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COOPERATIVE APPROACHES TO RESEARCH AND DEVELOPMENT OF ORPHAN DRUGS

EDITORS: Melvin H. Van Woert
Eunyong Chung

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COOPERATIVE APPROACHES TO RESEARCH AND DEVELOPMENT OF ORPHAN DRUGS

Proceedings of a Conference held in New York, New York
April 9 and 10, 1984

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WELCOME

Dr. James F. Glenn, President

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Good morning to all of you. I think it is very gratifying to see so many of you here to attend the conference in an area that I think is increasingly important to us. I congratulate Dr. Van Woert and Dr. Hauck and their associates for organizing this program and focusing attention on what appears to be a significant problem, something with which both government and the private sector are involved. Mt. Sinai is very pleased to take an active role, a leadership role, in trying to establish organized programs in support of the orphan drugs, and I think it is indicative of the spirit of Mt. Sinai that this is being done. The institution has a long tradition of being an innovator, careful to nurture new ideas and that is what this conference in intended to do.

Those of you who are Mt. Sinai associates may be interested in knowing that the institution is facing a challenge today, a new growth ring. We are in the final process of application for a Certificate of Need to rebuild the institution. About one half of the institution will be replaced with new construction and the remaining portion will be totally renovated. Every bed will be either replaced or refurbished. We are building an entirely new infrastructure to the institution, the chassis of support services that are so necessary to a modern medical center. At the same time that we do that, we are facing similar challenges on the academic side. We are in the process of identifying a new Dean and I will tell you that we are very encouraged by the interest that has been shown in this process. We have a small group of finalists in the selection process and we hope to make an announcement in the very near future.

It is a pleasure to have you here and I wish you great success with this important conference.

Contents

Contributors ix

Welcome
James F. Glenn xi

Session I. CURRENT ACTIVITIES AND FUTURE GOALS OF ORPHAN DISEASE AGENCIES

Introduction
Melvin H. Van Woert. 3

Orphan Drug Act
Melvin H. Van Woert. 7

Orphan Products Development and Some Methods for Maximizing the Usefulness of Research on Rare Diseases
Marion J. Finkel 11

The Orphan Products Board of the Department of Health & Human Services
Glenna M. Crooks 19

The National Institutes of Health Small Business Innovation Research (SBIR) Program: Opportunities for Orphan Drug Development
Lily O. Engstrom. 25

Discussion 1. 31

The Pharmaceutical Manufacturers Association Commission on Drugs for Rare Diseases
George S. Goldstein 35

Generic Pharmaceutical Industry Association Orphan Drug Institute
William Haddad 41

National Orphan Drugs and Devices Foundation
Joel Bennett. 47

The Consumer's Role in Development of Orphan Drugs
Abbey S. Meyers. 51

Discussion 2. 63

Session II. EXAMPLES OF CURRENT ORPHAN DRUG DEVELOPMENT PROGRAMS

The National Cancer Institute's Drug Development Program
Saul A. Schepartz. 73

The Antiepileptic Drug Development Program: An Example of Government-Industry Collaboration
B.G. White 83

The Development of Orphan Drugs—A Pharmaceutical Company Perspective
Jacob C. Stucki 95

The Design and Development of Therapeutic Agents for Neuromuscular Diseases
Neil J. Lewis 105

Discussion 3. 111

Session III. ACADEMIC CENTER APPROACHES TO ORPHAN DRUG RESEARCH AND DEVELOPMENT

Academic Center Approaches to Orphan Drug Research and Development
Fred P. Hauck, Eunyong Chung and Melvin H. Van Woert 115

The Fuel to Run the Orphan Drug Engine: A Medical School-based Orphan Disease Center Program
George J. Brewer 123

List of Voluntary Disease Organizations Which Participated in the Poster Session 139

Session IV. EXAMPLES OF INDIVIDUAL ORPHAN DRUG RESEARCH

Zinc as a Treatment for Wilson's Disease—An Orphan Among Orphans
George J. Brewer and G.M. Hill 143

