Panel 4: How it all started: The Contributions of the NGO Community to Advancing the Cause of Rare Diseases

The Global Gathering for Rare Diseases: Inaugurating the NGO Committee for Rare Diseases

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This presentation represents the views of Ms. Meyers and not any NGO, company, group or person.

Abbey S. Meyers

The problem of the pharmaceutical industry ignoring the needs of people with rare diseases had been a societal problem for at least 2 decades before the

American *Orphan Drug Act* became law in 1983. It was during John Kennedy's Presidency in the 1960's that Thalidomide was discovered to cause horrendous birth defects. Even though the drug had not been approved for sale in the USA by the Food & Drug Administration (FDA), it was given away to American doctors who were able to give samples to their patients. The tragedy of Thalidomide showed the American government it needed to revise its laws to prohibit distribution of investigational drugs, and to require manufacturers to prove their drug is safe AND effective before it could be used in the United States. Previously, American drug companies simply had to prove their drugs were safe, but they were not required to prove their drug was actually effective.

The amendment to the *Food, Drug and Cosmetics Act* became known as the "*Kefauver-Harris Amendments"*, and because of the new requirement to prove efficacy of new drugs, the cost of research and development grew substantially in the United States. By the mid 1970's American doctors lamented that treatments for rare diseases were unavailable because drug companies were unwilling to spend millions of dollars to develop a drug that would be sold to a small number of people. The size of a **potential market** became a bedrock factor in corporate decisions about which drugs to develop, and which to ignore.

The FDA and the National Institutes of Health (NIH) were most disturbed about this growing problem, so they convened 2 separate "Interagency Task Force(s) on Significant Drugs of Limited Commercial Value" during the 1970's. Those reports recommended that something should be done to relieve the orphan drug problem, but the volumes of studies and recommendations were put on a shelf and nothing was done.

Personal Family Issues

During the late 1970's, after years of seeking answers, my oldest son was diagnosed with Gilles de la Tourette syndrome (TS). This neurological movement disorder is characterized by involuntary repetitive movements and noises. We were desperate to relieve his symptoms because they were so intense he could not dress himself, write or even eat because his arms flew around uncontrollably. But only one drug was being used to treat TS, and it was a major tranquilizer that put him to sleep. His doctor tried other drugs that were used for various neurological conditions, but either they didn't work or they had severe side effects. Finally his doctor said there was an experimental drug that might work with fewer side effects if my son was willing to go into a clinical trial. We agreed, and the drug did in fact work.

Every 3 months we had to go back to the doctor, report on my son's progress, and get another 3 month supply of pills. But on one visit to the doctor handed me the bottle of pills and said, "This is the last supply of pills that I can give you". He explained that the manufacturer was developing the drug for a common disease and clinical trials proved that it was not effective on that condition. Even though patients with Tourette syndrome reported significant relief from the drug, the manufacturer was unwilling to spend money developing any treatment for Tourette syndrome because the disease was "too rare". It was then that I first heard the term, "Orphan Drug".

The rest of the story of my family's experience is only important as an illustration of the necessary seeds that firmly root the foundations of patient driven support organizations. I decided to contact the leaders of several rare disease organizations and ask them if they had experienced problems with orphan drugs that private companies refused to develop. Some of the support groups said yes, they knew of treatments developed by academic researchers that drug companies refused to adopt, while other support group leaders told me there were no known treatments for their disease but they knew if the "orphan drug" problem wasn't solved, a treatment or cure for their disease would **never** be developed. We decided to work together to solve the orphan drug problem because individually we represented small populations of patients, but together we represented millions of suffering human beings.

Nature of the Problem

The Orphan Drug problem was an **economic problem** that cried out for an **economic solution**. Together the rare disease support groups were able to foster publicity that encouraged healthy people to ask, "Could this happen to me if I get a rare disease?" Finally, Congress got involved and an influential Congressman (Rep. Henry Waxman of California) formulated an economic solution, the *Orphan Drug Act of 1983*.

