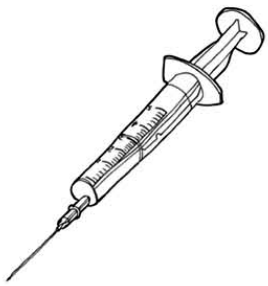
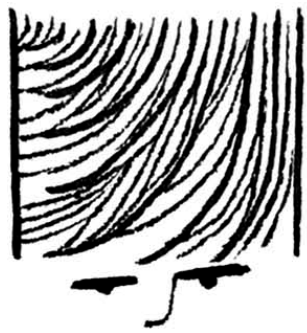
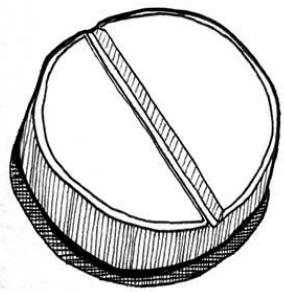
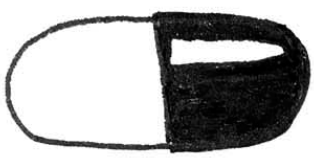
Translation of academic medicinal products towards clinical practice

Wilde, S.P. de

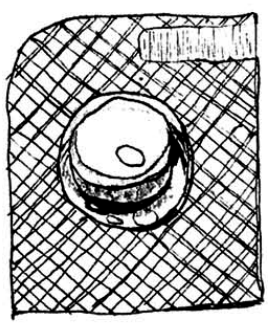








PART II - UNLICENSED PHARMACEUTICAL PREPARATIONS



CHAPTER 7

Unlicensed pharmaceutical preparations for clinical patient care: ensuring safety

Sofieke de Wilde, Maria G.H. de Jong, Paul P.H. Le Brun, Henk-Jan Guchelaar, Kirsten J.M. Schimmel

Pharmacoepidemiology and drug safety. 2017 October 19

Abstract

Most medicinal products dispensed to patients have marketing authorization (MA) to ensure high quality of the product, safety, and efficacy. However, in daily practice, to treat patients adequately, there is a medical need for drugs that do not hold MA. To meet this medical need, medicinal products are used in clinical care without MA (unlicensed), such as products prepared by (local) pharmacies: the pharmaceutical preparations. Three types of pharmaceutical preparations are distinguished: (i) reconstitution in excess of summary of product characteristics; (ii) adaptation of a licensed medicinal product (outside its official labelling); (iii) medicinal products from an active pharmaceutical ingredient. Although unlicensed, patients may expect the same quality for these unlicensed pharmaceutical preparations as for the licensed medicinal products. To assure this quality, a proper risk-benefit assessment and proper documentation in (centralized) patient registries and linking to a national pharmacovigilance database should be in place. Based on a risk assessment matrix, requirements for quality assurance can be determined, which has impact on the level of documentation of a pharmaceutical preparation.

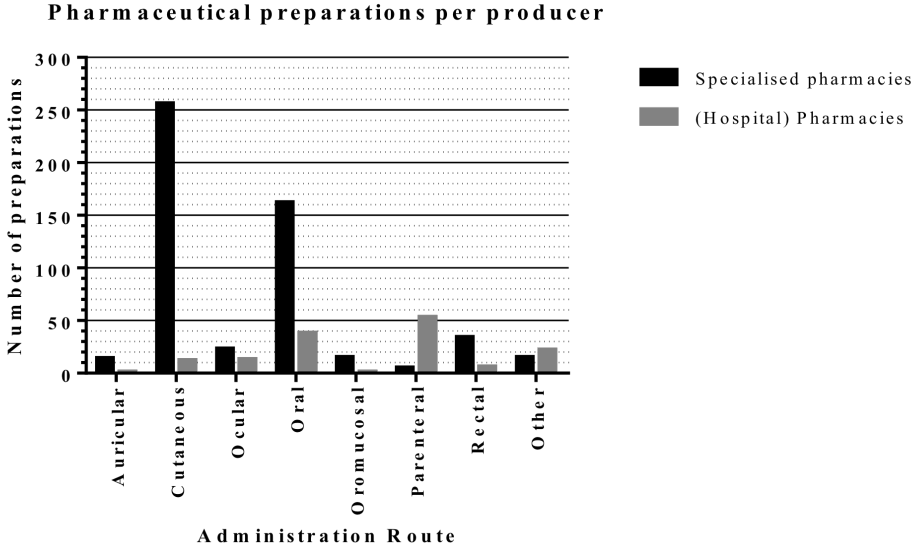
In this paper, the approach for good documentation including quality assurance and benefit-risk assessment will be discussed and possibilities for patient registries are described to make these crucial preparations available for regular patient care.

