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Generic and therapeutic orphans

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This commentary discusses the need to develop methods to ensure the availability of non-profitable, off-patent medicines to children and other populations. The history and some of the shortcomings of legislative attempts to provide drug therapy to children are briefly reviewed. Some examples of the inability of the current generics and non-generics pharmaceutical industry as well as the current development and drug production system to adequately respond to the needs of children and other 'orphan' populations are then discussed. Finally, some potential solutions are mentioned.

Keywords: Off-patent drugs, orphan, paediatric

A decade ago Dr Harry Shirkey coined the term 'therapeutic orphans' to describe the plight of children as a result of the drug development, labelling and marketing process [1]. While the situation has improved somewhat for children over the last decade, inadequate paediatric drug development continues despite major legislative, infrastructure and scientific advances.

Legislative initiatives, initially in the US and later in Europe and other countries, have done perhaps the most to improve paediatric drug development and use. These include parts of the FDA Modernization Act (FDAMA) and the Best Pharmaceuticals for Children Act (BPCA, Title V of Public Law 110-85) which provided financial incentives for testing of on-patent drugs in children. Additional improvements came as a result of the Pediatric Research Equity Act (PREA, Title IV of Public Law 108-155) which gave FDA the authority to mandate some paediatric testing. While there is support to make these temporary initiatives permanent, they are subject to legislative renewal every five years—next in September 2012 along with renewal/revision of the

Prescription Drug User Fee Act [2]. This combination of incentives and mandates have begun to produce more paediatric data, clinical trial infrastructure, paediatric friendly formulations and drugs especially for on-patent, brand name drugs labelled for paediatric use [3]. The success of these initiatives is likely to have encouraged the EU to develop similar, improved, and more permanent programmes to encourage the development of both on- and off-patent paediatric drugs [4].

Despite major legislative, pharmaceutical and medical advances in the development of products to treat children, there remain patient populations underserved by current drug development processes. The goal of this brief commentary is to stimulate discussion of possible solutions to these problems especially as they relate to the generic drug industry.

The generics industry has been very effective in developing products to compete with or even to improve the availability and testing of profitable drug products. However, the generics industry has done little to make non-profitable off-patent drugs available at any price.

There are a few examples of private, e.g. Gates and Clinton Foundations; and public-private partnership programmes, e.g. the not-for-profit Novartis Coartem malaria initiative; that target infectious diseases seen mainly in the developing world [5], that are designed to make drugs available even when there is no potential for profits. There is also an off-patent programme run by the National Institute of Child Health and Human Development (NICHD), and an EMA programme, both of which will be described briefly. However, too little is done to either encourage or mandate the testing, improvement or labelling of unprofitable, off-patent drugs. In fact, there are growing problems just maintaining the availability of such off-patent drugs.

There are many patients, both children and adults, in the developed as well as developing world who are treated with off-patent drugs for which generic versions are simply not being developed. These include drugs that were either: never adequately tested to allow marketing approval today; that do not represent enough of a market to stimulate generic drug development; or are not produced in appropriate formulations.

There are some programmes for the development, testing, production and marketing of 'new' treatments for rare, 'orphan' diseases for which no effective therapies are available [6]. These programmes target a different, although related, problem which is beyond the scope of this commentary.

This commentary calls attention instead to marketed, apparently effective, off-patent drugs for which little or no generic drug development occurs. These include drugs which need new formulations developed, of which drug shortages occur, or production even stops and for which neither the brand nor generic drug industries have adequately addressed.

Of the many possible examples, only bromides, valproic acid, and the drugs tested by the NICHD off-patent BPCA testing programme will be mentioned briefly to illustrate some of the problems with the current, economically driven, drug development process.

