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Mark Wigglesworth and Terry Wood

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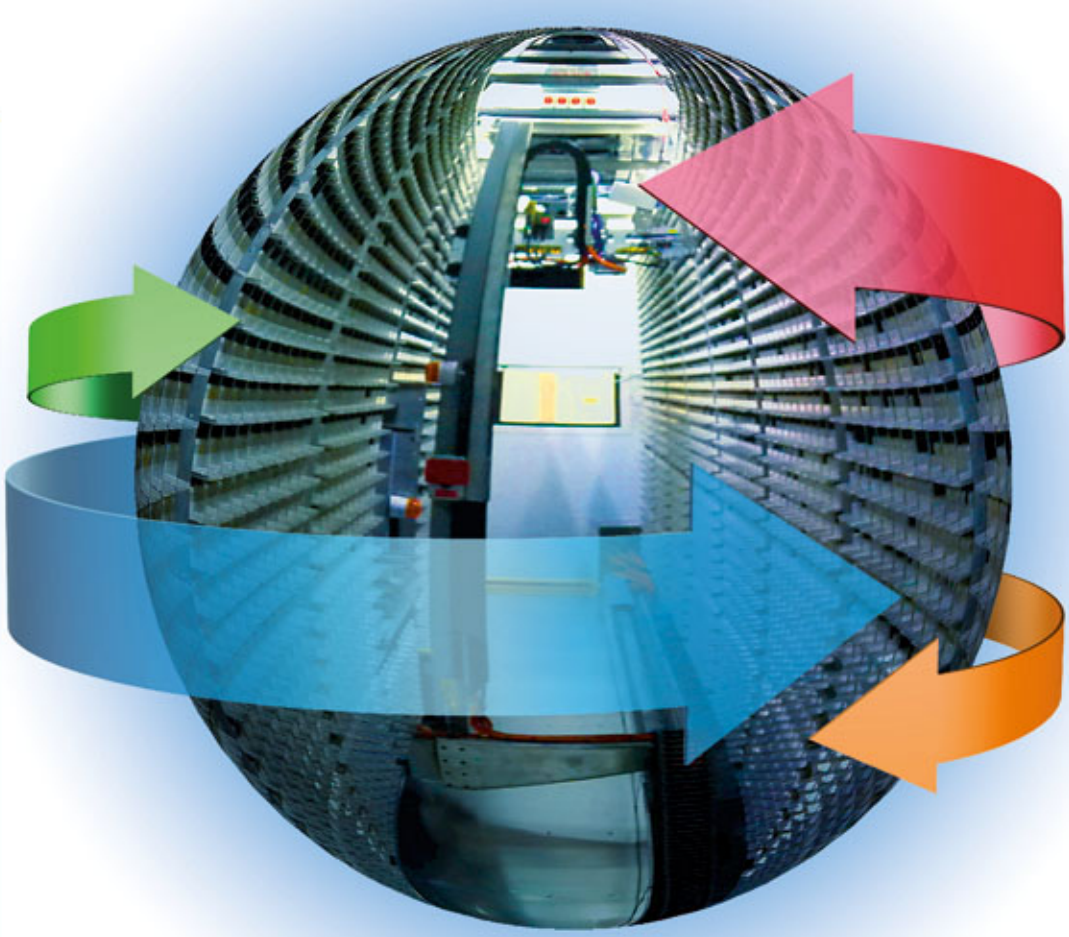
Management of Chemical and Biological Samples for Screening Applications



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Management of Chemical and Biological Samples for Screening Applications

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Dedication

We would first like to thank everyone that has contributed to this book and hope that it is a text which helps promote and project forward the science of Sample Management. We have both found our work within the pharmaceutical industry rewarding not least because it is an opportunity to make the medicines that help other people. To this end we pledge our editorial honoraria to Cancer Research UK, which is a beneficiary close to both our hearts. Finally we would like to dedicate this work to our families; we thank them for their patience and hope that we have made this world a better place for them.

The royalties from the sale of this book will be donated to Cancer Research UK.

Cancer Research UK is the world's leading cancer charity dedicated to saving lives through research. Our ground breaking work into the prevention, diagnosis and treatment of cancer has seen survival rates double in the last 40 years. But more than one in three of us will still get cancer at some point in our lives. Our research, entirely funded by the public, is critical to ensuring more people beat it.

The views and opinions within this book are those of the Authors, and are independent from the work of Cancer Research UK.

in aid of
CANCER RESEARCH UK

Contents

Preface

Within this book we present a modern, practice-orientated overview of concepts, technology, and strategies for the management of large entity collections, encompassing both chemical and biological samples. This book reports expert opinion in this area and documents the evolution, current best practice, and future goals of Sample Management in a form never previously achieved.