1 Introduction

In the ideal world, all medicinal products dispensed to patients have marketing authorization (MA) to ensure high quality of the product, safety, and efficacy. However, in daily practice, it turns out that there is a medical need for medicinal products which are not licensed. To meet this medical need, medicinal products are used in clinical care without gained MA (unlicensed), such as off-label use of licensed medicinal products[1], licensed medicinal products which are imported from other countries[2,3], and products prepared by (local) pharmacies: the pharmaceutical preparations[4,5]. This last category is commonly used in regular clinical care; for example in The Netherlands, approximately 300 unlicensed active pharmaceutical ingredients (API) preparations are listed in the Dutch drug database. An illustration of the various administration routes of the pharmaceutical preparations adopted in this Dutch Drug Database per producer type is shown in box 1.

Box 1. Overview of the unlicensed pharmaceutical preparation adopted in the Dutch Drug Database

In the Netherlands, approximately 700 unlicensed pharmaceutical preparations, from which 300 are APIs, are adopted in the Dutch Drug Database, enabling pharmacovigilance. Most unlicensed pharmaceutical products in the Dutch Drug Database are prepared by specialized pharmacies with large production facilities. Mostly, these facilities produce low-risk preparations for cutaneous and oral administration for large indication areas in primary care. In contrary, the (hospital) pharmacies have fewer preparations adopted in this drug database; most frequently, high-risk preparations, eg, intravenous administration, are produced compared with the company preparations. The category "other" includes low numbers of products per administration route, such as inhalation and vaginal administration.



7

Although pharmaceutical preparations have not been officially approved, patients may expect the same quality as the licensed medicinal products. However, there has not been a formal benefit-risk assessment for these unlicensed products[3]. In this paper, we discuss the different types of pharmaceutical preparations and describe the possibilities to ensure safe use of these products by adequate quality and an appropriate benefit-risk assessment focused on Europe and The Netherlands (see box 2 for a short description of the situation in the United States). Subsequently, the approach for good documentation will be discussed and the possible use of patient registries is described with the aim to make these essential pharmaceutical preparations available for clinical patient care.

2 Unlicensed pharmaceutical preparations

Unlicensed pharmaceutical preparations, are defined in the European Pharmacopeia and Directive 2001/83/EC, and can be prepared at two different scales: Magistral formulas and larger batches for stock.[6–8]

Box 2. Pharmaceutical compounding drugs in the USA

In the USA a magistral formula is defined as pharmaceutical compounding drug, which is described in the US Pharmacopoeia as a preparation produced based on a prescription of a physician or based on the 'practitioner-patient-pharmacist-compounder relationship[6]. To ensure safety and quality of these compounding drugs the so-called 'Pharmaceutical Quality, Security and Accountability Act' was initiated by the Senate and House committees of the USA[6]. Up to now, the assurance of drug quality, safety, and efficacy has to be performed in accordance with the federal quality standards, which is not verified by the Food and Drug Administration (FDA)[31]. However, the FDA wants pharmacies to register themselves, to ensure safe use of these compounding drugs by being able to perform FDA inspections according to good manufacturing[32].

Magistral formulas, also known as extemporaneous preparations, are formulas prepared in a pharmacy on prescription by a physician[9]. The prescribed medicinal product is for individual use, and no commercial product is available or sufficiently effective. Before preparation, a risk assessment on the pharmacotherapeutic field is executed by the producer and documented to perform a decision based on efficacy and safety of the preparation for treatment of the patient. Finally, pharmaceutical quality assurance of the preparation is performed, as described in the Resolution CM/RES(2016)[8].

2.1 Pharmaceutical quality assurance

The different types of pharmaceutical preparations are accompanied by different aims of quality levels depending on the associated risk. Whereas uniformity of these aims was lacking for the member states of the EU, recently, the Resolution CM/ResAP(2011)1[10] was adapted into the CM/Res(2016)1 to assure pharmaceutical quality and estimate the risk of unlicensed pharmaceutical preparations using a risk assessment matrix[8,10]. In case of high-risk pharmaceutical preparations, quality has to be guaranteed by meeting with good manufacturing practices (GMP)[8]. The pharmaceutical quality of low-risk medicinal products can be assured by using the Pharmaceutical Inspection Co-operation Scheme Good Preparation Practices (PIC/S GPP) guide[8,11]. A drawback of the resolution is that the focus is on the product quality only and patient need is not considered.

