International Journal of Pharmaceutics 514 (2016) 11–14

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Commentary

Pharmacy preparations: Back in the limelight? Pharmacists make up your mind!☆

Daan J.A. Crommelin[a,*], Yvonne Bouwman-Boer[b]

[a] (Formerly) Dept. of Pharmaceutics, Utrecht University, Utrecht, The Netherlands
[b] (Formerly) Royal Dutch Pharmacists Association KNMP, Laboratory of Dutch Pharmacists, The Hague, The Netherlands

ARTICLE INFO

Article history:
Received 3 May 2016
Accepted 10 May 2016

Keywords:
Unlicensed pharmaceutical preparations
Pharmacist
Formulation design
Pharmacy education
Precision medicine
Quality management systems

ABSTRACT

In this contribution to the theme issue recognizing prof. Florence's achievements as editor –in-chief of the Int. J. Pharmaceutics, we analyze the future of pharmacy preparations (also known as extemporaneous preparations or compounded products). Pharmacy preparations, long considered as an endangered part of the pharmacy profession on its way to extinction, may be at the brink of a revival. Drivers of this revival are a set of changes related to new clinical concepts and supply shortages. Moreover, new production and IT paradigms are being developed that facilitate the preparation processes and provide the necessary quality management systems. Finally, more detailed legislation (EU) and guidelines (US) gets a better hold on preparation in pharmacies.

The question is now: is the pharmacy profession willing to accept preparation of high quality medicines in the pharmacy as an integral part of its professional tasks? If so, institutions for pharmacy education should provide the required competences to the pharmacy student. If not, alternative scenarios with other disciplines taking the lead should be considered. Whatever the choice made, the 'Physicochemical principles of pharmacy: in manufacture, formulation and clinical use' by Florence and Attwood (2016); will be on the engineer/pharmacy student's desk.

1. Introduction

In many countries, the role of the pharmacist has evolved to a patient medication oriented health care professional. The FIP, the International Pharmaceutical Federation, states in the preamble of its mission statement: 'Over the past 25 years, Pharmacy Practice has been moving from its original "product focus" to a "patient focus" at least in the developed countries of the world'. In a recent publication of the European PHAR-QA project, Atkinson et al. (2016); community pharmacists ranked required competences in pharmaceutical technology low, echoing the FIP message.

There are good reasons for choosing that direction as medication errors are a main cause of hospitalization and death for patients (AMCP, 2010; Harm Report, 2006) and measures should be taken to improve the quality of use of medication by the patient. The pharmacist should have the necessary competences to take the lead here.

For a long time the presumption was that in developed countries high quality, under GMP manufactured, medicines are available supported by a well-organized and monitored supply chain. This was a joint effort of regulatory bodies and the innovative and generic pharma industry. But the scene may change and that may happen fast: big may not be so beautiful after all in every situation.

Which drivers cause the change from large scale to small-scale manufacturing and which consequences do we face for pharmacy practice, the quality management system, regulations and the education of pharmacists, both at the BS and MS degree level and for lifelong learning programs? Can we sustain the 'one track fits all model' in pharmacy education, i.e. maintain the present patient-focus with little attention paid to competences related to (hands on) small-scale manufacturing.

☆ Commentary for the IJP in theme issue dedicated to Prof. Sandy Florence stepping down as editor in chief of IJP.

* Corresponding author.
E-mail address: D.J.A.Crommelin@uu.nl (D.J.A. Crommelin).

http://dx.doi.org/10.1016/j.ijpharm.2016.09.031
0378-5173/

2. Drivers to small-scale manufacturing of medicines

At present, large scale manufacturing of medicines for the global market is the rule. Economic reasons and robust quality assurance systems provide the patient in developed countries with (in general) affordable and high quality medicines. However this situation may change. An analysis of trends in the field of medicine gives a number of reasons for the preference of small-scale above large scale manufacturing:

1. A move to personalized medication or to precision medicines, including advanced therapies.
2. Systems approaches leading to tailor-made combination therapies
3. Shortage of medicines e.g. because of economic reasons
4. Growing interest in orphan drug based interventions.

'Classical' requirements for the use of patient-specific preparations remain, such as a patient's allergy to excipients in the licensed product, required change in dosage form because of problems with swallowing, dosages in paediatrics or medicines for the elderly (Florence, 2008; Wikipedia compounding).

We will work out the four points mentioned above in more detail.

Re 1. Clinical implementation of the concept of 'personalized medicine' or 'precision medicine' stimulated by the development of (gene based) biomarker assays is gaining momentum. A pubmed analysis shows for 'personalized medicine' 200 hits in 2000 and 5200 hits in 2015. The FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (FDA, 2016) is growing at a rapid pace. The clinical indications in this table cover a broad range of diseases, from oncology to dermatology. One of the results of the precision medicine approach will be: a smaller number of patients for a therapy with more diverse dosing requirements: i.e. small scale manufacturing or pharmacy preparation.