The field of Sample Management has evolved in the last 20 years from a necessary, if somewhat haphazard, occupation of a screening scientist into a highly controlled, scientific discipline, incorporating logistics and automation management. This evolved scientific discipline is a pivotal part of every pharmaceutical and biotechnological organization across the globe, yet holding these samples in huge warehouses has no intrinsic value in itself. The samples must be subjected to High-Throughput Screening, population-based clinical research, and/or many other techniques that form part of the drug discovery pipeline before that one single chemical structure is identified which will lead to a life-changing discovery (see Figure 1). These single samples, at the end of many years of research, are the ones of value, and nurturing them and ensuring that you are able to find them within your collection is the role of the Sample Manager.

This book will guide the reader through the complex paths of Sample Management, starting with a view of what it represents for both chemical and biological samples and the reasons why this discipline has had to be developed. We present views on sample quality and the importance of quality in both establishing collections and maintaining them once created. We present the rationale for the subdivision of collections for efficient screening, and provide an overview of automation, from large-scale storage devices through to bench-top liquid handling technology for compound dispense. We further examine the latest and most advanced technologies available and how these are being implemented within the industry. Rarely do organizations exist in isolation; hence we examine the logistics of sample storage and transportation, taking in the practical and legal elements. One of the biggest potential issues within Sample Management is the tracking of data and samples within an inventory, from sample receipt through dissolution, dispense, and utilization. An IT system that interacts with automation and tracks the movement of every sample is key to establishing reliable delivery of samples

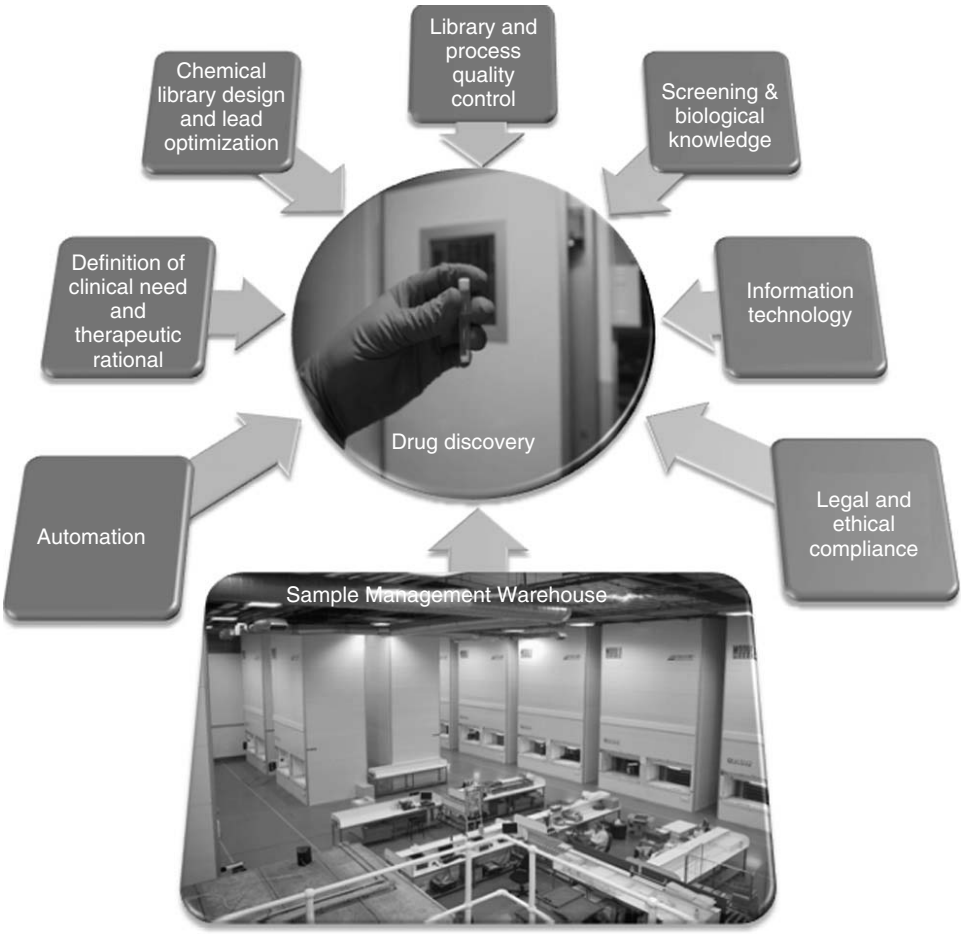

Figure 1 A schematic showing Sample Management as a contributor to drug discovery: only when many elements work cohesively together can the value in what we do be realized.

and data integrity. Hence, we present two chapters introducing bespoke database systems through to examples of the off-the-shelf systems that fulfill this need.

In order to survive in an increasingly complex business environment, many companies are turning to process efficiency techniques that were made popular by the automotive industry, such as LeanSigma. Sample Management has many similarities to a production activity, and hence we examine these new techniques and show how they can be applied to improve process efficiencies and deliver key insights. In a further drive for efficiency, the pharmaceutical industry has focused on reducing attrition. This in turn has focused on changing the chemical properties of small-molecule collections, leading to new thought on how collections should be generated.