2.2 Pharmacovigilance

While health practitioners are obliged to report adverse events of both licensed and unlicensed medicinal products, there is no systematic check on safety, efficacy, and pharmacovigilance for the unlicensed products. According to a review from the European Medicines Agency (EMA), it turned out that adverse events of unlicensed (and off-label used) medicinal products were under registered[1,12]. Furthermore, in cases of registered adverse events, unlicensed medicinal products were more frequently associated with adverse events than licensed medicinal products[1,12]. To ensure safety for these patients the adverse events of unlicensed medicinal products should be documented. This is in line with Regulation (EU) No 1027/2012, which states that the producer of the unlicensed medicinal products is responsible for documentation of the prescribing physician, patients and adverse events[13,14].

2.3 Documentation

Ensuring full documentation, by completing all topics of the product dossier, is not always possible because it may cause a delay in delivery of the medicinal product with unmet medical need.[8] For such individual cases, both the prescriber and the preparing pharmacist have an important role in ensuring quality and safety of the product and informing the patient. There should be a good balance between the benefit of the magistral formulas and the risk of receiving a product with lower quality assurance than a product with MA. Finally, pharmaceutical quality and safety of pharmaceutical preparations practice should be verified via inspections executed by the national healthcare inspectorate or other competent authorities[8].

Whereas magistral formulas are based on physician's prescriptions and intended for individual patients, for-stock pharmaceutical preparations can be prepared for a small (in-house) patient cohort[6]. These for-stock unlicensed medicinal products are prepared by pharmacists or other institutions with a "license for manufacturing"[8]. In these cases, licensing of the individual products

is not required[9,15].

The requirements for magistral and stock preparations are the same; however, for for-stock preparations more controls (eg, analytic end control) are needed compared with the magistral formulas. For such preparations, documentation is required in a format of a product dossier as described in Resolution CM/Res(2016)1[8], which is more extensive than for magistral formulas[15]. For example, information about the release quality control (QC), validation, and stability should be included[15]. Also, for these products, national competent authorities will execute more extensive inspections of the quality and safety of the pharmaceutical process[8].

2.4 Pharmaceutical preparation types

Although there is 1 definition of these pharmaceutical preparations in the EU, there is no uniformity in the interpretation of these preparations among all the countries because it is mostly regulated by national authorities[6,8]. Here, we provide an overview of the different types of pharmaceutical preparations including their requirements and practical elaboration of these requirements for quality assurance and benefit-risk assessments, see figure 1, consisting of reconstitution in excess of SmPC preparation instructions, adaptation of a licensed medicinal product, and medicinal products from an API[15,16].

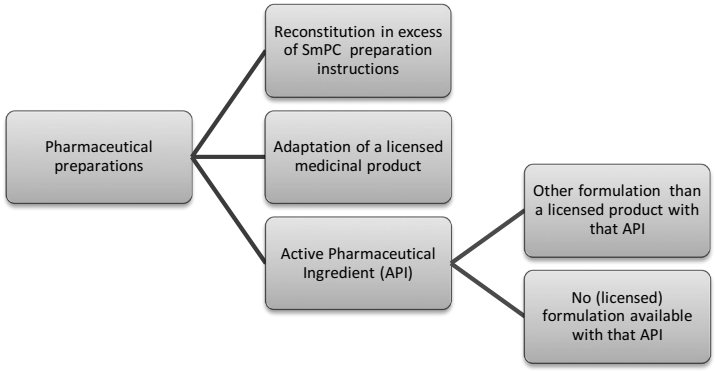


Figure 1. Schematic overview of pharmaceutical preparations. Pharmaceutical preparations can be divided into three different types: reconstitution in excess of SmPC preparation instructions, adaptation of a licensed medicinal product, and medicinal product from an active pharmaceutical ingredient. API = active pharmaceutical ingredient, SmPC = Summary of Product Characteristics.

