Monitoring the manufacturing and quality of medicines: a fundamental task of pharmacovigilance

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Ther Adv Drug Saf

2021, Vol. 12: 1–17

DOI: 10.1177/20420986211038436

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***Abstract*:** The collection and assessment of individual case safety reports (ICSRs) is important to detect unknown adverse drug reactions particularly in the first decade after approval of new chemical entities. However, regulations require that these activities are routinely undertaken for all medicinal products, including older medicines such as generic medicinal products with a well-established safety profile. For the latter, the risk management plans no longer contain important risks, considered important safety concerns, on the basis that routine pharmacovigilance activity would not allow their further characterisation. Society assumes that unexpected adverse reactions causally related to pharmacological activity are very unlikely to be detected for such well-established medicines, but important risks can still occur. For these products, a change in the safety profile which is brand or source specific and usually local in nature, associated with failures with the adequate control of quality of manufacturing or distribution are important safety issues. These may be the consequence of manufacturing and pharmacovigilance quality systems that are not fully integrated over the product life cycle (e.g. inadequate control of quality defects affecting one or multiple batches; inadequate impact assessment of change/variation of manufacturing, quality control testing, storage and distribution processes; inadequate control over the distribution channels including the introduction of counterfeit or falsified products into the supply chain). Drug safety hazards caused by the above-mentioned issues have been identified with different products and formulations, from small molecules to complex molecules such as biological products extracted from animal sources, biosimilars and advanced therapy medicinal products. The various phases of the drug manufacturing and distribution of pharmaceutical products require inputs from pharmacovigilance to assess any effects of quality-related issues and to identify proportionate risk minimisation measures that often have design implications for a medicine which requires a close link between proactive vigilance and good manufacturing practice. To illustrate our argument for closer organisational integration, some examples of drug safety hazards originating from quality, manufacturing and distribution issues are discussed.

Plain language summary

Monitoring the manufacturing and quality of medicines: the fundamental task of pharmacovigilance

Pharmacovigilance is the science relating to the collection, detection, assessment, monitoring, and prevention of adverse reactions with pharmaceutical products. The

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collection and assessment of adverse reactions are particularly important in the first decade after marketing authorisation of a drug as the information gathered in this period could help, for example, to identify complications from its use which were unknown before its commercialization. However, when it comes to medicines that have been on the market for a long time there is general acceptance that their safety profile is already well-established and unknown adverse reactions unlikely to occur. Nevertheless, even older medicines, such as generic drugs, can generate new risks. For these drugs a change in the safety profile could be the result of inadequate control of their quality, manufacturing and distribution systems. To overcome such an obstacle, it is necessary to fully integrate manufacturing and pharmacovigilance quality systems in the medicine life-cycle. This could help detect safety hazards and prevent the development of new complications which may arise due to the poor quality of a drug. Pharmacovigilance activities should indeed be included in all phases of the drugs' manufacturing and distribution process, regardless of their chemical complexity to detect quality-related matters in good time and reduce the risk of safety concerns to a minimum.

Keywords: adverse drug reaction, counterfeit, falsified, GDP, GMP, GVP, lack of efficacy, manufacturing, pharmacovigilance, product quality complaints, product recall, quality defect, safety, side effects

Received: 13 May 2021; revised manuscript accepted: 23 July 2021.

Introduction

The SARS-CoV-2 pandemic has highlighted the need to develop and maintain robust, efficient and resilient processes in response to unpredictable and catastrophic scenarios.

On a positive note, the accelerated development of new vaccines has shown it is possible through more efficient system functioning to accelerate the development and launch of new medicines when the world needs them. At all times, processes to ensure uninterrupted availability of safe and effective medicinal products to the public are the primary responsibility of marketing authorisation holders.

In the European Union (EU), confirmation that the active substance has been manufactured in accordance with good manufacturing practice (GMP) for medicinal products is the responsibility of qualified person (QP) as defined by the Community Code 2001/83/EC Art. 49.[1] In addition, a responsible person exists who oversees good distribution practice (GDP). The responsibility for supervising the pharmacovigilance system and product safety profile lies with the QP responsible for pharmacovigilance (QPPV) as defined by Art. 104 of the same Community Code. Although the QP and QPPV supervise different processes, requiring different knowledge/skill-sets, and have distinct responsibilities, their interaction is increasingly common and is aimed to facilitate the identification of risks pertaining to a product or to specific batches. Therefore, both the QP and QPPV have joint responsibilities to ensure quality and optimal benefit/risk profile of medicines over their life cycles.

