Commentary

More Efficient Compliance with European Medicines Agency and Food and Drug Administration Regulations for Pediatric Oncology Drug Development: Problems and Solutions

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ABSTRACT

The morbidity and mortality toll of pediatric cancer affects the public health of children worldwide, but despite the gains in the fight against cancer, more progress needs to take place against this disease, which is a leading cause of death and chronic disability in children. In response, leading regulatory authorities in the developed world have been ratcheting up their efforts to induce the private sector to expand their research and development focus during drug development for adult cancers to include children. In mid-May 2016, the Center for the Study of Drug Development at Tufts University held a roundtable workshop on pediatric oncology to explore how companies could maximize the efficiency of pediatric assessment of adult cancer indications while minimizing resource expenditures to comply with regulatory requirements under the European Medicines Agency and the U.S. Food and Drug Administration. Although worldwide a child is diagnosed with cancer every 3 minutes, pediatric cancer is a rare disease, and trial participants are hard to come by. Thus, the market hardly sustains research and development expenses, advances in pharmacogenomics are not reaching down the age scale, and even in the public sector, basic research funding for pediatric cancer pales in comparison to the amount spent on cancer overall. The goal of the roundtable was to acknowledge these problems, and more importantly, to raise the level of awareness of potential solutions, including: more efficient use of the data hierarchy of informative events in clinical trials; new innovative clinical trial platforms for rapid assessment of new drugs in children; new developments in formulation technology; and optimization of speed in pediatric drug development through a multi-stakeholder network collaboration separate from the adult development plan. (*Clin Ther*. 2017;39:238–245) © 2017 Published by Elsevier HS Journals, Inc.

Key words: pediatric studies, oncology, EU &US regulations, roundtable summary.

INTRODUCTION

Worldwide each year, almost 100,000 children die from cancer before the age of 15 years, >90% of them in resource-limited countries.[1] Cancer is also the leading cause of death in children after accidents in the United States and Europe.[2] In 2014, an estimated 16,000 children (age: from birth to 19 years) were diagnosed with cancer in the United States,[3] compared with >1.6 million cancers diagnosed overall in 2016.[4] Yet, on the whole, pediatric cancer thankfully is a rare disease. Therefore, trial participants are hard to come by, and like most pediatric disease areas, such a small market hardly sustains research and development (R&D) expenses,[5] providing a relatively small incentive to

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invest in R&D for new treatments. These circumstances consist of a crucial "Catch 22" for the biopharmaceutical industry—a deadly disease in the most vulnerable patient populations, highly rewarding in terms of societal goodwill and promotion of the public health, but low priority in terms of return-on-investment. Recognizing these hard facts, and the failed history of past attempts to coerce industry to remedy this situation through compulsory regulation, pediatric health advocates in the United States pushed through a voluntary incentive program under the Best Pharmaceuticals for Children Act (BPCA) of 2002 (Public Law 107-109), which together with mandatory requirements under the Pediatric Rule, which eventually became the Pediatric Research Equity Act (PREA) of 2003 (Public Law 108-155), make up the "carrot-and-stick" program administered by Food and Drug Administration (FDA).

A few years later, Europe put together a similar program. However, for certain disease areas, such as cancer, the voluntary incentives have not been sufficiently attractive to overcome a number of commercial and technical disincentives in the view of industry. Results have been seen by some as equivocal; in the European Union, for example, of 26 oncology drugs approved during a recent 5-year period that had mechanisms of action potentially relevant for pediatric cancer, only 4 were approved for use in children,[6] whereas in the United States from 1998 to 2012, there were 466 pediatric labeling changes, but only 15 for oncology.[7] Therefore, the agencies have begun to double-down on the mandatory component of the incentive program.

In mid-May 2016, the Center for the Study of Drug Development of Tufts University School of Medicine (Tufts CSDD) held a workshop entitled, "Pediatric Oncology Drug Development: Maximizing Efficiency While Complying with FDA & EMA Regulations."[8] The workshop was held in Boston and attended by nearly 40 invited participants from small and large biopharmaceutical companies, academic medical centers, government institutes, and R&D service providers. The primary focus was on maximizing efficiency while minimizing resource expenditures for pediatric drug development, conducted to comply with the regulations under the European Medicines Agency (EMA) and the FDA. Over the years, these regulations have become increasingly complex (Figure 1), at the same time that regulatory agencies are becoming increasingly emphatic in their implementation. The EMA published the findings of its review of the class waiver list for required pediatric assessments in July 2015. As a result of this, it revoked 8 class waivers and updated 15 class waivers. Some of the most significant changes were in the area of oncology, in which, for example, waivers were revoked for kidney and renal pelvis cancer, as well as liver cancer.[9] According to the Paediatric Committee of the EMA, the previous class waiver list had resulted in "insufficient opportunities" for the agency to consider the potential benefits of some new medicines for children.[10]

Most companies will conduct pediatric studies under one or all of the regulatory schemes depicted below – the mandatory US pediatric assessment (PSP, PREA), the voluntary incentive (BPCA) and/or the mandatory EU requirement (PIP – Pediatric Investigation Plan) with variations in the scope and timing of submissions for plans and study reports.

For its part, the FDA has been active as well. In July 2016, it published its Report to Congress on the progress of the BPCA and PREA under Food and Drug Administration Safety & Innovation Act (FDASIA) (the latest iteration of the Prescription Drug User Fee Act [PDUFA V], which contained several provisions intended to fill perceived gaps in the pediatric studies initiative, pediatric oncology being one of them). This report stated that: since the enactment of Food and Drug Administration Safety & Innovation Act (FDASIA) (mid-2012), there have been a number of advances in the pediatric oncology arena, including 6 new drugs, 21 oncology products in clinical trials, and 12 new Written Requests (permission from the FDA for a company to initiate pediatric trials of adult drugs under the BPCA).[11]

Such results surprised no one because trickle down effects from the impact of the regulations on the overall R&D environment for pediatric oncology studies were anticipated, mainly because there is so much R&D in adult cancer, as seen in Table I, which is based on an analysis from Tufts CSDD New Marketed Products Database.

Output from R&D in the field of oncology has reached dramatic levels, which is at 21% of total new molecular entities for all diseases over the last decade. This is not new news, cancer remains second only to heart disease as the number 1 cause of mortality in the United States,[12] and it is the number 1 health threat for years-of-life lost.[13] Yet the disparity between the therapeutic output for pediatric cancer and adult