Re 2. Systems approaches leading to tailor-made combination therapies

For many years the Western paradigm of treating disease has been: 'one-drug-fits-all'. The less (different) drugs, the better: One drug for one receptor to treat the disease. This is an oversimplification. Systems medicine analyzes the disease characteristics in a particular patient and the options for interventions using sophisticated modelling techniques (Boissel et al., 2015). Experience in oncology and infectious diseases taught us already that combination therapies attacking the disease from different angles/through different pathways, improve efficacy and –in these cases of critical importance- minimize the chances of building up drug resistance. This disease and patient oriented approach may call for tailor-made interventions with medicines.

Re 3. Shortage of medicines e.g. because of economic reasons

Jenzer and Fenton-May (2015) list a number of multifactorial reasons for medicine shortages. Economic reasons such as discontinuation of production because of high cost/low prices and gains are often mentioned. But demand spikes and quality issues occur as well. Shortage of medicines is increasing as is demonstrated by statistics of different countries. In the US shortages rose from 70 in 2006 to 267 shortages in 2011; for the Netherlands these numbers were 91 in 2004 to 242 in 2011 en 625 in 2015 (KNMP, 2015). The impact of shortages in hospital pharmacies is well described by an EAHP overview (EAHP, 2014).

The pharmacist is seen as the first member of the health care team to solve the shortage problem and secure the supply line. In the EU the legal framework for preparation of medicines in pharmacies has been created by the Ph Eur monograph Pharmaceutical preparations (European Pharmacopoeia, 2013) and the Council of Europe Resolution CM/ResAP (Resolution CM, 2011) on quality and safety assurance requirements for medicinal products prepared in pharmacies (pharmacy preparations) for the special needs of patients. This document states: ' . . . the preparation of medicinal products in pharmacies, which may be required as a consequence of the individual or medical condition of the patient in the absence or unavailability of appropriate medicinal products on the market, is indispensable for accommodating the special needs of individual patients in Europe' and ' . . . . pharmacists can legally prepare medicinal products in the pharmacy by virtue of their professional education, professional license and licensing of the pharmacy's premises' and this document (Resolution CM, 2011) works out operational details in its appendix. . . . . But it also mentions ' . . . . . pharmacy preparations are not advisable if a suitable pharmaceutical equivalent with a marketing authorization is available. Before preparation the pharmacist should verify whether a pharmaceutical equivalent is available on the national market, taking into consideration the pharmaceutical form and the strength'. Thus, 'as a last resort' the pharmacist may decide to follow the pharmacy preparation route ensuring quality and safety of the preparation.

Re 4. Increasing interest in orphan drug based interventions

Over the years there has been an increasing interest in orphan medicines for the treatment of rare diseases. In 2000 the term 'orphan drugs' was used in the title of 41 publications (pubmed); this number has grown to 196 in 2015. The term 'rare disease' is defined by EMA as ' life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in EU. This is equivalent to around 250,000 people or less for each disease' (EMA, 2016). In this document the EMA further details the definition of rare diseases and the regulatory pathways to register designated orphan medicinal products to treat them. The trend of better understanding the etiology of diseases by using proper diagnostics leads to personalized medicines (cf. point 1) and therefore more and more medicines end up in the class of orphan medicines. This can be clearly seen in oncology.

Many medicines for rare diseases are and have been produced in the past by pharmacies. In a commentary Dooms et al. (2013) clearly point out the pros and cons of the EMA orphan medicinal product designation of already existing (hospital) pharmacy preparations and the implications for reimbursement and risk for investments in registered orphan medicinal products.

3. What are we talking about? Terminology

The trends as described above under 1–4 will lead to the manufacture or preparation of unlicensed medicines. Bouwman-Boer et al. (2015a) discriminate the classical process of pharmacy "Preparation from raw materials" from the more recent come into practice: "Preparation by adapting the dosage form of an existing (mostly licensed) medicinal product", "Reconstitution in excess of SPC instructions", "Repackaging or replenishing" and "Reconstitution". Fig. 1 schematically pictures these processes that may be necessary to dispense a medicine to the patient. All processes except 'Reconstitution' produce 'unlicensed pharmaceutical preparations'. Only pharmacists are authorized for performing these activities or processes, so pharmacists should have the necessary competences. The terminology of manufacturing or preparing 'unlicensed pharmaceutical preparations', is to be preferred to the terms that are often used with different meanings, e.g. compounding, extemporaneous, pharmacy or magistral preparation. In this commentary we may use the term 'pharmacy preparation' as a brief term for those activities that produce unlicensed pharmaceutical preparations.