As defined by the World Health Organisation (WHO), pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine-related problem. Despite this far-reaching definition, it is common practice for pharmaceutical companies to allocate most of their resources for pharmacovigilance departments mainly to the collection and assessment of individual case safety reports (ICSRs), for example, scientific literature, websites, EudraVigilance, FDA adverse event reporting system (FAERS) and so on, with the primary aim of identifying and reporting undesirable side effects in compliance with the applicable regulatory requirements and timelines. A large proportion of these ICSRs represent well-known side effects of medicines. While this is important to detect unknown adverse drug reactions (ADRs) for several years after first approval of new chemical entities, regulations require that these activities are routinely undertaken for all products

including older medicines such as generic medicinal products with well-established safety profiles. For the latter, in many instances, the risk management plans (RMPs) have removed risks that were considered important safety concerns based on the reasonable expectation that by that time the risks are already well characterised and managed by standard clinical practice.[2]

The emergence of novel side effects related to pharmacological activity that have not yet been detected is unlikely for such well-known drugs with a well-established safety profile,[3] although the relatively recent discovery of increased risk of some skin cancers with use of hydrochlorothiazide first demonstrated in an epidemiology study from Denmark[4] illustrates that continued investigations of safety even for older drugs have value. However, for these products, a change in the well-established safety profile is more likely to brand or source specific and local in nature, often associated with inadequate quality of the raw materials used to manufacture the drugs or with failures in the control of product quality throughout their manufacturing and distribution. Changes in the safety profile of a drug at a product brand and batch level can also be due to a change of its manufacturing process, especially for biologicals.[5] These changes may be the consequence of chemistry, manufacturing and control, supply chain, toxicology and pharmacovigilance quality systems not fully integrated over the product life cycle (e.g. suspected transmission of an infectious agent, contamination, inadequate control of quality defects affecting one or multiple batches; inadequate impact assessment of change/variation of manufacturing, quality control testing, storage and distribution processes; inadequate control over the distribution channels including the introduction of counterfeit or falsified products into the supply chain).

Interaction between GMP/GDP and GVP

The interaction between QP activities, primarily defined by GMP[6]/GDP[7] standards, and QPPV, primarily defined by good pharmacovigilance practices (GVP),[8] is a consolidated standard in contemporary pharmaceutical quality systems influenced by other ICH quality guidelines such as ICH Q9 (quality risk management)[9] and ICH Q10 Pharmaceutical Quality System.[10]

Various phases of the manufacturing and distribution of pharmaceutical products require input by pharmacovigilance to assess whether deviations from established processes have effects on the safety of products and whether any activities are required to mitigate the resulting risks. This is even more so for advanced therapies which may require specialised manufacturing and distribution processes. It is not unusual for biological or biotechnological products to undergo variations in their production both during the pre-approval and post-approval periods. Demonstration of comparability of the pre- and post-change product is a sequential process, beginning with quality studies (limited or comprehensive) and supported, as necessary, by non-clinical, clinical or pharmacovigilance studies.[11]

The GVP mention about the need for the notification of significant manufacturing changes to the pharmacovigilance in order to allow the detection of any emerging risks as early as possible following the implementation of variations to the production of a medicine.[5]

Pharmacovigilance can identify changes in safety profiles which require consultation with manufacturing to determine whether production issues affecting the quality of the product were responsible (e.g. when there is a suspicion that certain clusters of adverse events – especially if occurring with the same batch – can be the consequence of the poor quality of the material used to produce the drug, contaminated source material). In other cases, identified deviations in the manufacturing process itself which have been detected after the product release may require an assessment of any potential health hazard.

Departures from standard processes, procedures and quality defects detected during the manufacturing, distribution and use of medicinal products require assessment by pharmacovigilance for potential impact on product safety and efficacy; these can include, but not be limited to

product quality complaints;
out-of-trend stability studies;
cross-contaminations;
regulatory actions against manufacturers following inspections;
temperature excursions outside the labelling storage conditions during distribution;

counterfeit/falsified products detected in the supply channel.

A medicinal product consists of active pharmaceutical ingredients (APIs) and excipients with the whole product including the package leaflet and the carton all of which must be manufactured to acceptable standards. Spontaneous product complaints can occur about any component.

Assessments of such complaints require an investigation into the reported issue, and as appropriate, evaluation of the need for activities to minimise risks through, for example, warning communications or batch recall.[12]

Although, periodic reconciliation processes between adverse events, medical information enquiries and product quality complaints are performed as required by the current regulations,[8] there is mounting evidence to suggest that the current reactive approach, which primarily relies on the detection and assessment of unwanted events, is no longer adequate. A more proactive, preventive approach is required based on a system methodology with attention paid to human performance.

The inadequacy of the current best industry practices is a result of reliance solely on regulatory systems based on an old model, which are no longer flexible enough to adapt to the current global complex sociotechnical system for medical products. Because the system is no longer fit for purpose, we are struggling to ensure medicines remain as safe as possible and of the highest quality as society demands faster conditional regulatory approvals of new products or generics, faster drug commercialization and development, with increasing global demand for more of the existing products and availability of new products in the shortest period.

Therefore, we need to examine more carefully the best approach to the integration of product quality and classical pharmacovigilance to develop more agile and effective Quality Systems throughout the product life cycle to meet global societal expectations. As example, Quality System including procedures engaging the pharmacovigilance in the assessment of changes to production processes throughout the product life cycle, from the upstream to the downstream phases, may contribute to potentially predict possible impacts that such changes could have on the safety and efficacy of a medicine.

