clinical Pharmacy in 2019 from the Faculty of Pharmacy and Biochemistry, University of Zagreb. She is a member of Croatian Chamber of Pharmacists. In her free time, she enjoys travelling, walking with her dog and hanging out with her friends.

Gordan Sarajlić born on June 25th 1988, in Zagreb, Croatia, obtained a degree in Medicine from the University of Zagreb in 2013. During his student days he won a Dean's Award for the best student science paper 2009/2010 "Effects of bone morphogenic proteins BMP2 and BMP7 on bone metabolism of rats without the thyroid and parathyroid glands". After an internship at the "Sveti Duh" clinical hospital in Zagreb and passing his State license exam, he started working in PLIVA Croatia as a Drug Safety Associate. His work included the preparation of risk management plans (RMPs) and answers to various health authority requests. In 2019. Gordan started medical residency in epidemiology at the Croatian Institute of Public Health where he is employed today. In his free time, Gordan is a passionate amateur actor, participating in a wide range of projects – from TV commercials and film to theater and performing arts in general.

Petra Lazarić Bošnjak was born on 02 April 1985 in Zagreb, Croatia. She obtained a degree in Pharmacy in 2008 and a postgraduate degree in Clinical Pharmacy in 2015 from the Faculty of Pharmacy and Biochemistry, University of Zagreb. Petra worked for six years in a community pharmacy before she joined Teva pharmacovigilance team, first as a drug safety associate with main tasks of preparing PSURs, and currently as a local Qualified Person for Pharmacovigilance in Croatia. Professionally, she has interests in pharmacovigilance regulation, pharmacovigilance in clinical trials, epilepsy and antiepileptic drugs, and biopharmaceuticals. So far, she has published one article in Pharmaceutical herald of Croatian Pharmaceutical Society in Croatian language. Personally, she enjoys playing with her sons, walking with her dog, reading books, and attending music events.

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