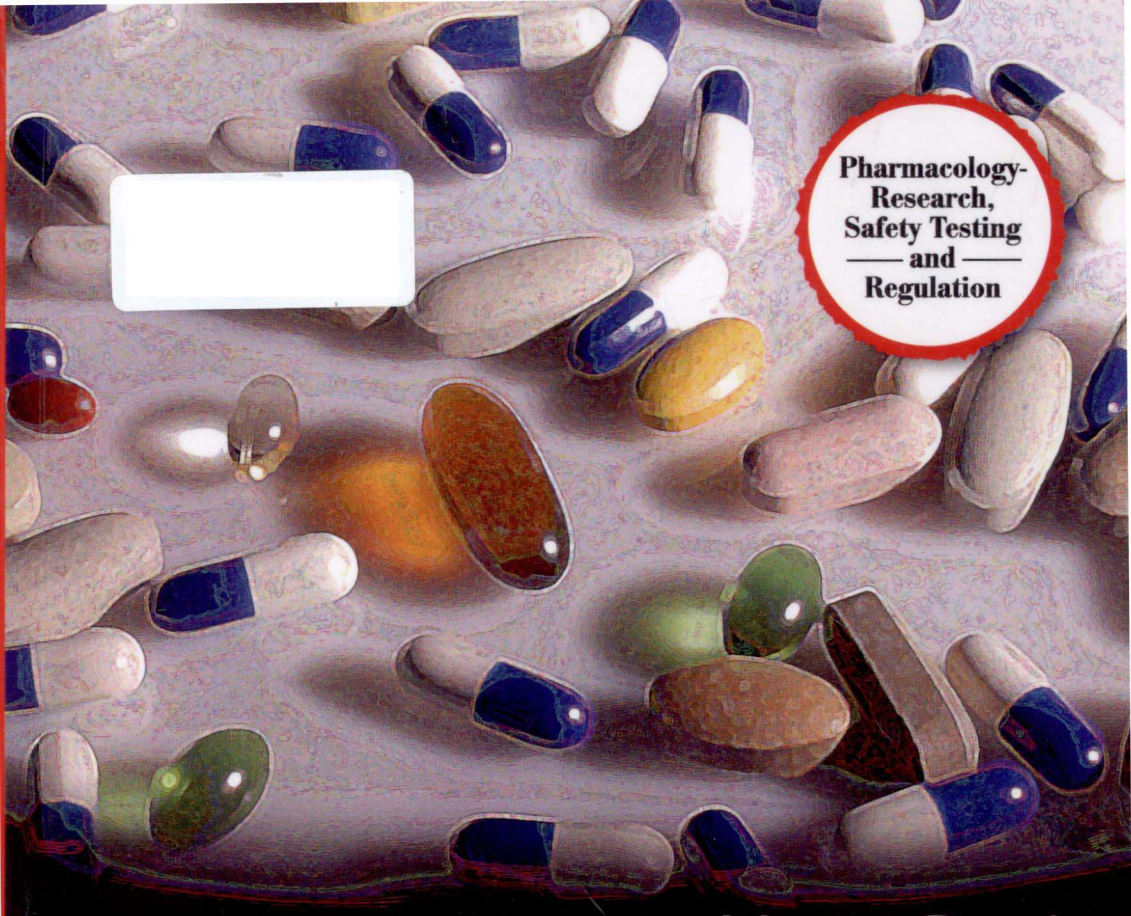

Marco Rossi
Santina Bertone
Editors

Drug Development

Principles, Methodology and Emerging Challenges

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PHARMACOLOGY - RESEARCH, SAFETY TESTING AND REGULATION

DRUG DEVELOPMENT

PRINCIPLES, METHODOLOGY AND EMERGING CHALLENGES

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AND
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New York

Library of Congress Cataloging-in-Publication Data

ISBN: 978-1-62417-790-3

Library of Congress Control Number: 2012955910

Published by Nova Science Publishers, Inc. † New York

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PREFACE

In this book, the authors discuss the principles, methodology and emerging challenges of drug development. Topics include outsourcing and technology transfer in pharmaceutical companies; analytical tools and chemometrics in the drug development process; the use of cytometry for drug development of cell cycling inhibitors; and the antiproliferative effects of phenolic compounds isolated from the Brazilian propolis.