Drug safety hazards identified from product quality defects

For many years, pharmaceutical companies have collected lack of efficacy cases which necessitates a unified strategy between GMP and PV quality systems for each manufacturer. Despite these efforts in the last few years, hundreds of products have been recalled from the US[13] and European[14] markets that were reported by EU authorities and US Food and Drug Administration (FDA) to be associated with late detection of failures occurring during the manufacturing and distribution of products with a potential impact on product safety and efficacy (please refer to Supplementary material 1 and Supplementary material 2 available in the online version of this article).

In the last years, the MHRA issued several alerts and recalls for drugs and medical devices because of product quality defects.[15]

While these were mostly precautionary in nature and the defects did not result in patient harm, they all required input from pharmacovigilance and medical assessment to determine the level of mitigation activities (from warning letters to full product recall) required to ensure patient safety. Due to the intrinsic risk of parenteral formulations, it is not surprising that a relatively large proportion of the recalls regarded these products because of potential lack of sterility or due to the presence of particulate matter in the solution for injection.

The following paragraphs summarise examples of product quality deficiencies reported in the last few years that required a significant effort to identify the root causes and consequent reconsideration of the quality standards to avoid future similar occurrences.

Product contamination from raw materials

Recently, there has been a significant issue concerning manufacturing quality and presence of carcinogenic impurities in several pharmaceutical products. For example, the carcinogenic contaminant N-nitroso dimethylamine (NDMA) was discovered in medicinal products containing valsartan in June 2018. The API was sourced from

Table 1. Examples of WHO Alerts of falsified products.

WHO Ref.	Product	Falsification issue	Region
Product Alert No. 2/2021[38]	COVID-19 'BNT162b2' vaccine	Falsified glass vials and label (batch number and expiry dates)	Mexico
Product Alert No. 7/2020[39]	HARVONI (ledipasvir/sofosbuvir)	Misrepresentation of its identity, composition and source	WHO regions of the Americas and Europe
Product Alert No. 5/2020[40]	Defitelio (defibrotide)	Falsified batches not containing the expected active ingredient, contaminated with mould (*Cladosporium sp.* and *Aspergillus niger*)	Argentina, Australia, Latvia, Malaysia and Saudi Arabia
Product Alert No. 4/2020[41]	Chloroquine/Hydroxychloroquine	Misrepresentation of its identity, composition and source	WHO regions of Africa
Product Alert No. 3/2020[42]	COVID-19 diagnostics	Falsified *in vitro* diagnostics and laboratory reagents	Not reported
Product Alert No. 11 /2019[43]	Amoxicillin and Clavulanic Acid	Falsified batches and labelling and packaging inconsistencies	Haiti
Product Alert No. 8 /2019[44]	Rabies Vaccines (Verorab, Speeda and Rabipur) and Anti-Rabies Serum (Equirab)	Falsified label (batch number and expiry dates)	Philippines
Product Alert No. 7/2019[45]	Meglumine antimoniate ampoules (Gulucatime/Glucantime)	Falsified label and products produced not according to the GMP requirements	Iran and Pakistan
Product Alert No. 6 /2019[46]	Hydrochlorothiazide	Found to contain glibenclamide instead of hydrochlorothiazide	Cameroon

GMP, good manufacturing practice; WHO: World Health Organisation.

Table 2. Example of MedDRA preferred terms[a] that may be indicative of potential substandard medicines.

Product issue (SOC) **MedDRA Preferred Term**	
Product packaging issue	Product process control issue
Product label issue	Product quality issue
Product shape issue	Product reconstitution quality issue
Liquid product physical issue	Product size issue
Manufacturing production issue	Suspected product quality issue
Out of specification product testing issue	Product commingling
Physical product label issue	Product adhesion issue
Product barcode issue	Product container seal issue
Product sterility lacking	Product reconstitution issue
Product colour issue	Product closure issue
Product coating issue	Suspected counterfeit product

(Continued)

Table 2. (Continued)

Product compounding quality issue	Product blister packaging issue
Product identification number issue	Product contamination chemical
Product gel formation	Product contamination microbial
Product solubility abnormal	Product contamination physical
Product quality control issue	Suspected product contamination
Product origin unknown	Product contamination with body fluid
Product blister packaging issue	Product contamination
Product outer packaging issue	Suspected product contamination
Product container issue	Product label on wrong product
Product lot number issue	Product substitution issue
Product taste abnormal	Product distribution issue
Product odour abnormal	Product dosage form issue
Product counterfeit	Device defective
Product label counterfeit	Device colour issue
Product packaging counterfeit	Device chemical property issue
Suspected counterfeit product	Device kink
Out of specification test results	Device material issue
Physical product label issue	Device material opacification
Inappropriate release of product for distribution	Device mechanical issue
Product deposit	Device physical property issue
Product lot number issue	Needle issue
Product measured potency issue	Device malfunction
Product physical consistency issue	Device ineffective
Product physical issue	Device issue
Product primary packaging issue	Needle issue
SMQ Lack of efficacy/effect (SMQ) MedDRA Preferred Term	
Absence of immediate treatment response	Therapeutic product effect delayed
Atypical dose–response relationship	Therapeutic product effect variable
Drug effect less than expected	Therapeutic product ineffective
Drug half-life reduced	Therapeutic reaction time decreased
Drug ineffective	Therapeutic response decreased

