IOM Review of FDA-Approved Biologics Labeled or Studied for Pediatric Use

abstract

BACKGROUND: Studies have examined the extent to which public policies such as the Best Pharmaceuticals for Children Act have increased pediatric information in drug labeling. Little attention has focused on pediatric labeling of biologics. This analysis examines the extent to which biologics are labeled for pediatric use or have been studied in children.

METHODS: The analysis covers the 96 biologics (excluding vaccines) that were first licensed by the Food and Drug Administration between 1997 and 2010 and were still marketed as of 2010. Product labeling was consulted for information on approved pediatric uses, pediatric studies, or pediatric safety warnings based on analyses of adverse events. The online database ClinicalTrials.gov was searched for registered pediatric studies of these biologics. A separate analysis examined labeling and studies for 55 vaccines.

RESULTS: For ∼60% of the 96 biologics, labeling shows approved pediatric use or pediatric study information or both. Approximately 85% of the biologics have ≥1 registered pediatric trial completed, underway, or planned. Overall, ∼90% are labeled for pediatric use, have pediatric information in the label, have a registered pediatric study, or have some combination of these characteristics. For the 55 analyzed vaccines, the corresponding figure is 95%.

CONCLUSIONS: A majority of biologics approved in the past 15 years include some pediatric information in their labeling, and pediatric trials have been registered for a substantial majority of these products. Pediatrics 2013;131:328–335

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KEY WORDS biologics, pediatrics, drug safety, clinical research/trials

ABBREVIATIONS

BPCA—Best Pharmaceuticals for Children Act
CBER—Center for Biologics Evaluation and Research
CDER—Center for Drug Evaluation and Research
FDA—Food and Drug Administration
HBIG—hepatitis B immune globulin
IOM—Institute of Medicine
IVIg—intravenous immunoglobulin
PREA—Pediatric Research Equity Act

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For more than a century, biologics in the form of preventive vaccines and antitoxins have been common and central elements of care to protect and improve the health of children.1 In the early and middle decades of the 20th century, research yielded new biologics such as insulin, growth hormone, and anti-hemophilic factors.2–4 More recent scientific and technological advances have led to innovative or significantly modified biologic products to treat a range of serious conditions, many of which affect both children and adults. These conditions include enzyme deficiency disorders, inflammatory diseases such as rheumatoid arthritis, and infections such as hepatitis C.5–7 Harms to children from defective products were major stimuli for the regulation of drugs and biologics beginning in the early 1900s, but testing of products for safety and efficacy in pediatric age groups has lagged behind testing in adults.8,9 In the late 1990s, Congress and the Food and Drug Administration (FDA) responded by creating both requirements and incentives for pediatric studies of drugs. These were later incorporated in the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA).10,11 The requirements that are today part of PREA applied to biologics from the outset. In 2010, Congress extended the incentives of BPCA (ie, 6 months of additional marketing protection for the completion of requested pediatric studies) to biologics, although implementing regulations and guidance have not yet been issued.12 FDA staff have reported on the contribution of BPCA to pediatric labeling of drugs,13 but the extent to which biologics have been approved for pediatric use or studied in children has not been systematically assessed. In 2011, consistent with provisions of the Biologics Price Competition and Innovation Act,14 the FDA asked the Institute of Medicine (IOM) to identify, among other tasks, biologics that had not been studied in children. In 2012, an IOM committee reported its findings,15 which are summarized and expanded here with additional data and commentary.

METHODS

On the basis of statutory definitions amended in 2010, the FDA classifies vaccines, antitoxins, blood and blood components, tissues, allergenics, proteins (except chemically synthesized polypeptides), and similar products as biologics.16 Biologics may comprise macromolecules (sugars, proteins, nucleic acids, or combinations of these) or may be living entities such as cells and tissues. They are included within the regulatory definition of a drug, but they typically are more complex in their structures and manufacturing processes than conventional, chemically produced drugs.16

Because FDA documentation is limited for older biologics, this analysis focused on products that were first approved by FDA between January 1, 1997, and December 31, 2010 and that were still marketed as of the latter date. It excluded reagents, assays, and similar products; allergenic products such as patch tests and extracts; and vaccines, which were analyzed separately. In addition to FDA assessments under PREA, pediatric needs for vaccines are a major focus of other federal activities, including the National Vaccine Program.