2.5 Reconstitution in excess of SmPC preparation instructions

Reconstitution can be defined as “manipulation to enable the use or administration of a medicinal product for products with a marketing authorisation issued by any competent medicines regulatory authority, the reconstitution is carried out in accordance with the instructions given in the SmPC or the package leaflet”, according to the European Directorate of Quality of Medicines (EDQM)[8]. Meaning, a preparation of a licensed medicinal product according to the SmPC via good nursing

practice[15–17]. In practice, reconstitution can be done in a more efficient way by preparing products on a larger scale in central units; eg, ready-to-administer syringes can be used as service products by various departments in the hospital. These pharmaceutical preparations are graded as high risk[8]. Like the magistral formulas, these preparations are based on the SmPC of a product and reconstitution by the pharmacy reduces risks of miscalculations and contamination[18,19]. Reconstitution can be executed conform good nursing practice in clinical areas, where upscaling above a certain volume leads to increasing risks because a deficient product may affect the health of a considerable number of patients. This requires enhanced quality assurance via release controls and an increased level of documentation in the product dossier. Due to production of batches, the preservability of the products must be extended. Microbiological validation will require several actions such as process validation and environmental monitoring[20]. Because these manipulations are executed with licensed medicinal products, pharmacovigilance would be possible. It is possible to submit pharmaceutical preparations to a (national) database for pharmacovigilance, and in case this preparation is based on a licensed product, the pharmacovigilance information is already available and can be used in the database. However, it comes under the responsibility of the producer instead of the MA holder.

2.6 Adaptation of licensed medicinal products

Sometimes, administration of licensed formulations may not be possible. In that case, adaptations of medicinal products take place outside the official labelling, eg, phenprocoumon oral suspension 1 mg/ml prepared from 3-mg licensed tablets[21]. An example is amending the dissolution stated in the SmPC or changing the concentration when needed to adequately treat a patient. To ensure patient safety, a concise product dossier, including a substantiated rationale, should be prepared. Furthermore, it is necessary to evaluate efficacy and safety of such manipulations and add this information to the product dossier[15]. When there is a frequent need for this manipulation of an existing product, it can be modified from magistral to for stock preparation. This will lead to more extensive QC and documentation. Based on documentation in the product dossier of magistral formulas, data are available to endorse safety and efficacy of such preparations. Pharmacovigilance can be performed based on the information from the SmPC of the licensed formulation, which is again the responsibility of the producer.

2.7 Active pharmaceutical ingredient

For some patients, preparing from APIs can be necessary[21]. Examples of these products are polymyxin-neomycin tablets and isoniazid injections[22]. As described in section 2.6, for these unlicensed APIs, a concise product dossier to ensure safety is necessary. Results from studies investigating efficacy and safety can improve such dossier[15]. Moreover, risk assessment will decide

whether GPP is enough or if preparation conform to GMP is necessary. Upon upscaling of these individual active ingredients, expansion of the dossier and QC is necessary[8].

3 Pharmaceutical preparations toward marketing authorization approval

There are some examples of (orphan) APIs which used to be prepared by a (hospital) pharmacy, after which a pharmaceutical company converted these preparations into licensed medicinal products.

Interestingly, the prices of these medicinal products sometimes increased excessively, e.g. amifampridine for Lambert-Eaton-myasthenic syndrome (LEMS) and zinc acetate for Wilson's disease[23]. For such pharmaceutical preparations, it may be interesting to assess the possibility to start an MA process in a not-for-profit organisation, based on data from experience in regular care and through a well-established use procedure. However, currently for the MA process, a well-designed clinical trial is preferred showing safety and efficacy. This may give rise to ethical dilemmas because once the medicinal product is already in use in patient care it is difficult to setup a placebo-controlled trial. Furthermore, acquiring MA of pharmaceutical preparations may not be considered in scope of academic institutions[24]. Box 3 describes an example of how the available data of the pharmaceutical preparation for LEMS differed from data used for obtaining MA of the licensed formulation.

4 Ensuring safety

Currently, there are national formularies that provide guidance for quality and rationality for usage of pharmaceutical preparations by standardization of a series of pharmaceutical preparations[25], eg, the German Formulary (NRF) and the formulary of Dutch pharmacists (FNA)[15]. In the Dutch situation, the acronym "FNA" can be used when a preparation conforms to FNA requirements. But when the preparations are distributed toward (other) pharmacies, the official FNA license has to be retrieved provided by the overarching "LNA (Laboratory of Dutch Pharmacists)." Subsequently, these FNA licenses are adopted in the Netherlands Pharmacovigilance Centre Lareb database, monitoring adverse events and safety issues. This example from the Netherlands shows that there are possibilities of performing pharmacovigilance with unlicensed pharmaceutical preparations.