(Continued)

Table 2. (Continued)

Drug level abnormal	Therapeutic response delayed
Drug level decreased	Therapeutic response changed
Loss of therapeutic response	Therapeutic response shortened
Missing dose–response relationship	Therapy non-responder
Paradoxical drug reaction	Therapy partial responder
Tachyphylaxis	Treatment failure
Therapeutic product effect decreased	Vaccination failure
Therapeutic product effect incomplete	Virologic failure
Pregnancy, puerperium and perinatal conditions (SOC) MedDRA Preferred Term	
Unintended pregnancy	
Unwanted pregnancy	
Pregnancy on oral contraceptive	
Pregnancy with contraceptive patch	
General disorders and administration site conditions (SOC) MedDRA Preferred Term	
Therapeutic response increased	
Therapeutic response prolonged	
Injury, poisoning and procedural complications (SOC) MedDRA Preferred Term	
Counterfeit product administered	
Out of specification product use	
Poor quality product administered	
Recalled product administered	

MedDRA, Medical Dictionary for Regulatory Activity; SMQ, Standardised MedDRA Query; SOC, MedDRA System Organ Class.
[a]MedDRA version 23.1.

the Chinese manufacturer Zhejiang Huahai. A preliminary investigation identified changes of the materials used in production as root cause of contamination which impacted multiple marketing authorisation holders globally.[16]

Thereafter however, reports of new NDMA contamination in valsartan and other sartans were received from other manufacturing sources. NDMA and N-nitrosodiethylamine (NDEA) were found in several preparations, including metformin, pioglitazone and ranitidine. Shortly after the discovery of the incident, the European Medicines Agency (EMA) launched a review of drugs containing sartans.[17] An assessment of potential patient harms because of the presence of NDMAs as an impurity of sartan production was made and the risk determined to be low although not negligible.[18]

The late detection of nitrosamine contaminations required, and still requires, significant effort by

manufacturing & control and pharmacovigilance functions of pharmaceutical companies to assess and mitigate risk for patients. The outcome of the nitrosamines contamination assessment on sartan products determined that in the vast majority of cases, undetectable or very low concentrations of nitroso impurities were present.

A review of regulatory activities and lessons learned associated with these manufacturing issues was published by EMA in June 2020.[18]

The EMA recommended that all companies manufacturing medicinal products containing sartans review their manufacturing processes and introduce appropriate testing procedures to detect the lowest concentrations of these contaminants. The EMA set limits for the amount of permissible nitrosamine impurities allowable.[19,20] Following the contamination of the sartan containing products, the US FDA and the WHO requested the manufacturers and marketing authorisation holders to review all chemical and biological medicines for human use for the possible presence of nitrosamines and test products at risk.

This incident highlights how the lack of oversight of the suppliers of raw materials and manufacturers, combined with a lack of adequate understanding of the potential for the generation and introduction of hazardous chemicals in the manufacturing process, can jeopardise the quality, safety and possibly efficacy of medicinal products.

Drug safety hazards involving manufacturing issues identified by pharmacovigilance

Small molecules: generic medicinal products

In 2011, the US FDA received multiple reports of a generic lansoprazole as an oral disintegrating tablet (ODT) causing clogging of oral syringes and feeding tubes. The prescribing information of the reference product included the potential for administration through nasogastric tubes. However, when compared with the reference product, the generic lansoprazole ODT tablets were found not to fully disintegrate in water, forming clumps adhering to the inside walls of oral syringes and feeding tubes. Some patients required surgical replacement of obstructed permanent feeding tubes. In some cases, patients needed emergency medical assistance when their clogged feeding tubes had to be unclogged, removed or replaced. After an FDA Drug Safety Alert was posted on the FDA website, the manufacturer withdrew their generic drug from the market.[21] This example shows the importance of consideration of all aspects of use of a medicine when approving new formulations of old products.

In 2009, the US FDA Office of Generic Drugs (OGD) identified clusters of lack of efficacy reports associated with a new marketed generic medicated patch of clonidine (Transdermal System USP 0.1 mg/day, 0.2 mg/day or 0.3 mg/day). Compared with the reference listed drug, RLD, the generic patch was larger (32.4 cm^2 *versus* 10.5 cm^2 of the RLD) and presented a diminished or lack of adhesion. The FDA identified significant manufacturing issues with this clonidine transdermal system which also included residual active ingredient in the discarded patch that would cause environmental contamination and unacceptable risks as diminished adhesion meant reduced efficacy. A warning letter was issued, and the manufacturer of the generic product stopped the production of the clonidine patch in 2011.[21] This is an example of the importance of pharmacovigilance surveillance specifically of individual brands of generic products.

