Commentary

New Drugs for Rare Diseases in Children

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ABSTRACT

Purpose: United States (US) Pediatric Legislation (PL) was introduced in 1997 to improve children's health. The European Union PL (EUPL) has been in force since 2007. Both PLs facilitate additional pediatric research on primarily adult drugs. The EUPL declares that the forces of the market are not sufficient for children. Without a pediatric investigation plan, new drugs can no longer be registered with the European Union. New ways on how to facilitate drug development for rare pediatric diseases are being proposed.

Methods: US PL, EUPL, and implications of modern labels for medical decision making are discussed.

Findings: Modern drug labels constituted a step from eminence-based towards data-based medical decision making. However, approval by regulatory authorities did not replace knowledge transfer in medicine, which continued in university education, through conferences, consensus papers, and so on. Children were successfully treated with off-label drugs in pediatric oncology and in many other diseases. Describing children as "therapeutic orphans" reflected an overestimation of drug labels and an underestimation of nonregulatory systematic clinical testing. Therapeutic breakthroughs have occurred, for example, in acute myelogenous leukemia and cystic fibrosis. Rare diseases need new innovative drugs and therapeutic concepts for further breakthroughs.

Implications: The focus of PL on additional pediatric measures for predominantly adult new drugs reflects a tunnel view. Similar to the introduction of modern pharmaceutical legislation that triggered comparable laws in most countries worldwide after 1962, we currently need new worldwide steps to reward innovative treatment concepts for rare diseases—not against, but through the market. Created by philanthropy, parents, and other supporters, new therapeutic concepts should be rewarded upon meeting regulatory milestones. This market is limited today. It needs not only a boost by pioneers, but also acceptance, welcome, and re-thinking about drug development in academia, politics, and by the general public. (*Clin Ther*. 2017;39:246–252)

Key words: pediatric ocology, pediatric drug development, pediatric legislation, European Pediatric Legislation, European Medicines Agenca, Creating Hope Act.

INTRODUCTION

The emergence of modern medicines has not been simple and linear. The scientific discovery of penicillin occurred well before World War II in the United Kingdom, but its industrial production did not begin until during World War II in the United States.[1] The medical revolution penicillin triggered occurred through its industrial production and worldwide availability, which was done by the chemical industry, which eventually became pharmaceutical, and then life sciences industry. Drug development gradually moved away from academic research towards profit-driven industry, establishing an imaginary boundary between noble academic research and less noble applied research and development (R&D). Medical doctors who administered life-saving

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treatment came to be perceived differently than the industry that developed new drugs. Soap operas, media, and self-perception of clinical academia maintain a romanticized world that depicts hands-on caring as positive and profit-making from developing and selling medicines as negative. The pharmaceutical industry does not have the best reputation, although it is not any more profit-driven than any other industry. Each of the main pillars of the triangle of medical progress—industry, regulatory authorities (RAs), and clinical academia—has a life of its own, but is also part of the world that is becoming global, but that is governed locally. Although companies compete in converting monoclonal antibodies, interleukin antagonists, receptor blockers, and other new concepts into new marketable compounds, basic research continues. Sometimes, new paradigms emerge, for example, new cancer concepts or the change from searching for a single "magical bullet" toward combination therapy in HIV and cancer.[2]

Modern labels were introduced in 1962 as a response to the thalidomide catastrophe, which caused thousands of children to be born with malformed arms and legs. Modern drugs could only emerge in an industrialized world. They are efficacious, but can have serious side effects, and cannot be marketed like articles of daily use without control.[1,3] RAs became an additional pillar in healthcare. Modern labels require proof of efficacy in clinical (and other) trials. Most trials are regulatory trials, sponsored by industry and executed by clinicians to obtain drug marketing approval. Drug development has been rather steady over the last few decades; it is also complex,[4] expensive,[5,6] and controversial.[7–9]

Pediatric pharmaceutical legislation (PPL) was introduced both in the United States as the Food and Drug Administration (FDA) Modernization Act[10] and in the European Union (EU)[11] driven by the desire to improve child healthcare. However, child healthcare had never been better when PPL was introduced. Adults represent a larger pharmaceutical market than children. Where children's diseases represented a sufficiently profitable market, pharmaceutical companies undertook R&D (e.g., for growth hormone, lung surfactant, or vaccines). In other areas, children also profitted as much, or even more than adults from pharmaceutical progress. The 1962 requirements for modern labels resulted, inter alia, in a new concept: off-label versus on-label treatment. Pediatricians and general practitioners treating children had now to pay attention to the legal framework. A few years after the introduction of modern labels, Dr. Shirkey, a pediatrician, coined the term "therapeutic orphans" for children to express the general concern that children were not in the focus of drug development, and referring to the danger of damage lawsuits by embittered parents if anything went wrong.[12] Doses for children were estimated using poorly or unvalidated tables and formulas. This was often adequate, but then pediatric clinical pharmacology showed that in very young children many assumptions about drug absorption, distribution, metabolism, and excretion that were the basis of tables and formulas were incorrect, making intensive testing in this age group more important than previously recognized.[13]

Two key factors changed the perception of off-label use. First, the gradual evolution of thinking that on-label means safe, whereas off-label means unsafe.[14,15] There is no true medical basis for this in the use of most pediatric or adult drug use. The transition into adulthood on the 18th birthday is a legal, not a medical transition. The body does not change overnight. However, the legal transition is a serious factor in medical decision making. Damage lawsuits brought by parents in despair, concerns by hospital administrators lacking medical expertise, and reimbursement institutions' refusal to pay are examples of how this affects medicine. The Cochran collaboration was formed to facilitate choices in health interventions based on evidence-based medicine.[16] Some enthusiastic followers believe so firmly in multicenter, randomized, double-blind clinical trials that they reject the value of common sense.[17–19] The second key factor was the emergence of PCP. Dosing in very young children is often quite different than previously thought. The conviction evolved that the more pediatric clinical trials would take place, the more children's treatment would improve.[20]

PEDIATRIC ONCOLOGY

The extraordinary successes of pediatric oncology (PO) did not emerge through the development of new drugs; rather, these successes happened by the systematic testing of existing adult chemotherapeutic compounds in children, in combination with surgery, radiation, and advances in intensive care.[21] As of 2000, this has reached a plateau.[22] PO needs further