Chapter 1 – Pharmaceutical companies are becoming increasingly reliant on outsourcing to increase capability and capacity, with the objectives of decreasing costs and improving efficiency and productivity. However, outsourcing strategies also drive an increased requirement for technology transfer between different sites. Typically, technology transfer can occur at different stages in the life-cycle of the product. It can occur between (i) R and D and production, (ii) between two different production sites, (iii) as part of an outsourcing initiative, where the process/methods will be transferred from either R and D and/or production into an external CRO/CMO (contract research organisation/contract manufacturing organisation), (iv) or between an external CRO/CMO and production (or even R and D), as part of an in-licensing scenario. The greater the experience and understanding that the receiving site can gain of the product and the process/methods prior to formal manufacture of the pivotal batches (clinical, regulatory, commercial, etc.), then the lower will be the ultimate risk. This essentially translates into several key questions: Will the manufacturability of the product be the same using the receiving site's equipment and input materials? Will the process/methods work in the receiving site's facility? The key knowledge that needs to be embedded into the receiving site prior to manufacture is critical to successful transfers. A case study exemplifies the challenges and issues facing transfer of a pharmaceutical process. There is also greater regulatory scrutiny in the area of

outsourcing of drug manufacturing and in particular, on the technology transfer of analytical methods. As part of the recent revision process for EU GMP regulations, EMA (European Medicines Agency) indicated that suspected out-of-specification (OOS) results are sometimes attributed to issues associated with the transfer of analytical methods. The transfer process has evolved from the initial IPSE (International Society for Pharmaceutical Engineering) good practice guide for technology transfer into the current USP (United States Pharmacopeia) general chapter for Transfer of Analytical Procedures <1224>. The different Industry approaches to method transfer; including comparative testing, co-validation of methods between laboratories, complete (or partial) re-validation by the receiving unit and a waiver of transfer procedures are discussed. Several case studies exemplified the challenges and issues facing transfer of analytical method(s). The sheer number of analytical method transfers is likely to encourage risk-based approaches in the future; allowing the correct level of resourcing to be applied to the highest risk activities. Low risk activities will utilise knowledge-based transfers, whereas, medium risk methodologies will use method confirmation (testing at receiving site); finally, the highest risk methods will utilise classical comparative testing. Although, sophisticated hyphenated methods (HPLC-MS-MS or GC-MS-MS) used for the detection and control of genotoxic impurities have been historically transferred into production, the continued support of these methods is extremely difficult. Going forward, many companies have made the strategic decision not to transfer these methodologies into production and leave them within R and D. These companies have accepted that the greater regulatory scrutiny from routine GMP audits (in addition to pre-approval inspections) is a lower risk to the organisation compared to maintaining highly sophisticated hyphenated methods within a production environment.

Chapter 2 – Drug development is a time-consuming and costly process. Recently, the need of very sensitive and selective assays for the complete characterization of New Chemical Entities (*NCE*) has become very stringent. From Analytical Chemists, a partial answer to this problem was the development and validation of new methods that permit an improvement in terms of productivity (*"high-throughput"*), sensitivity and selectivity, especially using very recent hyphenated analytical assays, such as HPLC-MS/MS, GC-MS/MS or further complex couplings, that can provide more complete information in a single analysis. All data obtained by these novel techniques require a very deep and multifaceted analysis, in order to check the principal and fundamentals variables and to reject the others. In this scenario,

chemometrics provide scientists with useful tools to interpret the large amounts of data generated by these complex analytical assays and allows for quality control, classification procedures, modelling studies. Discrimination between different molecules available as novel drugs and molecules having no interesting biological activities is easy by means of multivariate analysis. chapter 2 reports recent advantages in analytical method hyphenation and chemometric approach applied to drug development.