For biologics regulated by the Center for Drug Evaluation and Research (CDER), FDA staff provided an initial list of products compiled from the Web site Drugs@FDA17; they then reviewed the final edited list. For products regulated by the Center for Biologics Evaluation and Research (CBER), FDA staff verified a list compiled by IOM staff from a CBER Web site that identifies biologics with publicly available supporting documents (eg, approval letters).18 The final list of products included 96 biologics. The separate analysis of vaccines included 55 products for which FDA has posted supporting documents.

For each identified product, the current labeling (also called prescribing information or package insert) was consulted to determine whether the product was labeled for pediatric use, included information in the labeling from pediatric studies; or had safety warnings about pediatric use based on FDA analyses of postmarketing reports of adverse events. The primary examination of product labeling was undertaken in July and August 2011.

In addition, ClinicalTrials.gov, the congressionally mandated registry of publicly and privately supported clinical trials, was searched for completed, ongoing, or pending studies that included pediatric age groups.19 For each biologic, the search strategy included the generic name (what FDA terms its proper name), the brand name, and “child,” which the registry defines as birth through age 17. Studies with a lower age limit of 16 were excluded from the analysis. For the listings generated by the search, more detailed trial descriptions were reviewed to verify whether children actually were eligible and whether the study involved the brand name product. For some products with multiple studies involving the same condition, age range, and phase and for some similar products (eg, intravenous immunoglobulins [IVIgs]) for which brand names were frequently not noted in study descriptions, studies were grouped for the final analysis. The registry database includes studies undertaken before federal registration requirements. For products without pediatric information in the label and without registered pediatric studies, additional information sources were consulted (primarily the PubMed database). The main search of trial listings took place between August and December 2011.
RESULTS

Pediatric Labeling

Approximately 60% (59 of 96) of the biologics examined are labeled for pediatric use (47 or 49%), have some information in their labeling based on pediatric clinical studies (10 or 10%), or only include safety warnings based on FDA analyses of adverse event reports (2 or 2%; Table 1). For most of the remaining products, the labeling states only that safety and efficacy in pediatric populations have not been established. Labeling for a few of the latter products includes safety warning based on nonclinical information such as animal studies. For example, labeling for denosumab (Prolia, Amgen, Thousand Oaks, CA) warns against pediatric use, citing studies in rats and primates that showed impairment in bone growth and dentition.20 For products without approved pediatric uses but with study information in the labeling, the labeling may report pharmacokinetic data, negative safety or efficacy studies, or inconclusive results.

Table 2 presents examples of selected categories of biologics and their FDA-approved uses with children. Some products, such as clotting factors and many vaccines, have had pediatric uses approved from the outset. Although none have yet been approved for marketing, gene therapies with pediatric uses are anticipated.

Labeling does not always explicitly state that a product is indicated for use with children. That such use is indicated may, however, be clear given other information (eg, specific dosing instructions for children as in the labeling for basiliximab [Simulect, Novartis Pharmaceuticals Corporation, East Hanover, NJ], an immunosuppressive agent used for patients undergoing renal transplantation).044

Registered Pediatric Studies

Of the 96 biologics in this analysis, a sizeable majority (81 or 84%) is the subject of registered pediatric trials (Table 1). Two biologics without registered pediatric studies, both hepatitis B immune globulins (HBIG) (HepaGam B [Cangene Corporation, Winnipeg, Canada] and Nabi HB [Biotest Pharmaceuticals Corporation, Boca Raton, FL]), are labeled for pediatric use on the basis of previous studies of another HBIG product.38,45 CDER-regulated products are somewhat more likely than CBER-regulated products to have registered pediatric trials, possibly reflecting the higher proportion of CBER products that are already approved for pediatric use or have pediatric study information in the labeling. Most products have a mix of industry and non–industry funding of studies.