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Bromide was first described by Sir Charles Locock in 1857 [7], as an effective treatment for seizures [8]. It is still used in veterinary medicine [9, 10] where it is available in solid and liquid dosage forms. Unfortunately, central nervous system and dermatologic toxicity, but not lack of efficacy, was a major problem with its use in humans. It is beyond the scope of this article but much if not most of its toxicity was the result of improper dosing. Because of its extremely long half-life (weeks), it should be dosed using a single loading dose followed by very small, infrequent (perhaps weekly) dosing. However, bromide can be very effective. Until about 20 years ago it was used successfully to treat patients with seizures resistant to other available, traditional anti-epileptic drugs (AEDs). However, then a number of new AEDs were developed [11] and a number of older AEDs had generic versions developed. There was and continues to be no incentive for either brand or generics manufacturers to test bromide adequately to obtain marketing approval. Because of this it became essentially impossible to obtain bromide, even for patients whose seizures were totally responsive only to bromides. No 'sponsor' was willing to test, manufacture or sell bromide; and practitioners were unwilling or unable to complete and keep up with the FDA investigational new drug paperwork required to allow its investigational use in patients. In addition, marketing of both the older, generic drugs but especially the newer, more expensive, brand name drugs to physicians was extensive. These newer drugs had the advantage of both expensive, rigorous scientific testing data and well-funded marketing programmes. It became essentially impossible to test the reasonable hypothesis that there are patients whose seizures are responsive only to bromide. It is possible but highly unlikely that funding from public, non-commercial sources could be obtained and there is absolutely no incentive for any for-profit company to perform such testing for a treatment that cannot be patented even if expensive human testing were completed.

This is analogous to the situation that existed when valproic acid was discovered to be an effective AED [12]. Valproic acid remains one of the most effective AEDs and is used in other neuro-psychiatric conditions, but it was tested and marketed in the US only because of a unique, National Institutes of Health (NIH) funded AED development programme.

The generics industry has been very effective in developing and getting approved new, usually cheaper generic versions of commercially viable brand name drugs. Neither the brand name nor generic drug industries have done much to improve the testing, formulation and labelling of non-profitable off-patent drugs for either new indications or new, small patient populations. Only when there is enough of a patient/disease population to guarantee profits is there any chance that the testing necessary to find new indications or develop new formulations will be performed.

The BPCA off-patent drug development programme [13] was developed in an attempt to deal with one of the underserved 'orphan' populations; paediatric patients. The BPCA included language to allow the NIH to do such testing and formulation development using funds that were promised to be donated to an NIH foundation by the brand name pharmaceutical industry. The amounts actually donated are totally insufficient to fund even this small programme and no funds have come from the generics industry. Therefore this programme is funded using existing NIH funding (always uncertain). There are no provisions for non-voluntary, brand or generics pharmaceutical industry support for this activity.

This NIH funded programme is designed to obtain the information necessary for FDA approval to market and label products for small, mostly paediatric populations. It is hoped that once such data are available, at no cost, industry partners will be found who will be willing to market these products. This is essentially the model that was used successfully by the NIH to develop both valproic acid as well as many of the newer anticonvulsants. Unfortunately, this is an extremely small and underfunded programme compared to the problems it is attempting to solve.

The BPCA programme uses a complicated, evolving system to prioritise drugs for study based on frequency of use in the paediatric population, severity of the conditions being treated and the potential for providing a health benefit in the paediatric population. The list of drugs needing study greatly exceeds the minimal resources available but illustrates the wide range of drug treatments for which the current drug development process

does not adequately serve all paediatric populations.

A listing of recently prioritised drugs [14] illustrates the scope of this issue and includes such routinely used products as antibiotics (clindamycin, doxycycline, tetracycline, trimethoprim-sulfamethoxazole, benzathine penicillin G, ampicillin, griseofulvin, and Tb drug formulations), cardiac drugs (hydrochlorothiazide, ACE-inhibitors, beta-blockers, and sodium nitroprusside), asthma drugs (albuterol and delivery devices), anaesthetic/sedative agents (ketamine, isoflurane, and lorazepam), treatments for possible terror attacks (pralidoxime and antibiotics), cancer drugs (13-cis-retinoic acid, methotrexate, vincristine, daunomycin, actinomycin-D, prednisone/prednisolone, dexamethasone, methylprednisolone, and dexamethasone), psychiatric drugs (lithium and atypical antipsychotics), neurologic drugs (baclofen), neonatal drugs (betamethasone, opiates and meropenem), hydroxyurea for sickle cell disease, hydroxychloroquine for connective tissue diseases, and metoclopramide for reflux. The development of new drug formulations is a related, important need which is also beyond the scope of this commentary [15, 16].