Chapter 3 – Pharmacological investigations of cell cycle inhibitors are a main focus of anticancer researches. These activities include all steps required to link lab bench to initiation of clinical trials. Preclinical activities generally include proof of concept of target inhibition during target identification and validation process, confirming its role in a known disease context, find molecules able to inhibit a specific cellular pathway for identification of a lead candidate from several hits, and taking into consideration the experimental tumor pharmacology, the characterization of novel anticancer compounds in a preclinical setting which includes the evaluation of mechanism of action, metabolism, route and duration of exposure and interaction with cellular mechanisms of resistance. Besides anti proliferation and enzymatic inhibition assays, flow cytometry is an extreme flexible analytical platform for profiling mechanism of action. Compounds scored as hits in primary screening are typically subject to secondary assays in order to refine mechanism of action in cells that should be consistent with target inhibition by analyzing specific phenotype changes such as cell death induction and cell cycle arrest. For these features, multiparametric analysis based on BrdU incorporation could dissect cell cycle stages allowing a complete relationship between a target inhibition and DNA synthesis arrest. This chapter shows the analytical approach regarding the case study of a topoisomerase I inhibitor, Edotecarin, in phase I, in comparison to the well-known drug Irinotecan, either in vitro or ex-vivo experiments in tumor bearing mice, describing principles, methodologies and future prospective in cell cycle field. Moreover these studies demonstrate that the mechanism by which edotecarin inhibits proliferation of human cancer cells is consistent with topoisomerase I Inhibition, and further suggest that edotecarin may have unique efficacy against human cancer.

Chapter 4 – Propolis has been used for as a traditional medicine in Eastern Europe as an antifungal, antimicrobial, antiviral, anti-inflammatory, and anticarcinogenic agent. The author isolated three cinamic acid derivatives and one flavanol derivative from Brazilian propolis and determined their structures by spectroscopic analysis. Results were assayed, the anticancer drug potential of these compounds to identify new drug candidates, by determining the

potential to inhibit proliferation and induce apoptosis in various cancer cell lines. Kaempferide was the most effective compound among the four compounds tested, increasing apoptosis in MDA-MB-231 cells about 2-fold compared to control cells. Kaempferide is a promising anticancer drug; however, further studies are required to determine the mechanism of kaempferide-induced proliferation inhibition and apoptosis induction.

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In: Drug Development
Editors: M. Rossi and S. Bertone

ISBN: 978-1-62417-790-3

Chapter 1

OUTSOURCING AND TECHNOLOGY TRANSFER

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ABSTRACT

Pharmaceutical companies are becoming increasingly reliant on outsourcing to increase capability and capacity, with the objectives of decreasing costs and improving efficiency and productivity. However, outsourcing strategies also drive an increased requirement for technology transfer between different sites. Typically, technology transfer can occur at different stages in the life-cycle of the product. It can occur between (i) R and D and production, (ii) between two different production sites, (iii) as part of an outsourcing initiative, where the process/methods will be transferred from either R and D and/or production into an external CRO/CMO (contract research organisation/contract manufacturing organisation), (iv) or between an external CRO/CMO and production (or even R and D), as part of an in-licensing scenario.

The greater the experience and understanding that the receiving site can gain of the product and the process/methods prior to formal manufacture of the pivotal batches (clinical, regulatory, commercial, etc.), then the lower will be the ultimate risk. This essentially translates into several key questions: Will the manufacturability of the product be

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the same using the receiving site's equipment and input materials? Will the process/methods work in the receiving site's facility? The key knowledge that needs to be embedded into the receiving site prior to manufacture is critical to successful transfers. A case study exemplifies the challenges and issues facing transfer of a pharmaceutical process.

There is also greater regulatory scrutiny in the area of outsourcing of drug manufacturing and in particular, on the technology transfer of analytical methods. As part of the recent revision process for EU GMP regulations, EMA (European Medicines Agency) indicated that suspected out-of-specification (OOS) results are sometimes attributed to issues associated with the transfer of analytical methods.

The transfer process has evolved from the initial IPSE (International Society for Pharmaceutical Engineering) good practice guide for technology transfer into the current USP (United States Pharmacopeia) general chapter for Transfer of Analytical Procedures <1224>. The different Industry approaches to method transfer; including comparative testing, co-validation of methods between laboratories, complete (or partial) re-validation by the receiving unit and a waiver of transfer procedures are discussed. Several case studies exemplified the challenges and issues facing transfer of analytical method(s).