Most products with a registered pediatric study (71 of 81 [88%]) are the subject of >1 study, some for a single indication and some for multiple indications. Multiple studies for multiple indications are particularly common for the IVIgs and certain of the monoclonal antibodies.

That children are eligible for a trial does not, however, guarantee that enough children will in fact be studied to support conclusions about safety and efficacy, particularly for a study with a broad age range that includes adults. (Of the 370 trial entries examined in this analysis for which children were eligible, almost half [172] specified no upper age limit or an upper age limit of ≥40 years.) The FDA has approved pediatric labeling of biologics based on studies with small numbers of pediatric subjects, for example, 11 children and adolescents among 46 subjects described in the labeling for the IVIg Octagam 5% (Octapharma USA, Inc, Hoboken, NJ).46 In contrast, the labeling for the IVIg Flebogamma, 10% (Grifols Biologicals, Inc, Los Angeles, CA) states that the clinical trial of the product includes too few children (2) and adolescents (1) among the 46 subjects studied to establish efficacy and safety in that population.47

Some trial listings include links to published results. Overall, however, the required reporting of results through the ClinicalTrials.gov Web site has lagged behind expectations.48 To increase public access to study data as evaluated by FDA staff, the IOM committee proposed that FDA explore with National Institutes of Health the inclusion of FDA scientific reviews in the PubMed and ClinicalTrials.gov databases.

Table 1 Biologics First Approved Between 1997 and 2010 With Pediatric Information in Labeling or Pediatric Studies Listed at ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Status of Products</th>
<th>CDER n = 57</th>
<th>CBER n = 39</th>
<th>All n = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Products with pediatric information in labeling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labeled for pediatric use</td>
<td>30 (53)</td>
<td>29 (74)</td>
<td>59 (61)</td>
</tr>
<tr>
<td>Not labeled for pediatric use but with pediatric study information</td>
<td>23 (40)</td>
<td>24 (62)</td>
<td>47 (49)</td>
</tr>
<tr>
<td>Safety warning only (based on adverse event data)</td>
<td>5 (9)</td>
<td>5 (13)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Products with at least 1 registered pediatric trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry funded studies only</td>
<td>50 (88)</td>
<td>31 (78)</td>
<td>81 (84)</td>
</tr>
<tr>
<td>Non–industry-funded studies only</td>
<td>13 (26)</td>
<td>11 (35)</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Both industry and non–industry-funded studies</td>
<td>2 (4)</td>
<td>3 (10)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Totals: products with pediatric information in labeling or registered pediatric trials or both</td>
<td>50 (88)</td>
<td>35 (90)</td>
<td>85 (88)</td>
</tr>
</tbody>
</table>

Analysis does not include reagents, assays, and similar products; vaccines; allergens; and products no longer marketed as of December 31, 2010.
Table 2: Examples of Biologics Approved for Use With Children

**Therapeutic enzymes**
- Enzyme replacement therapy is used in diseases where enzyme functional activity, production, or storage is deficient. Since alglucerase (Ceredase, Genzyme Corporation, Cambridge, MA) was approved in 1991 as the first such therapy for a lysosomal storage disease (Gaucher disease), additional products approved for pediatric use include agalsidase β (Fabrazyme, Genzyme Corporation, Cambridge, MA) and galsulfase (Naglazyme, Biomarin Pharmaceutical Inc, Novato, CA).

**Toxins**
- Botulinum toxins, which can inhibit involuntary muscle activity for an extended period of time, have an increasing role in the treatment of neuromuscular disorders, many of which are refractory to conventional pharmacologic and surgical treatment. One older product, onabotulinumtoxin A (Botox, Allergan, Inc, Irvine, CA), is approved for pediatric use for blepharospasm or strabismus. This product and others are the subjects of pediatric studies for various conditions (see Table 3).