Risks of changes in efficacy and safety with certain generic versions of products with narrow therapeutic windows were highlighted by the suspension of marketing authorisation of Teva thyroxine by UK regulators in 2012.[22] The MHRA had received clusters of reports from patients with hypothyroidism, stable on replacement thyroxine therapy, reporting side effects indicative of inadequate thyroxine replacement when switching from their usual thyroxine medication to Teva thyroxine. Some of these reports were supported by biochemical markers confirming low thyroid hormone activity. Investigations by MHRA identified differences in dissolution between Teva and other thyroxine tablets as well as failures of manufacturing quality as the probable causes, leading to suspension of the marketing authorisation and recall of the product. This safety issue illustrates that even for a very old product, effective pharmacovigilance is required to detect issues arising when switching between different products.

In 2015, a high number of allergic reactions associated with solutions for injections containing

gentamicin were reported in Europe, including a fatal case in Italy.[23] All these ADRs occurred following use of batches of API sourced from the same active ingredient manufacturer. However, following further analysis, it was ascertained that not all batches of gentamicin were affected. The investigation results highlighted the presence of elevated levels of histamine in certain batches of the API. The cause of such out of specification was attributed to the fish peptone raw material utilised in the fermentation process that from the half of 2014 until mid-2017 had been sourced from a different supplier than previously used. As a consequence of an inadequate storage at the manufacturing site of this supplier, the fish decomposition prior to production of fish peptone allowed the bacteria in the decomposed fish to produce additional histamine from the free histidine present in the material. It is known that an amount of 7 µg of histamine administered intravenously may produce measurable effects in humans. The level of histamine in the drug substance gentamicin should not be mandatorily controlled according to the European pharmacopoeia. Following the identification of the public health risk which may arise from histamine contamination, the European pharmacopoeia was amended to include checks relating to the quality of the raw materials and more specifically test to measure the levels of free histidine in fish peptones. The implementation date for the revised monograph was 1 April 2018. Moreover, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended for some actions including the need for API manufacturer/supplier to specify in the dossier the source of peptone used (e.g. animal or vegetable origin), to ensure that declaration about the control of the histamine impurity within an agreed limit is mentioned in the label, and to amend the European Union reference dates (EURD) list to change the periodic safety update report (PSUR) submission frequency for gentamicin from 5 years to 3 years. This example shows the importance of the surveillance of the quality of raw materials to prevent the occurrence of ADRs.

Originator medicinal products (complex molecular substances)

A well-known example of the role of pharmacovigilance surveillance identifying manufacturing issues is the heparin scandal of 2008. The FDA had identified an increase in reports of heparin-associated adverse events of an allergic nature, some of which were fatal, starting in late 2007 into early 2008 during a national investigation of allergic-type events with heparin products. Similar clusters of these events were also reported in some EU countries. Investigation of these clusters of events identified a Baxter Healthcare-brand heparin product as having the strongest association with the events.

The FDA investigation identified, among other serious GMP deficiencies, contamination of heparin with oversulfated chondroitin sulphate (OSCS), a semi-synthetic heparin-like material possibly intentionally added in heparins sourced from Chinese manufacturers; OSCS contamination was identified as the most likely cause of the change in the safety profile of heparin.[24]

Heparin is a biological product obtained from mammalian organs; mainly swine and bovine, consisting of a heterogenic mixture of sulphonated polysaccharides, varying in length and composition (mean average molecular mass ranging from 5000 to 30,000 Da).

During the purification process, heparin is separated from its impurities, chondroitin and chondroitin sulphate, containing a lower content of sulphur, which are primarily used as nutraceutical products.

If submitted to chemical modification (sulphation), chondroitin moieties become sulphur-rich, over sulphated, thus of a similar chemical composition, but not biological activity, of heparin.

Forensic analysis of suspected batches of heparin, responsible of the toxicities mentioned above, quantified a contamination of 30% w/w OSCS.[25]

This incident brought to light multiple failures, including a lack of oversight from manufacturers and regulatory agencies of foreign suppliers of APIs, as well as a lack of suitable analytical procedures for batch acceptance aimed at characterising purity, safety and efficacy of well-established biological products.

As a consequence, new manufacturing quality tests and processes have been introduced to

ensure more consistent composition and quality of heparin products as well as enhanced inspections of facilities for heparin manufacture.[26]

New formulations and biosimilars

Subcutaneous administration of Eprex® (epoetin alfa) in patients with chronic kidney disease (CKD) was banned in the EU between 2002 and 2006 after increasing reports of anti-erythropoietin (EPO) antibody-mediated pure red cell aplasia (PRCA). An investigation revealed that the transient increase of anti- EPO antibody-mediated PRCA was associated with a change in the formulation/composition of the product. More precisely, the excipient of the formulation, human serum albumin, was replaced with polysorbate-80 (PS-80) in order to minimise the risk of patient exposure to virus and adventitious agents (i.e. prions) given by human serum albumin.[27]

The introduction of PS-80 into the product, which is formulated in pre-filled syringe, enhanced the extraction of curing and vulcanizing agents from the uncoated bromobutyl rubber stopper of the syringe into the product solution.