Currently, international organisations are also initiated to collect and analyze adverse drug events, such as the worldwide Uppsala Monitoring Centre set up by the World Health Organization (WHO)[26]. By combining these, the quality assurance, and pharmacovigilance database, safe use of products is well monitored.

Unfortunately, for active pharmaceutical preparations indicated for (ultra) orphan indications such

FNA license is often not available, due to small patient numbers and centralized treatment. Thus, quality and a proper benefit-risk assessments should be ensured by good documentation of the preparing pharmacy. Furthermore, pharmacotherapy control and pharmacovigilance are not yet standard available for APIs. Pharmaceutical preparations with a long history of use and for (ultra) orphan indications, such as 3,4-DAP (see box 3), should leverage on the available documentation in patient files covering information of the treatment, including preparation batches, adverse events, and efficacy data. By collecting more data from clinical experience, eg, in patient registries, an appropriate benefit-risk assessment can be made, which also generates more possibilities in pharmacovigilance for these products.

Nowadays, patient registries are available in all different formats and can be organised by different organizations and/or different parties such as healthcare practitioners (including researchers) or patients, resulting in nonuniform data collections[27]. By creating a (central) patient registry for specific orphan medicinal conditions, the effectiveness of treatments can be collected and safety data can be assessed after a specific time of use[28]. Patient-powered patient registries are mostly controlled by patients and/or their family and cannot be filled in by all patients correctly, for example, due to limited education and understanding of medical terms[29]. Nevertheless, such design led to good uniformity of self-reporting compared to an electronic medical data[30]. On the contrary, when a patient registry is controlled by healthcare practitioners, more representative data and medically validated effects of a pharmaceutical preparation can be collected[30]. Once a patient registry is well designed, it can be linked to a monitoring database, such as the Uppsala Monitoring Centre, which creates opportunities to increase the pharmacovigilance for orphan unlicensed medicinal products.

In conclusion, ensuring pharmaceutical quality and performing a proper benefit-risk assessment, followed by good documentation will guarantee safe use of pharmaceutical preparations. While national formulary labels confirm quality and have implemented pharmacovigilance of the products, this license is mostly unavailable for ultra-orphan preparations. Therefore, good documentation of these treatments can be collected in centralized patient registries and should be combined with existing information in (inter)national databases and self-reflection of patients. Such registries will enable pharmacovigilance and control of the usage of these medicinal products. Linking these patient registries to a centralized database for adverse drug events is highly recommended as it increases safety control of the (ultra) orphan pharmaceutical preparations. Follow-up of a recently started patient registry for LEMS and Myasthenia Gravis patients is an interesting development to monitor the safe use of 3,4-DAP. This approach provides a solution to ensure safe use of

pharmaceutical preparations and at the same time prevents unacceptable high costs charged by the pharmaceutical industry for products which are already used in clinical care and have a proven record regarding safety and efficacy.

References

[1] Sutherland A, Waldek S. It is time to review how unlicensed medicines are used. Eur J Clin Pharmacol 2015;71:1029–35. doi:10.1007/s00228-015-1886-z.

[2] Matthews G. Imported unlicensed medicines: requirements and current examples. The Pharmaceutical Journal n.d.;281:705.

[3] Donovan G, Parkin L, Wilkes S. Special unlicensed medicines: what we do and do not know about them. Br J Gen Pract 2015;65:e861-863. doi:10.3399/bjgp15X688033.

[4] Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. Drugs R D 2013;13:1–8. doi:10.1007/s40268-013-0005-9.

[5] Buurma H, de Smet PA, van den Hoff OP, Sysling H, Storimans M, Egberts AC. Frequency, nature and determinants of pharmacy compounded medicines in Dutch community pharmacies. Pharm World Sci 2003;25:280–7.

[6] Minghetti P, Pantano D, Gennari CGM, Casiraghi A. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. Health Policy 2014;117:328–33. doi:10.1016/j.healthpol.2014.07.010.

[7] Pharmaceutical Preparations - European Pharmacopoeia 8.0 2013.

[8] Committee of Ministers, Council of Europe. Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients 2016.

[9] Official Journal of the European Communities. DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use 2001.