The Orphan Drug Act recognized that pharmaceutical companies spend millions of dollars to test new drugs and commercialize them. If the number of patients who will use the drug is small, companies felt they could have no expectation that they will recoup their investment and earn a profit. So the law proposed economic incentives that would assure drug companies that their niche drug market is protected from competitors for a number of years, hence to stand a good chance of making a profit if they developed an orphan drug. Of course the drug would have to be designated as an official "orphan drug" and to be approved as medicine with a marketing authorization for a rare disease, in order to qualify for the incentives.

The most important incentives of the *Orphan Drug Act* include:

- Seven years exclusive marketing rights, without competition.
- Tax credits for clinical research expenses.
- Competitive research grants for clinical testing expenses.

There are other incentives in the law, but these are the most important. Having a monopoly on the drug for 7 years was not like a patent extension. The law prohibits the FDA from approving any similar drug if it will be used to treat the same disease. In the United States the government does not control prices, so a drug manufacturer can charge any price for the drug during that 7 year period. Additionally, FDA is permitted to approve a "different" version of the drug if the sponsor can prove that it is "clinically superior" to the original drug. The intent of the law is not to block competition if a company can show its medicine is better than the original medicine for the same disease.

During the first four or five years there was little interest in the law primarily because there were a few inconsistencies that needed to be re-drafted. For example, the original law did not define the term “rare disease” except to say a disease had to be “rare in the United States”. This made it too difficult for FDA to determine whether a disease was rare or not. So an amendment was enacted to define a rare disease as a condition that affects fewer than 200,000 people in the United States. That population size was based on knowledge of treatments that were languishing undeveloped because drug companies decided the market was not large enough.

Once the inconsistencies were remedied, drug companies became interested in orphan drugs. It was like a slow awakening, but originally it was not the large Pharma companies that we expected. The 1980’s marked the birth of biotechnology, and it was the small start-up biotech companies that saw the ODA as a remedy for uncertainties surrounding patents on biologic products. In general these companies were desperate for investment capital. Because they were not yet profitable they could not use the tax credits in the law. A few years later we added to the law a “carry-back” and “carry-forward” provision so these companies could use the tax credits in a year when they became profitable.

Success of the Law and International Interest

As you all know the success of the American *Orphan Drug Act* has been spectacular. Over 500 orphan drugs are on the U.S. market, about 1/3 of them are for rare cancers, a majority of them treat serious diseases of children, and among them are the rare diseases that the initial “orphan drug” support groups represented: Tourette syndrome, Narcolepsy, Multiple Sclerosis, Huntington’s disease, Cystic Fibrosis, Myoclonus, Wilson’s disease and many, many more serious and life threatening diseases. Even the dreaded Thalidomide, which sparked the Kefauver-Harris amendments to the FD&C Act, is an orphan drug on the market today for treatment of several rare blood cancers such as Multiple Myeloma, and for Leprosy (which is a very rare disease in the United States). Besides, it is worth highlighting in this Committee at the United Nations, that the American Orphan Drug Act has attracted the investments in the two first

medicines to be approved for Aids treatment at the onset of the epidemic before it became the worldwide HIV epidemic we know.

The success of the American Orphan Drug Act attracted attention from other countries. Some small countries, such as Singapore, did not have to formulate a law to promote development of new orphan drugs, but they did need to reformulate their importation laws to enable emergency shipments of orphan drugs from America and Europe to reach needy patients quickly. Others did develop legislation that they thought would promote their drug industry's interest in orphan drugs. But some of those laws were not very effective if, instead of developing financial incentives to promote for-profit motivations, they created funding that would underwrite the costs of research and development. Companies were less interested in taking government funds for development of new products when they were unsure who, in the end, would actually own the product once it got on the market.

Be Careful What you Ask For!

However, out of all the blessings the Orphan Drug Act has brought to humanity there is an underside that we must be concerned about. That is the "cost" of orphan drugs for the healthcare systems. For some orphan drugs costs may be reasonable in comparison to the costs of not treating the disease with effective medicines (e.g., cystic fibrosis, hemophilia, etc). But some of the prices of orphan drugs are not merely unreasonable, but frightening.