It is assumed that compounds with adjuvant activity leached by PS-80 from plastics and rubber materials in uncoated stoppers induced an anti-EPO immune response which was associated with loss or lack of effect (LOE) and increased antigenicity.[28]

This example was associated with an absence of regulatory guidance pertaining to the so-called extractable and leachable substances study from plastic material in pharmaceuticals at the time of its occurrence, and highlighted the importance of an effective and integrated GMP/GDP-GVP Quality System with regard to safety assessment, before and immediately after a change of the product composition including excipient and primary packaging components. The absence of regulatory guidance should act as a red flag for heightened pharmacovigilance.

Furthermore, it demonstrates the importance of active pharmacovigilance of biosimilars after marketing approval and particularly after significant manufacturing changes. Biosimilars are biologic medicinal products which are highly similar to already licenced reference innovators with no clinically meaningful differences between the two products in safety, purity and potency. It is however recognised that biologics exhibit a high molecular complexity and as such may be sensitive to changes in manufacturing processes (including significant micro-heterogeneity and batch-to-batch variability). Small differences in the starting material or even slight changes in specific phases of the production or purification process can significantly affect the quality and purity of the product such as to determine a variable efficacy and safety profile compared with the reference innovative product. In addition, following initial approval, biosimilars are mostly similar to the innovators. However, over time, unless there is both rigorous regulatory supervision and inspections, biosimilar and innovator medicines may potentially become less similar following minor manufacturing changes made both by innovator and biosimilar manufacturers. As a result of such changes, the concern arises that there is the potential for the safety and efficacy profiles of biosimilars to diverge from those of the innovator product. Therefore, long-term pharmacovigilance surveillance, tightly integrated with the manufacturing quality system based on brand is required to monitor and assure safety over time. Assessing each product has its own difficulty as determining the actual brand prescribed can be challenging. Europe has a GVP chapter on product-specific considerations for biological medicinal products,[5] which includes a requirement for traceability of individual products and advice that generic substitution, usual for small molecule products, should be avoided. However, full implementation of these requirements throughout Europe remains to be achieved.[29] Indeed, there is worrying evidence that health care systems are not adequately designed or prepared to track biological products as required in the regulations.[30] This justifies much closer integration of pharmacovigilance and distribution practices for these products and the need of fostering as much more as possible links and formal communication mechanisms between GMP (QP) and GVP (QPPV).

Interface between pharmacovigilance and manufacturing of advanced therapy products

The interaction between pharmacovigilance and manufacturing assumes a particular importance for advanced therapy medicinal products (ATMPs) due to the novelty of this type of product and the intrinsic product variability, which

may influence the safety and efficacy of such medicines. ATMPs can be classified into three categories: (a) gene therapy medicines, to treat genetic disease, cancer or long-term disease; (b) tissue-engineered medicinal products, containing cells or tissues that have been modified in order to repair, regenerate or replace human tissue; and (c) ATMPs containing one or more medicinal devices as part of the medicinal product, the so-called combined ATMPs such as cells embedded in a biodegradable matrix or scaffold.[31] EMA produced specific guidance concerning the oversight of safety and efficacy of these products in 2008.[32] This guidance is currently under revision in the light of additional experience accumulated in the last years.[33] Specific areas which may represent risks for patients as consequence of quality characteristics, storage and distribution of these products are highlighted in the guidance. Based on the origin of cells or tissues used to produce cell/tissue-engineered medicines may represent risks such as the transmission of diseases. Other characteristics which can make the difference and that shall be taken into account when engineering these medicines are the source of cells or tissues (autologous *versus* eterologous), the cell type, and the ability of cells to proliferate and differentiate (e.g. embryonic stem cells, iPSC). Risks of transmissible diseases may vary depending on the source of the cells or of the tissue. Infections from different pathogens (viral, bacterial, etc.) may regard to either the recipient of the products or health care professionals involved in managing the patients. The use of proliferating cells instead represents a recognised risk of tumorigenicity. This risk depends on the characteristics of the product and how it is manufactured (e.g. a processed based on extensive use of mesenchymal stem cells may increase the risk of tumorigenicity; risk of 'off target' or of unwanted and undesired 'on target' mutations may occur as complications from the use of gene editing techniques). For chimeric antigen receptor – T Cell Therapy (CAR-T) products the viability of the cells and levels of cytokines, for example, interferon gamma, can affect potency and safety. Finally, there are also risks related to the handling of the product before its use. For example, incorrect storage, transportation and distribution of the product, such as a break of the cold chain, may produce risks related to stability of the product. These could have an impact on the biological activity of the ATMP potentially leading to treatment failure. In the distribution of autologous products, it is important to maintain the chain of identity and custody. These practical issues concerning distribution and supply, which can be the most important safety concerns for a company and patients, are currently not included in the RMP despite being 'medicine related problems'.