The sheer number of analytical method transfers is likely to encourage risk-based approaches in the future; allowing the correct level of resourcing to be applied to the highest risk activities. Low risk activities will utilise knowledge-based transfers, whereas, medium risk methodologies will use method confirmation (testing at receiving site); finally, the highest risk methods will utilise classical comparative testing. Although, sophisticated hyphenated methods (HPLC-MS-MS or GC-MS-MS) used for the detection and control of genotoxic impurities have been historically transferred into production, the continued support of these methods is extremely difficult. Going forward, many companies have made the strategic decision not to transfer these methodologies into production and leave them within R and D. These companies have accepted that the greater regulatory scrutiny from routine GMP audits (in addition to pre-approval inspections) is a lower risk to the organisation compared to maintaining highly sophisticated hyphenated methods within a production environment.

OUTSOURCING

The challenges facing the pharmaceutical industry in 2012 are significant. There is a perceived decline in the productivity of R and D, significantly higher regulatory hurdles to market entry (particularly in the key US market),

pricing pressures (particularly in Europe) and erosion of profits due to earlier generic entry (Raska et al., 2010). This has resulted in drivers to simplify operations in order to maximise efficiencies.

As a consequence, pharmaceutical companies are increasingly utilizing outsourcing to address internal resource constraints; as well as increasing flexibility, increasing specialised knowledge /skills, broadening risk, reducing costs, and decreasing time to market. These perceived advantages are examined in more detail below (Piachaud, 2002):

a Greater flexibility: Outsourcing allows pharmaceutical firms to cope with the peaks and troughs experienced during product life-cycles without the need to invest in greater internal capacity (people and equipment).

b Specialised knowledge and skills: Outsourcing allows the company to develop new capabilities (enhancing the knowledge base or acquiring new skills) and remain competitive, without the need to commit valuable internal resource and with a view to bringing in-house only the most promising new research initiatives (de-risking).

c Concentrate on core functions: The outsourcing of peripheral or non-core functions allows the company to focus on its core capabilities enabling it to sustain competitive advantages for extended periods.

d Reduce costs: Outsourcing can reduce costs, by driving efficiency gains and allowing better utilisation of internal resources.

e Reduced time to market: Outsourcing provides an attractive alternative to expedite development times as resources are available when required rather than building internal capacity and capability (Grote, 2012).

However, there are a number of key risks (Piachaud, 2002):

a Supplier dependence: Outsourcing can result in too much dependence on a single supplier leading to lack of control and increased risk and vulnerability. This can lead to quality concerns and delays, as well as misunderstanding (and sometimes mistrust), especially in partners that don't have an established long-term relationship.

b Lack of shared vision and objectives: Most successful CROs (Contract Research Operations) support a number of different and often competitive clients resulting in potential priority conflicts and delays.

c Lack of critical skills: Companies run the risk of sacrificing long term gains for short term benefits. What are classified as tactical and low value activities today can become strategic, high value and core values tomorrow.

d Evaluating supplier performance. Companies must set in place clear guidelines for assessing supplier performance and a core in-house resource (including knowledge base and expertise) must be retained to facilitate that assessment. Critically, outsourcing does not remove accountability. Time, money and resource are still required to effectively manage an external portfolio to ensure that the work meets appropriate standards and time lines (Van Arnum, 2007).

It is interesting to note that the same drivers appear to apply to outsourcing irrespective of the size of the sponsor company. Thus, it would appear that all organisations, irrespective of size, outsource for the same fundamental reasons; because they are deficient in the appropriate resources to conduct some critical activity. What differentiates large, medium or small companies is typically 'how they define appropriate resource' (Grote, 2012). For the small virtual companies this means little if any, in-house resource to deliver the activity on time and on budget. In contrast, for larger companies there are so many competing drivers for the core in-house resource that there are insufficient resources at the right time and in the right place to deliver the activity on time and on budget.