The EU through its EMA developed the paediatric-use marketing authorisations (PUMA) legislation to deal with this problem. As part of its legislation designed to develop paediatric drugs, EMA approved legislation to deal with the failures of generic paediatric drug development. The centralized PUMA programme was just launched with the granting of the first PUMA approval, for Buccolam (midazolam, oromucosal solution) to ViroPharma, Inc [17]. While too soon to be certain how well this will work, it is important to note some very powerful aspects of this European initiative. This programme allows for: a) ten-year data protection/exclusivity for developed generic drugs; b) use of the original brand name by the generics developer (with a superscript P); and c) use of the innovator's brand label and claims without requiring permission of the innovator. These mandates have the potential to greatly increase development of needed generics products. A priority listing of off-patent drugs for which studies are suggested has been posted [18]. The much greater success of the EMA paediatric on-patent drug development process compared to the

off-patent, generics process is illustrated by the EMA 2010 report (ec.europa.eu/health/human-use/paediatric-medicines/developments/index_en.htm).

A different, important but related problem with generic drugs which is also beyond the scope of this commentary is that of drug shortages. The number of drug shortages reached a record number (178) in 2010 which is three times the numbers there were in 2005 (61) and 2006 (58). For details, visit www.fda.gov/drugs/drugsafety/drugshortages. Shortages have included cancer drugs, anaesthetics, opiates, antibiotics, and important, emergency 'sterile injectables' which are 'crash cart' drugs. While not all were generics products and the result of a variety of reasons including FDA recalls, supply chain and manufacturing problems, the number, importance, and range of products for which shortages exist indicate major problems. Responses to such shortages can be prompt for products for which large profits exist. It is not so clear that responses are as prompt for low profit drugs such as those used in small, less profitable populations. It is also at least possible that as profits for brand name products are eroded by generics competition that the ability of companies to respond to such shortages might decrease.

There are clearly problems with the current drug development process which are not being adequately addressed by either the brand name or generics industries. Processes are needed that increase the testing, formulation development, marketing and reliable production of minimally profitable drugs. It is hoped that methods will be developed to induce or mandate changes so that small, non-profitable patient populations will benefit from the advances in pharmaceutical drug development that benefit larger, more profitable populations.

Current systems do not work well when markets are small or when marketing exclusivity is unavailable or unprofitable. In such situations it is highly unlikely that: a) new treatments will be developed; b) testing to prove old products are effective will be done; c) new formulations will be created; or d) less profitable treatments will continue to be marketed or even made available.

There is a need for a combination of private, governmental, academic, and indus-

try action to deal with this problem. The current development of generics products increases the access to and decreases the cost to use a number of products. However, it does little to insure access to products, no matter how effective, when there is limited financial incentive to develop, improve or even continue to manufacture such products. The current system also does not encourage the continued manufacture of lower cost alternatives to more profitable, no more effective brand name products.

Unless or until reliable sources of funding are identified which supports the testing, development and manufacturing required, perhaps some of the funds 'saved' by insurers or 'generated' by manufacturers could be set aside for this.

For patients

For many years little was done to test medicines given to children. Some laws in the US and now in Europe have helped to change this for new drugs being developed or still protected by patents.

However, there is little or no incentive for industry to test or develop generic versions of some old, yet very important, drugs used in children or for very rare diseases. Governments, patients/parents, academic institutions, and the pharmaceutical industry share responsibility to find a way to develop and adequately test medications to be used in children as well as other non-profitable patient groups.

Conflict of interest

Professor Walson is paid by the EMMES Corporation to act as Chair of the Data Safety and Monitoring Committee which monitors paediatric off-patent drug trials sponsored by the NICHD/FDA under the BPCA.

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