Drug safety hazards resulting from quality issues and distribution management issues

The final stage of distribution of medicines to end users is also an area requiring careful control and surveillance. However, this presents significant challenges to the industry and regulators because of the large number of organisations involved in these processes across global environments. One of the most striking examples of unsafe distribution and prescribing practices has caused an epidemic of abuse with extended-release and long-acting opioids such as oxycodone in the United States. The authors of a recent analysis concluded that there is insufficient evidence that the FDA's efforts to mitigate risk from opioids has been successful. These authors concluded that the FDA had tools that could have mitigated opioid risks more effectively if the agency had been more assertive in using its power to control opioid prescribing, manufacturing and distribution.[34] This illustrates the need for more joined-up thinking and action.

The importance of the oversight of all aspects of local manufacturing and local distribution of medicinal products is exemplified by the withdrawal of the oral contraceptive Microvlar in Brazil in 1998.[35]

At that time, a number of contraception failures associated with this product were reported in Brazil. The manufacturer, Schering, had set up a new production line of the product in that country. As part of the set-up activities, the company manufactured dummy packages of the product with placebo tablets. The company outsourced the destruction of these dummy packages to another company, but they were stolen before being destroyed and were found to have been illegally distributed on the Brazilian market. This resulted in the reported LOE of the product and unwanted pregnancies.[36]

The problem of counterfeiting and the widespread falsification of medicinal products has become a major problem in the pharmaceutical

field. A falsified medicinal product is any medicinal product with a false representation of its identity, including its packaging, labelling, name or composition about any of the ingredients including excipients and the strength of those ingredients; its source, including its manufacturer, country of manufacturing, country of origin or marketing authorisation holder; or its history, including the records and documents relating to the distribution channels used.[37]

The problem of counterfeited/falsified medicines was highlighted by the WHO that reported this issue has worsened due to the ease with which it is possible to find such products through unregulated websites, social media platforms and smartphone applications. This phenomenon can cause harm to patients, including treatment failure.[37] Some examples of falsified products for which the WHO issued alerts are provided in Table 1.

As it can be seen from the above examples, the presence of counterfeit, falsified medicinal products is particularly common in those countries where access to medicines to treat and prevent widespread diseases is made difficult due to a combination of complex distribution issues and relatively underdeveloped regulatory systems. The WHO estimates that up to two billion people around the world may be exposed to this problem which continues to grow as global supply chains become more complex, meaning that products manufactured in one country can be packaged in a second country and distributed across borders to be marketed or sold to consumers in a third country.[47]

Pharmacovigilance personnel must therefore be alerted when, for example, they are faced with spikes in reports of lack of efficacy generally or in specific geographies which may be due to falsified products or that could raise the suspicion of contaminated products and therefore potentially be harmful.[12]

A proactive and efficient interaction between GMP/GDP and GVP is essential at promptly detecting signals of falsified or counterfeit products as these products are more likely to produce not only reports of lack of efficacy or unknown adverse events but also reports of quality complaints (e.g. product discolour, cosmetic differences, different taste, label text readability, particulate matter).

Identifying manufacturing, distribution or counterfeiting issues from pharmacovigilance data

Spontaneous reporting systems can help to identify substandard/spurious/falsely labelled/falsified/counterfeit medical products that are the cause of ADRs or lack of efficacy. The Uppsala Monitoring Centre (UMC) performed a study which tested an algorithm applied to VigiBase, the WHO's global ICSR database, to identify reporting patterns suggestive of substandard medicines in spontaneous ADR reporting. The algorithm identified some historical clusters of ADRs that were subsequently confirmed to be related to substandard medicines.[48]

A warning signal must be activated when there are clusters of reports of lack of efficacy, poor quality or in presence of reports which raise the suspicion of contaminates or potentially harmful adulterations.

As pointed out by the UMC, the Medical Dictionary for Regulatory Activities (MedDRA) contains a list of preferred terms (PTs) that could be indicative of ineffective drugs and product quality issues which may be potentially due to the use of substandard medicines.

Following the example provided by the UMC, the authors have selected from the MedDRA version 23.1 a list of MedDRA PTs that could help identifying manufacturing issues or malfeasants, which may also relate to combination products (please refer to Table 2), with potential consequences on the safety and efficacy. For example, the MedDRA PTs 'Liquid product physical issue' [which includes the lowest level term (LLT) 'Particle present in liquid'] or, 'Product reconstitution quality issue' could be the cause of infusion-related complications, such as thromboembolic adverse events. Generally, to prevent such complications, that are the consequence of the presence of particles in solutions for infusion (e.g. precipitate of active ingredient in reconstituted vials), in-line filters are used. However, should the filtration reduce the potency of the solution (because the active ingredient is retained by the filter), lack of efficacy could occur.

Other examples are manufacturing issues identified by the MedDRA PTs 'Product sterility

lacking', 'Product contamination microbial', 'Product contamination chemical' and 'Product contamination physical' that could be the cause of infections and other adverse reactions.