**Therapeutic cytokines**
- Therapeutic cytokines may be used to help evoke an immune response in conditions such as certain immune deficiency disorders or viral infections. Products approved for pediatric use include interferon γ-1B (Actimmune, InterMune, Inc, Brisbane, CA) for treatment of chronic granulomatous disease and osteopetrosis and peginterferon alfa-2A (Pegasys, Hoffman-La Roche, Inc, Nutley, NJ) and peginterferon alfa-2B (Pegintron, Schering Corporation, Whitehouse Station, NJ), which are approved for treatment of hepatitis C in adults and children.

**Monoclonal antibodies**
- Many biologics approved since 1997 are monoclonal antibodies, which are targeted therapies that bind to specific antigens and block certain immune system responses. Several are labeled for use with children, including adalimumab (Humira, Abbott Laboratories, North Chicago, IL) and tocilizumab (Actemra, Genentech, Inc, South San Francisco, CA), both approved for treatment of juvenile idiopathic arthritis.

**Other immunobiologics**
- Many immunobiologics are FDA-approved for prevention of diseases affecting children (e.g., measles, chicken pox, meningitis, diphtheria, tetanus, pertussis). Others are approved for pediatric use:
  - **Vaccines**: Products that use antigens to induce active immunity. Vaccines may be live attenuated or inactivated. Examples of vaccines used in children include those for hepatitis B, pneumococcal, and varicella infections.
  - **Toxoids**: Inactivated bacterial toxins that induce production of antibodies against the toxin. These also induce active immunity and include products such as diphtheria and tetanus toxoids, which are often grouped with vaccines.
  - **Antitoxins and Antivenoms**: Products used as antidotes to plant and animal toxins. One botulinum antitoxin approved by FDA (BabyBIG, Baxter Healthcare Corporation, Westlake Village, CA) was developed by the California Department of Health for treatment of infant botulism. Although FDA has approved other botulinum antitoxins for use with adults, they are no longer marketed.
  - **Immunoglobulins**: Products derived from human blood and provide passive immunity for a wide variety of indications. Those specific to an infection are termed “anti-infective” and nonspecific products are termed “broad spectrum.” An example of the former is an HBIG (Nabi HB, Biotech Pharmaceuticals Corporation, Boca Raton, FL) that is used to prevent hepatitis B infection in newborns born to infected mothers. An example of a broad spectrum product is Gamunex-C (Talecris Biopharmaceuticals, Inc, Research Triangle Park, NC), which is approved to treat primary humoral immunodeficiency and idiopathic thrombocytopenic purpura in pediatric patients.

**Clotting factors**
- Both plasma-derived and genetically manufactured coagulation factors are used for factor replacement in disorders such as von Willebrand disease and hemophilia. The first recombinant factor VIII concentrate was licensed by FDA in 1992, and several such products are now approved for use in children and adults with hemophilia.

**Fibrin sealants**
- Since 1998, the FDA has approved several of these recombinant or human-derived products containing fibrinogen and thrombin. Two human-derived fibrin sealants are licensed for pediatric use: Artiss (Baxter Healthcare Corporation, Westlake Village, CA) to promote adherence of skin grafts in burn patients and Evicel (Omrix Biopharmaceuticals, Ltd, Kiryat Ono, Israel) to limit bleeding during surgery.

**Products With No Labeling Information and No Registered Studies**
- Of the 11 products without pediatric labeling or registered pediatric studies, 4 are similar to (e.g., have the same generic name) other products that have pediatric labeling or pediatric studies (Table 3). Most of the other 7 products are approved for indications that are rarely or never diagnosed in children, for example, prostate cancer or chronic refractory gout.