[10] Committee of Ministers - Council of Europe. Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (Adopted by the Committee of Ministers on 19 January 2011 at the 1103rd meeting of the Ministers' Deputies) 2011.

[11] PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS 2014.

[12] EMA. Evidence of harm from off-label or unlicensed medicines in children 2004.

[13] Dutch Healthcare Inspectorate. Medicines without marketing authorization n.d. http://www.igz.nl/english/medicines/medicines_without_marketing_authorization/ (accessed July 12, 2016).

[14] Regulation EC. 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83. EC and Regulation (EC) No 2004;726.

[15] Bouwman-Boer Y, Fenton-May V 'lain, Le Brun P, editors. Practical pharmaceutics: an international guideline for the preparation, care and use of medicinal products. Cham Heidelberg New York Dordrecht London: Springer; 2015.

[16] Crommelin DJA, Bouwman-Boer Y. Pharmacy preparations: Back in the limelight? Pharmacists make up your mind! Int J Pharm 2016. doi:10.1016/j.ijpharm.2016.09.031.

[17] Fenton-May V 'lain. Unlicensed Medicines - Scope & Definitions n.d.

[18] Basu B, Dharamsi A, Makwana S, Makasana Y. Prefilled syringes: An innovation in parenteral packaging. International Journal of Pharmaceutical Investigation 2011;1:200. doi:10.4103/2230-973X.93004.

[19] Sacha G, Rogers JA, Miller RL. Pre-filled syringes: a review of the history, manufacturing and challenges. Pharm Dev Technol 2015;20:1–11. doi:10.3109/10837450.2014.982825.

[20] World Health Organization. Quality assurance of pharmaceuticals 2007. http://apps.who.int/prequal/info_applicants/Guidelines/QA_Pharmaceuticals-Vol2.pdf (accessed September 28, 2016).

[21] Florence AT, Lee VHL. Personalised medicines: more tailored drugs, more tailored delivery. Int J Pharm 2011;415:29–33. doi:10.1016/j.ijpharm.2011.04.047.

[22] Wiesner RH, Hermans PE, Rakela J, Washington JA, Perkins JD, DiCecco S, et al. Selective bowel decontamination to decrease gram-negative aerobic bacterial and Candida colonization and prevent infection after orthotopic liver transplantation. Transplantation 1988;45:570–4.

[23] Dooms M, Pincé H, Simoens S. Do we need authorized orphan drugs when compounded medications are available?: Unnecessary authorization of some orphan drugs. Journal of Clinical Pharmacy and Therapeutics 2013;38:1–2. doi:10.1111/jcpt.12006.

[24] de Wilde S, Guchelaar H-J, Herberts C, Lowdell M, Hildebrandt M, Zandvliet M, et al. Development of cell therapy medicinal products by academic institutes. Drug Discovery Today 2016;21:1206–12. doi:10.1016/j.drudis.2016.04.016.

[25] Wetenschappelijk Instituut Nederlandse Apothekers. Formularium der Nederlandse apothekers. Den Haag: Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie; 2013.

[26] WHO Collaborating Centre for International Drug Monitoring. Uppsala Monitoring Centre - who-umc.org n.d. http://www.who-umc.org/DynPage.aspx?id=96979&mn1=7347&mn2=7469 (accessed July 12, 2016).

[27] IOM (Institute of Medicine). Rare Diseases and Orphan Products: Accelerating Research and Development. Washington, DC: The National Academies Press; 2010.

[28] Reid CM. The Role of Clinical Registries in Monitoring Drug Safety and Efficacy. Heart Lung Circ 2015;24:1049–52. doi:10.1016/j.hlc.2015.04.184.

[29] Workman TA. Engaging Patients in Information Sharing and Data Collection: The Role of Patient-Powered Registries and Research Networks. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

[30] Dreyer N, Leavy M. Direct-to-Patient Registries: A New Approach to Pharmacovigilance. Bioscience Technology 2015. http://www.biosciencetechnology.com/article/2015/10/direct-patient-registries-new-approach-pharmacovigilance (accessed January 13, 2017).

[31] Research C for DE and. Compounding - Compounding and the FDA: Questions and Answers n.d. https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339764.htm (accessed June 15, 2017).

[32] Burton T. FDA Urges Compounding Pharmacies to Register; By Registering, Pharmacies Would Submit to FDA Inspection. Wall Street Journal (Online) 2014.