The MedDRA PTs 'Out of specification product testing issue', 'Out of specification test results', 'Product compounding quality issue', 'Out of specification product use' and 'Poor quality product administered' could be cause of hypersensitivity, immune system disorders, organ toxicities (e.g. nephrotoxicity, hepatotoxicity) and multi-organ failure.

The administration of products presenting quality issues may cause reversible or irreversible injuries to patients, and even death.

EudraVigilance as a useful source of data for the identification of potential safety signals due to product quality issues

Since the introduction of mandatory reporting of ICSRs to EudraVigilance in the European Economic Area, on 20 November 2005, the EMA has used the data held in EudraVigilance to detect safety signals and, incidentally, to determine if these signals were due to quality defects or medication errors.[49] Since the release of MedDRA version 19.0 in March 2016, a 27th MedDRA System Organ Class (SOC) 'Product issues' has been introduced. The LLTs of this SOC can be used to code ICSRs, in addition to ADR terms, and to send them to EudraVigilance.

In August 2010, the MA of an intravenous immunoglobulin was suspended, when an increase in the number of embolic and thrombotic events was detected. This was detected purely at the level of the reported PTs and was confirmed by a signal detection at the level of the broad SMQ 'Embolic and thrombotic events' by the authorities, using their version of EudraVigilance Data Analysis System (EVDAS), which allows more complex analyses than the currently available marketing authorization holder (MAH) version. In turn, this led to an in-depth analysis of the cases, the involvement of the MAH, concluding that a quality defect was involved.

With the increased number of reports submitted to EudraVigilance since 22 November 2017 (which now include consumer reports and non-serious EEA ICSRs) and the availability of EVDAS to MAHs, it is likely that product quality issues associated with ADRs will be more effectively detected.

Discussion

Quality issues associated with manufacturing or distribution are relatively common. More are identified quickly and have little significance for patient safety. The majority are rapidly reported to regulators and mitigation activities are undertaken generally through alert letters or recall of affected product. The nature of mitigation activities does however require input from personnel qualified to assess clinical risk.

More rarely (but still in significant numbers) product quality failures can have important clinical consequences for patient safety. Interestingly, most of these instances are identified once marketed as a result of safety surveillance demonstrating a change of safety profile undertaken by pharmacovigilance departments. This shows the importance of signal detection activities and the need for pharmacovigilance to closely cooperate with product quality. The mutual collaboration between the QPPV and QP is necessary to allow appropriate signal detection and evaluation of the benefit/risk profile of medicines over time.

Unforeseen side effects related to pharmacological activity are very unlikely to be detected for well-established medicinal products. For these products, a change in the well-established safety profile is most likely related to a specific brand or source of such medicines associated with failures of adequate control of quality of manufacturing or distribution, and this is when the interaction and collaboration between QPPV and QP comes of greatest importance.

This cooperation has become more important in recent years following the approval of an increasing number of generic and biosimilar products for which changes in the manufacturing process have shown to potentially affect their safety. Similarly, as the manufacturing of advanced therapy products and of biotherapeutics is associated with risks that do not pertain to the majority of small chemical molecules, there is the need for an increased collaboration between manufacturing

and pharmacovigilance. This is of particular importance as an increasing number of these products are being used. In addition, high demand for easily accessible and cheap drugs together with the possibility of buying medicinal products through the Internet have resulted in increased criminal activity to deliver falsified and counterfeit or poor-quality products, which often have implications for patient safety. In an ever changing world, the close collaboration between product quality and pharmacovigilance becomes ever more important.

However, this collaboration often relies on processes and practices which are reactive and not well suited for unforeseen and unanticipated contingencies, where proactivity and efficiency of the processes, including communication, are required. As example, exchange of information concerning any available exposure data by batch numbers and batch sizes may be necessary to link ADR reports to a source-specific risk. Early involvement of pharmacovigilance in discussions about planned changes to production processes, from the upstream to the downstream phases, may contribute to improve the evaluation of the possible impacts that such changes could have on the safety and efficacy of medicines.

We noted that GMP was an early strategic initiative of International Coalition of Medicines Regulatory Authorities (ICRMA). It would be advisable a discussion and publication of recommendations about how best PV regulations and quality regulations should always be assessed and updated together and not in isolation. This could also be a suitable forum to debate how ICRMA could take forward a much-needed international association for QPPVs, GMP QPs and GDP RPs. Global regulatory and industry leadership is needed to create better integrated GMP/GDP-GVP quality systems to create more proactive processes with preventive actions thereby enhancing the monitoring of the benefit/risk profile of medicines. Moreover, an effective collaboration could use scarce resources in a more efficient manner and should benefit from new technologies (automation, artificial intelligence) to augment predictive capabilities.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: The Editor-in-Chief of Therapeutic Advances in Drug Safety is an author of this paper; therefore, the peer-review process was managed by alternative members of the Board and the submitting Editor had no involvement in the decision-making process.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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