In general, people understand that a drug to treat a rare disease has to be more expensive than a drug to treat a common disease. Logically, if you add one cent of profit to every pill you sell to millions of people with high blood pressure, you will earn hundreds of millions of dollars (or perhaps Billions) in profit. But if you add a penny of profit to every pill that is sold to only 1,000 people with a rare disease, you will go bankrupt very quickly. Thus orphan drugs tend to be more expensive than drugs for common illnesses because the cost of research, development and profit is shared among very few patients.

Remember that even before the ODA became law the costs for keeping a person with Hemophilia, Muscular Dystrophy or Severe Combined Immune Deficiency (SCID) alive, was very high, and their lives were much shorter. Thus society should prepare for these expenses by creating special funding schemes and solidarity mechanisms for orphan drug purchases. Instead, they are telling hospital pharmacists that the cost of treating one patient with an orphan drug will drain their budget for all other drugs, leaving the hospital without antibiotics and other essential medicines. This is not right; this is not acceptable because no medical professional should be told to choose which patient will live and which will die because of budgetary constraints. The financial burden of orphan drug treatments should not be on the local healthcare providers. Every nation has people with rare diseases who will need orphan drugs in their lifetime. We need to find new funding schemes to bring therapeutic innovation to patients. For example, a special fund to pay for these drugs could be developed through a tax of several pennies on the sale of common drugs, including generics, in all countries.

On the other side of the issue is the question: Not all orphan drugs are high priced, most are reasonably priced, but a growing number are charged at sky rocketing prices. How are drug companies choosing what price to put on a new treatment? Why are new Enzyme Replacement Therapies in the range of $200 000 to $450 000. Is it really based on the clinical value of these medicines when indeed they are chronic life-long treatments? That's every year for the rest of these patient's lives! That's like buying a new house every year. Can a person apply to borrow a new mortgage on their life……annually….so they can buy the medicine need to stay alive? Are these medicines really providing the best value for money to society? Or is the price based on benchmarking and on what the market can bear? Why are first medicines for rare diseases without treatment so far so expensive up to $350 000 or $400 000 when they are not transformative drugs, rather with high uncertainties? Scientific innovation is not all, what is meaningful is the real clinical value for patients.

The first significant gene therapy approved in Europe developed by Telethon Italian and GSK is for an extremely rare disease, the ADA-SCID which affects 5 to 10 babies per year in EU, is priced $450 000; this is a good signal.

We need orphan drugs, but society cannot go bankrupt paying for them. Can we study the actual costs structure and cost drivers of orphan drug development and agree on realistic ways to reduce these costs all along the life cycle of the product, as well as agree on a formula for fair pricing? Can we create payment mechanisms – such as specific funds or other solidarity measures - that will subsidize the cost for patients? For example, should we ask manufacturers to put aside a percentage of their product for indigent patients who desperately need help, especially in the least developed nations? And should we expect that the pharmaceutical industry at large should show self-restraint and perhaps reduce their costs, such as the huge sums of money they spend on marketing, including TV adds, which is a very questionable practice from the perspective of good medical practice and healthcare system sustainability?

These are issues that need vigorous debate. We know for example that European countries have a 3 steps approval process: First the drug must be approved by the EMA, through a European centralized procedure, on the basis of safety and efficacy; second, the drug must be assessed for its relative effectiveness and its value in the national healthcare system through national health technology assessment; and last, thereafter, the manufacturer must negotiate with the national or local authorities in each country or regions for its price and reimbursement. These second and third steps can greatly delay the availability of an orphan drug in a European country, and in some nations the pricing authority may not agree on a price at all, leaving some orphan disease patients with no treatment options.

The international community at the United Nations should debate these issues and find solutions. It has been the dream of mankind to live in a world without pain and suffering. We have the first of these cures and treatments in our hands but we must now map their route to patients who need them. I hope that the NGO Committee for Rare Diseases will accomplish this. Thank you.