**Labeling and Study Registration for Vaccines**
- Of the 55 vaccines identified in a separate analysis, only 3 (5%) are neither labeled for pediatric use nor the subject of pediatric studies that are registered at ClinicalTrials.gov. Several vaccines (e.g., those for rotavirus and combination vaccines for diphtheria, tetanus, and pertussis) are labeled exclusively for pediatric use.

One of the 3 vaccines with neither pediatric labeling nor registered studies is an adenovirus type 4 and type 7 that was developed under contract with the US Department of Defense for use with military personnel ages 17 to 50 years. Another is a vaccine for persons at high risk of anthrax exposure. For both, FDA waived required pediatric studies on grounds of impossibility or impracticality. The agency waived pediatric studies for the third vaccine, which is approved for the prevention of shingles, because the product did not offer a meaningful therapeutic benefit over alternative products for children and was not likely to have substantial use in this population.

**DISCUSSION**
- Some of the registered studies identified in the current analysis should, when completed, result in the addition of pediatric labeling information for biologics that now lack it. In addition, some products that have not yet been studied in children may attract future...
investigation if expanded knowledge of their mechanism of action or other scientific advances suggests promise for conditions that affect children. At the same time, some biologics may never be studied in children, for example, if newer drugs or biologics have mostly supplanted a product or if no plausible pediatric uses are identified for investigation. Moreover, some planned or ongoing trials may be terminated on the basis of inadequate enrollment, changing sponsor priorities, newly recognized safety concerns, or other reasons. Studies also may not extend to all relevant pediatric age groups. Even when FDA requires pediatric studies, they may not be initiated or completed in a timely way. FDA does not report data separately for drugs and biologics, but in 2011, 19% of pediatric studies required under PREA (79 of 420 studies) were described as delayed (ie, behind the original schedule).70

To what extent has PREA contributed to pediatric studies of biologics and the addition of pediatric information to product labeling? Answering this question is not straightforward. One limitation is that Congress has not required the FDA to identify and post relevant documents for all PREA-related labeling changes involving biologics; public posting is only required for products with labeling changes made since September 27, 2007, as required by the FDA Amendments Act.71 Moreover, because FDA approval letters for biologics, particularly letters issued several years ago, do not routinely mention PREA requirements and because letters for some products are not publicly available, it is difficult to reliably identify older products with PREA-related studies. Another limitation is that the FDA did not initially require that study results be submitted by means of supplemental licensing applications, which are more readily retrievable by FDA than less formal submissions. In addition, the incentives of the Orphan Drug Act, which provide 7 years of marketing protection and are thus stronger than the incentives of BPCA, have likely encouraged some studies of products for rare conditions that affect children.72 Products with orphan drug designations (whether approved for that designation or not) are exempt from PREA requirements, but the

**TABLE 3** Biologics Approved Between 1997 and 2010 That Have No Indication of Pediatric Studies in Labeling or Clinical Trials Registry (ClinicalTrials.gov)

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>Autologous Cultured Chondrocytes (Carticel, Genzyme, Cambridge, MA): approved in 1997 for repair of cartilage defects of the femoral condyle caused by acute or repetitive trauma in patients who have had an inadequate response to a previous arthroscopic or other surgical repair procedure.</td>
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<tr>
<td>Pegloticase (Krystexxa, Savient Pharmaceuticals, East Brunswick, NJ): treatment of chronic gout in refractory to conventional therapy, a condition not likely to be diagnosed in children.</td>
<td></td>
</tr>
<tr>
<td>Tositumomab and iodine I 131 tositumomab (Bexxar, GlaxoSmithKline, Research Triangle, NC): treatment of non-Hodgkin’s lymphoma that is refractory to Rituximab and has relapsed after chemotherapy. Although the 2004 approval letter for the product does not mention pediatric study requirements, the sponsor has an orphan drug designation for this indication.</td>
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</tr>
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Products with orphan drug designations (exempt from pediatric study requirements)