However, outsourcing strategies also drive an increased requirement for technology transfer between different sites. Typically, technology transfer can occur at different stages in the life-cycle of the product. It can occur between (i) R and D and production, (ii) between two different production sites, (iii) as part of an outsourcing initiative, where the process/methods will be transferred from either R and D and/or production into an external CRO/CMO (contract manufacturing organisation), (iv) or between an external CRO/CMO and production (or even R and D), as part of an in-licensing scenario (Raska et al., 2010).

A growing trend is the late-stage outsourcing of commercial manufacturing activities. Conversely, there is also a commensurate increase in early

stage (pre-PoC) outsourcing aimed at maximising internal resources for later stage development programmes.

Drug discovery outsourcing was expected to have reached over $8 billion by 2010 (Fiscus, 2009). As a consequence, the global contract pharmaceutical manufacturing market has expanded significantly in the recent past. Obviously, the downside of any outsourcing strategy is the increase in risk for those programmes. Companies address these risks by investing heavily in 'their partners' collaborative activities (Valazza and Wada, 2001).

Quality still remains the No. 1 criteria for any outsourcing activity. Imports from third-party suppliers account for greater than 80% of APIs (active pharmaceutical ingredient) in the United States and 40% of medicinal products, yet the FDA (US Food and Drug Administration) continues to conduct far fewer foreign compared to domestic inspections (Mullin, 2011). Contaminated heparin was judged as the cause of 81 deaths in the United States in 2008. FDA traced the contaminated API to a Chinese supplier (Changzhou SPL Co.).

Heparin exposed the multi-layered nature of many supply chains and the high levels of manufacturer uncertainties that are present with regards to their raw materials supply base (Shanley et al., 2008). USP has also introduced a general chapter entitled Good Distribution Practices-Supply Chain Integrity <1083> to try and address these issues (USP, 2012a).

FDA has recently indicated that 'FDA's traditional model of manufacturing site inspections and border examinations is simply not adequate in today's transformed world' (Mullin, 2011). There is a general understanding that when companies outsource a function(s) to a CRO/CMO that these organisations in turn, become subject to the same regulatory responsibilities and scrutiny as their clients, i.e. control of the product's quality has to be maintained (Linna et al., 2008).

ICH Q10 (2007) stated that the responsibilities of quality systems extend to the oversight and review of outsourced activities, stating that 'the contract giver should be responsible for assessing the suitability and competence of the contract acceptor to carry out the work required'.

And further, that 'the responsibilities for quality-related activities of the contract giver and contract acceptor should be specified in a written agreement'. Similarly, ISO 9001 (2000) states that, 'Where an organization chooses to outsource any process that affects product conformity, the organisation shall ensure control over such outsourced processes. Control of such outsourced processes shall be identified within the quality management system.'

PROCESS TECHNOLOGY TRANSFER

ICH Q10 (2007) also addresses technology transfer and indicates that, 'Monitoring of scale up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Monitoring of transfer and scale-up activities can be useful in further developing the control strategy.' The following areas are viewed as being important for successful process transfer:

I. Environmental, Health and Safety (EHS) Evaluation

Each new product targeted for a site-transfer must be fully evaluated with respect to EHS (Environmental, Health and Safety). Key worker safety information such as hazard categorisation, handling instructions, sensitising potential, containment and/or the need for personal protection equipment (PPE) and their impact on the timings of the overall transfer process need to be assessed. Local interpretations on discharge regulations and allowable limits can vary widely. The overall objective is to 'protect those who will be producing the product' (Worsham, 2010). In addition, there are increasing requirements to assess the environmental 'fate and effect' of pharmaceuticals. An environmental risk assessment (ERA) is now required for all new pharmaceuticals in marketing authorisation applications. This is a 'phased' activity and characterises the potential risks that a pharmaceutical poses to the environment. (De Roode, 2010).

II. Process Understanding

Process understanding, which forms part of Quality by Design (QbD), is a critical element to the success of any transfer exercise (ICH Q8, 2005). Process understanding can vary from limited to extensive dependent on the nature of the interaction and the different stages in the life-cycle of the product. Thus an R and D into production transfer may have limited process understanding and none at the proposed commercial scale; whereas, a transfer between two different production sites, within the same manufacturing network may have extensive process understanding. Transfers between sponsors and CMOs and/or CMOs and sponsors probably cover the whole continuum of process understanding.