Therapy of Cystinosis
Jess G. Thoene 157

Interstitial Cystitis
Vicki Ratner 163

Session V. CHAIRMEN'S REPORT ON THREE WORKSHOPS

Workshop I Problems Associated With Developing Orphan Drugs Into Available Therapy
Melvin H. Van Woert. 171

Workshop II Approaches to Cooperation on the Discovery of New Therapies for Rare Disorders
Fred P. Hauck 175

Workshop III The Role of Voluntary Disease Organizations in Research and Development of Orphan Drugs
Ruby Horansky 179

Discussion 4. 183

Registrants 185

Index 197

Current Activities and Future Goals of Orphan Disease Agencies

Session I

Session Chairpersons – M.H. Van Woert, G. Brewer

Cooperative Approaches to Research and Development of Orphan Drugs, pages 3–6

INTRODUCTION

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Drugs which appear useful for treatment of a rare disorder, but have difficulty in finding a sponsor for development and marketing because the anticipated financial return is insufficient, are called orphan drugs or drugs of limited commercial value. Although the need for a single orphan drug may be confined to a small population, the total number of patients affected by the unavailability of orphan drugs is considerable.

Why does the orphan drug problem exist? Since 1902, when the first U.S. federal law regulating medical therapy was passsed, there has been progressively greater government supervision of the drug development process to allow introduction to the marketplace only drugs that have a highly favorable risk/benefit ratio. In response to the thalidomide disaster, Congress passed the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act in 1962, which mandated that permission be obtained from the Food and Drug Administration (FDA) to investigate new drugs in human subjects and required substantial proof of a drug's efficacy, as well as safety, prior to marketing approval. The price our society has had to pay for this protection from dangerous and ineffective medicines is a tremendous increase in time and cost of developing new drugs. Currently, the pharmaceutical industry estimates that the overall average cost of the research and development process, from initial discovery of a drug until completion of FDA required studies, takes from 7-10 years and costs 50 to 70 million dollars. Thus, factors such as patient population and patentability of new drugs have become major considerations in a pharmaceutical company's decision as to which medicines they will develop. Consequently, important and lifesaving drugs have been discarded

or neglected because their estimated economic returns have not justified research and development costs. Furthermore, the number of diseases whose population is too small to be considered a profitable market for a pharmaceutical company (orphan diseases) has rapidly increased.

The neglect of drug development for rare diseases was recognized as early as 1964 when the United States Public Health Service (PHS) conducted an investigation into the magnitude of the orphan drug problem. Further committee reports by the FDA and PHS in 1975 (Interim Report on the Committee on Drugs of Limited Commercial Value) and 1978 (Significant Drugs of Limited Commercial Value") documented the existence of the orphan drug problem. In fact, the National Cancer Institute (NCI) established the first formalized federal drug development program in 1955, because they considered the pharmaceutical industry's efforts to find new anticancer drugs insufficient. The NCI's program became the model for subsequent federal drug development programs for 11 more orphan diseases.

However, there were other orphan drugs, which were safe and efficacious in preliminary clinical trials, but were not being adopted by the pharmaceutical industry and did not fall into the category of the 12 government drug development programs. One of these was L-5-hydroxytryptophan (L-5HTP) used in the treatment of myoclonus. Mr. Burt Diamond, President of the National Myoclonus Foundation and myself met with representatives from the National Institutes of Health, the FDA, the Pharmaceutical Manufacturer's Association and a number of individual pharmaceutical companies seeking assistance for the further development of L-5HTP. Although everyone we met sympathized with the patients' suffering, due to their inability to obtain this medication, none were able to provide any solutions to this problem. By 1977, members of the National Myoclonus Foundation, frustrated by years of negative responses from both industry and government to their request to have L-5HTP made available, launched a letter writing campaign to members of Congress. These letters pointed out the unfairness of the American drug development program to patients with rare diseases and requested that Congress consider legislative action. Possible legislative solutions for the orphan drug problem were published in the New England Journal of Medicine.[1]. We were fortunate that one member of Congress, Representative Elizabeth Holzman (D, N.Y.) offered to meet with a myoclonus patient from her district and myself. After numerous sessions with Representative Holzman and her legislative assistant, the first orphan drug bill was drafted and was introduced in the U.S. House of Representatives in April 1980.