- **Collagenase Clostridium Histolyticum (Xiaflex, Auxilium Pharmaceuticals, Malvern, PA):** treatment of Dupuytren's contracture, which is rare in children.61
- **Pegloticase (Kryextxa, Savient Pharmaceuticals, East Brunswick, NJ):** treatment of chronic gout in refractory to conventional therapy, a condition not likely to be diagnosed in children.62
- **Tositumomab and iodine I 131 tositumomab (Bexxar, GlaxoSmithKline, Research Triangle, NC):** treatment of non-Hodgkin’s lymphoma that is refractory to Rituximab and has relapsed after chemotherapy. Although the 2004 approval letter for the product does not mention pediatric study requirements, the sponsor has an orphan drug designation for this indication.64

Products for which FDA waived pediatric study requirements

- **Interferon Alfacon-1 (Infergen, Boehringer Ingelheim, Biberach, Germany):** treatment of chronic hepatitis C in patients with compensated liver disease. In waiving pediatric studies, FDA explained that the product did not offer a meaningful therapeutic benefit over current therapies and was unlikely to be used by a substantial number of pediatric patients.65
- **Sipuleucel T (Provenge, Dendreon Corporation, Seattle, WA):** treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer. FDA waived pediatric studies because the condition is unlikely to occur in children.66
The majority of orphan drug approvals involve conditions that affect children.\(^7\)\(^3\)\(^,\)\(^7\)\(^4\)

Notwithstanding these complexities, it seems reasonable that the requirements of PREA and its predecessor policies have prompted pediatric studies that would not otherwise have been undertaken for products aimed at conditions most often found in adults but also affecting children. Although this analysis does not allow for direct comparisons with previous analyses involving conventional drugs,\(^13\)\(^,\)\(^7\)\(^5\) the extent of pediatric labeling of biologics appears roughly equivalent or possibly somewhat greater.

The extension to biologics of incentives for pediatric studies under BPCA could encourage additional pediatric studies. It is not yet clear, however, when or how those incentives will actually be available to either previously approved or newly approved biologics. In implementing the 2010 legislation that included this extension, FDA has focused on other issues, in particular, the drafting of guidance and regulations on the approval of products that are bio-similar to or interchangeable with an already licensed biologic. (Section 351 (i)(2) of the Public Health Service Act states that a biosimilar product “is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” In draft guidance, the FDA specified a higher standard for designating a product as interchangeable, essentially that “the product can be expected to produce the same clinical result as the reference product in any given patient” and that the risk associated with switching from 1 product to another is not greater than using the same product repeatedly for the same patient.\(^7\)\(^9\)

Important as it is, product labeling in itself is not an appealing vehicle for the direct dissemination of information to clinicians who treat children. Details about any pediatric studies or safety data are usually dispersed in several sections of a product’s labeling (eg, clinical pharmacology, clinical studies, warnings and precautions). In addition, labeling, especially for older products, is sometimes ambiguous. Rather than consult FDA-approved labeling, clinicians typically use various intermediary resources, for example, Micromedex\(^7\)\(^7\) and Lexicomp\(^7\)\(^8\) that incorporate information from product labeling as well as other sources.\(^7\)\(^9\) For these intermediaries and others, the structured labeling format adopted by the FDA in 2006 and other actions have improved the clarity of labeling; for example, labeling now includes an introductory highlights section and a table of contents that cites pediatric use and key safety warnings.\(^3\)\(^0\) Clinicians may also consult the published literature on specific products or classes of products.

Overall, this analysis indicates substantial investigation of pediatric uses of biologics by government, industry, and nonindustry sponsors of research. Such investigation has led to the inclusion of pediatric information in the labeling of the majority of biologics approved between 1997 and 2010; studies now planned, underway, or recently completed may lead to additional labeling changes. Most of the products with neither pediatric labeling nor registered pediatric studies are approved for indications that are rare or not diagnosed in children.

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