For the management of biological samples, which present their own, unique set of issues, we examine the challenges of obtaining tissues of high and comparable quality, looking at automation currently in use in this field as well as examining the potential of future technologies to assist biobanking. Tissue biobanking as well as the management of biological materials in the form of cell lines used within biological assays is discussed. We finish with a projected view of Sample Management, where outsourcing opportunities have delivered benefits to both chemical and biological sample management organizations and how utilization of the skills within Sample Management facilitate operating large scale processes. We also offer opinion on what the Sample Management department of the future might look like and how alterations in the drug discovery process may affect the process of Sample Management.

Above all we hope that this book will be a useful tool for any Sample Management organization, large or small, and will challenge you to take a fresh look at your organization and what it is doing. Think not just about how you will fulfill the next request, but also how you, in your role as a Sample Manager, can continue to expedite the essential business of drug discovery in years to come.

United Kingdom, November 2011 *Mark Wigglesworth, Terry Wood*

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Introduction to Sample Management

William P. Janzen and Andy Zaayenga

At its simplest level sample management is just inventory – where can one find a given item and retrieve it? But in the context of modern discovery efforts, be they drug discovery, agricultural, protein therapeutic, biobanking, or the plethora of other disciplines that collect and manage samples, the problem is far more complex. Today, sample management may have to manage millions of samples in a library that spans several continents but will also have to contend with a worldwide customer base. To make the problem more difficult the content of the samples must also be managed, which may involve complex chemical structures and storage conditions that may vary from room temperature under inert atmosphere to storage in liquid nitrogen. At this level the storage of these samples must now involve complex informatics and automation systems. This volume will capture the best practices compiled from experts in the field of sample management and will hopefully serve as a guide to both novice sample managers who need to track a few thousand compounds in room-temperature vials to professionals in multinational organizations.

As long as there have been chemicals there has been a need for sample management. One could imagine that for a seventeenth century druggist this was simply an inventory of the herbal extracts and remedies he compounded into salves and potions and the location where they were stored. This could be done from memory in most cases and probably evolved to a written inventory when searching for needed components became too slow and cumbersome. Early sample management evolved in parallel with drug discovery. What we consider sample management today came into being as pharmaceutical companies began to amass chemical libraries and test these in disease-focused assays. As these companies synthesized compounds, they retained samples and began to amass collections of chemical compounds that numbered in the tens of thousands. At the same time, the testing of natural product extracts became common practice, significantly boosting the number of samples to be stored [1, 2]. As the number of samples exceeded 100 000 (at that time a seemingly immense number), automated systems were developed to store and catalog them. Initially, these were simple robotic units or adapted card file systems that would simply present entire drawers or boxes of samples to an operator. Chemical structures were often still paper copies and stored

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elsewhere, and the amount in the inventory was rarely accurate if tracked at all. Storage labware formats were standardized to accommodate the large volumes of samples moving through the system and to facilitate liquid handling and detection platform development [3]. Improvements in liquid handling and detection enabled increasingly higher labware densities, allowing tighter environmental control, and larger libraries.

Sample integrity became paramount with a focus on environmental conditions and consistent sample history both in the storage units and in the reformatting/analysis areas. Significant numbers of legacy compounds which had been subjected to variable temperatures, water, oxygen, and light were found to be compromised. Container seal adhesives and labware mold components could introduce interferents to the assay results. Compound managers realized that consistent sample quality was a key to valid scientific data. Programs were employed to provide cradle-to-grave care as well as purity monitoring to insure repeatable sample integrity.

With the advent of combinatorial chemistry, parallel synthesis made the creation of large compound sets numbering in the hundreds of thousands viable and raised the stakes for compound management. High-throughput screening (HTS) groups began requiring that compounds be presented in 96 well plates dissolved in Dimethyl sulfoxide (DMSO) and consumed these plates at an alarming rate. At about the same time, the electronic storage and representation of chemical structures became possible [4]. As the numbers of samples increased, chemists could no longer rely on visual inspection of structures, so tools were developed to analyze synthetic sets to determine their degree of similarity or difference [5]. Compound management groups, that had often become underfunded corporate backwaters, suddenly found themselves under the spotlight as the bottleneck in an exciting new process.

In answer to this challenge, funding was allocated to revamp chemical stores, and a plethora of bespoke systems of automation and data management appeared [1, 6–8]. The linkage between automated preparation systems and data systems was a slow process and the systems that were created varied widely in their architecture and success but shared a number of traits that embody today's samples management system:

- Sample registration
- Usage of enterprise-wide standardized labware
- Positive sample tracking, usually using barcodes
- Cradle-to-grave tracking of samples stored in both vials and plates
- Sample security with user access tracking and control
- Accurate quantity tracking of both mass and volume
- Storage of compounds in DMSO solutions
- Control of environmental conditions to minimize water uptake, oxygen and light degradation, and temperature fluctuation
- High speed automated storage and retrieval
- Reduced freeze/thaw cycles by efficient daughter plate production or by multiple aliquotting