

Executive Summary

This report presents an overview of the exciting developments that are currently taking place in the field of alternative drug delivery—a phrase that describes the reformulation of drugs to enable lower doses, more convenient delivery routes, and supplemental therapeutic indications.

The pharmaceutical industry is in a long-lasting structural crisis that manifests as the collective corporate inability to close—or even narrow—the earnings gap that results from the aging of top revenue-generating drugs that lose patent protection. The industry’s traditional business model, which relies on new molecular entities to feed the development pipeline and push a constant stream of new drug products into pharmaceutical markets that enthusiastically receive such improved products, is no longer working to a degree that could compensate these losses. The estimated \$45.8 billion that the US pharmaceutical industry alone has invested in research in 2009 is not generating sufficient returns.

The numerous synergizing reasons for this critical development have been under scrutiny and discussion for years, but no obvious solution has emerged. Indeed, no easy solution for the “pharmaceutical productivity crisis” can be reasonably expected, because it actually is a crisis of the entire business environment and the way the industry responds to the scientific, regulatory, and political challenges of the changes in this

environment. A new holistic business model is needed to drive the pharmaceutical industry’s revenue as well as medical progress in the 21st century; however, its design and implementation is a continuous and integrated process, not a single dramatic event.

While this process is slowly beginning to take shape, the industry has turned its attention to aspects of innovation and business development that it had always employed on occasion, but not systematically exploited before. These involve finding new uses for known active ingredients, either by repurposing them to entirely new therapeutic fields, or by leveraging modern formulation technology to significantly improve their properties—sometimes to a point that could not be achieved by new chemical entities. This report describes the options that new technologies in formulation have created (and continue to create), and explores the medical and commercial perspectives.

The first chapter sets the scene by describing the main routes of drug delivery, their individual advantages and drawbacks, and the environment in which they are deployed. It also explains that “alternative” drug delivery is not so much about fundamentally different “roads into the unknown,” but rather about new dimensions of the known routes—in other words, that the alternative is one for the active ingredient, not for the route of delivery.

Chapter 2 addresses the enabling role of medical devices in drug delivery technology. Drug-eluting vascular stents, which effectively reduced restenosis (the closure of the stent by vascular endothelial growth) from a frequent late complication of percutaneous coronary intervention to an event that now has a 5% or less probability, are presented as a case study. Other implantable drug delivery devices, either mechanical or in the form of depots, are presented as well as externally applied devices—from the needle-free injector to the irradiation device that disintegrates drug-carrying particles in the bloodstream, and to even less conventional approaches such as medicated clothing.

Chapter 3 introduces the drug delivery applications of nanotechnology, which are now integral parts of formulations in all delivery routes. In contrast to the semi-intelligent “nanomachines” that are so often mentioned in popular writing, the drug-coated nanoparticles, the drug-encapsulating liposomes and nanotubes, and the tree-like dendrimers are already very much a medical reality. When combined with the appropriate targeting moieties, they enable organ and tissue targeting, most notably to malignant tumors.

The fourth chapter discusses biological barriers and how advanced drug delivery can overcome them. Actual anatomical barriers, which tend to exclude drugs from the space they enclose and protect, exist between the peripheral circulation and the brain and the retina as well as between the outer environment and the eye; these barriers can be tricked into allowing entrance to properly formulated active ingredients that would normally be excluded. Several companies specialize in such barrier-penetration technologies. Even more important are the functional barriers that make it difficult for drugs to reach the bulk of tumor tissues. We also touch on an interesting niche field of localized drug delivery: the prevention of growth of residual bacteria and accelerated healing of periodontal pockets.

Chapter 5 deals with the particularly fascinating subject of alternative delivery modalities for biotechnology-derived drugs. Peptides, proteins, and antibodies used to be administered by injection alone, but today, solutions for inhaled, transdermal, and even oral delivery are available or under investigation for most established products. While inhalable insulins have met rough conditions in their development (as well as—in a single case—on the market), promising developments are underway for vaccines and many other biotech products. Even where these maintain the injection delivery route, the actives have been massively improved in terms of shelf life, biological half-life, and reduced immunogenicity.

Chapter 6 makes a diversion into nucleic acid delivery technologies, which are not actually “alternative” but rather initially enabling for their novel cargoes because unprotected or untargeted delivery of gene therapies or interfering RNAs is inconceivable. The full armamentarium of nanotechnology is unleashed in this emerging field, which mostly attends to cancer today but has almost universal applicability.

Transdermal delivery technology, on which we have briefly touched before, is seeing an amazing resurgence. Chapter 7 discusses the most recent developments, which include active systems where delivery through the skin is driven by microneedles or energy applied through ultrasound or even lasers. A case study on drugs for Alzheimer’s disease that had formerly been available only as tablets and have been reformulated for transdermal sustained delivery is presented. We also discuss vaginal drug delivery, currently a niche field for several reasons but with some potential for systemic delivery.

Chapter 8 brings us to the role of alternative delivery in drug lifecycle management. Two case studies exemplify how cleverly applied technologies can reinvigorate drugs that have already lost patent protection, or have not fully exploited their potential. Two

technology case studies present unique corporate technologies with broad applicability in alternative drug delivery. Such efforts make sense only if patents can be obtained for the new products, which—though a specialist task—is neither as trivial nor as impossible as is frequently believed. At the end of this chapter, we address the regulatory pathways and timelines for this process.

Chapter 9 is an extensive corporate showcase of 29 drug delivery companies, their technological approaches to the various challenges and opportunities, their pipelines, and their deals with other pharmaceutical companies. This chapter shows that a flourishing scenery of platform and “boutique” companies has developed in addition to the original major players.

Chapter 10 presents an outlook to what we call the “Preprogrammed Rise of Alternative Drug Delivery”—an unavoidable development driven by the fact that lifecycle management and recouping of value from existing resources will continue to rule the pharmaceutical industry’s business throughout the 2010s. Given the fact that launching a new formulation of a marketed drug currently returns more than twice as much for each invested dollar as does a new chemical entity, we do not believe that innovation in newly designed or discovered molecular entities, or the exploitation of new drug targets, could turn the tables on this situation within the present decade.

Using advanced drug delivery technology to intelligently reformulate marketed active ingredients is true innovation, but just as repurposing a drug for new therapeutic fields (a move that often requires reformulation), it is a different kind of innovation than the one pharma has gotten used to. As long as new chemical entity development was sufficiently rewarding from the global perspective, despite its high risk and long timelines, companies could focus on comparatively simple delivery modalities and on obvious applications and leave much of the remaining potential unexploited, and even unexplored. Today this is no longer an option. Drug repurposing and reformulation technologies can recoup such value from earlier investments in drug discovery and development, and reformulation can create entire new markets if the “old” active ingredient is now delivered in a way that addresses new patient strata. In the present environment for the industry, applying alternative delivery is essential to medical progress as well as to the economic sustainability of the pharmaceutical business model throughout the long period of restructuring that it will need in the years to come. Once an almost languishing field called “galenics,” drug formulation is a resurging and exciting field today, and it will occupy more of our attention in the future.