This orphan drug bill was reintroduced by Congressman Ted Weiss (D, N.Y.) in February 1981 and again in December 1981 by Congressman Henry Waxman (D, CA). The National Myoclonus Foundation was advised that wide-spread public support for this legislation was essential if the bill was to pass. Initially, we were able to convince the Tourette and Hutington's Disease Association that the L-5HTP and myoclonus predicament could and most probably would happen to them unless legislative action was taken. As Marjorie Guthrie of the Committee to Combat Huntington's Disease said, "If L-5HTP cannot get developed, the same problem could, in the future, prevent patients with Huntington's disease from receiving new breakthrough therapy."[2] Interest in the orphan drug bill rapidly spread to other voluntary disease organizations such as the Cystic Fibrosis Foundation, Wilson's Disease Association, The American Narcolepsy Association and others which formed the National Coalition for Rare Diseases. The concerted efforts by members of this coalition to make the public aware of the orphan drug problem and the need for new legislation was successful in bringing about the passage of the Orphan Drug Bill. The National Coalition for Rare Diseases eventually became the National Organization for Rare Diseases (NORD) after the passage of the Orphan Drug Bill.

Prior to the Orphan Drug Act, leads and scientific breakthroughs on rare diseases often were not pursued. The Orphan Drug Act and the newly formed orphan disease/drug agencies, which are participating in this conference, have greatly improved the environment for the development of identified drugs for rare diseases and sponsors have been found for over 20 orphan drugs during the past two years.

Since the machinery is now in place to develop known orphan drugs, other approaches to stimulate and facilitate preclinical and early clinical research on orphan drugs/diseases are now needed so that a constant supply of new orphan drugs will become available.

This conference was organized to provide opportunities for interested representatives from industry, government, academia, and voluntary disease organizations to exchange ideas and hopefully find new approaches to cooperative efforts in facilitating orphan drug development.

I believe this conference has raised pertinent questions which

should provide a renewed stimulus for future discoveries of new therapies for rare disorders. The success of any conference depends on many factors. I take this opportunity to thank those whose financial support made this conference possible:

The Food & Drug Administration
The Pharmaceutical Manufacturers' Association
The Generic Pharmaceutical Industry Association
The Myoclonus Research Fund

In addition, many thanks are due to those who gave formal presentations in the conference as well as to those who participated in the various workshops, poster sessions, and discussions.

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Cooperative Approaches to Research and Development of Orphan Drugs, pages 7–9

ORPHAN DRUG ACT

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In the 1970's, the Public Health Service created two orphan drug task forces, and during the Carter Administration the White House appealed to the pharmaceutical industry to develop more drugs for rare diseases. However, it was not until the spring of 1980 that Congress became involved in the orphan drug issue. At that time, the first orphan drug legislation was introduced in the House of Representatives by Congresswoman Elizabeth Holtzman (D, N.Y.). This bill called for the establishment of an Office of Drugs of Limited Commercial Value in the National Institutes of Health. Its primary responsibility would be to provide financial assistance, including loans, grants, contracts and coordinate efforts of the public and private sector for new drug development. A series of congressional hearings was held by Representative Waxman (D. CA) from 1980 to 1982 in which representatives of the Pharmaceutical Manufacturers Association (PMA), Food and Drug Administration (FDA) and representatives from research and voluntary disease organizations were invited to testify. The same orphan drug bill was reintroduced in February 1981 by Congressman Ted Weiss (D, N.Y.). In December 1981, Representatiave Waxman, Chairman of the House Subcommittee on Health and Environment, modified the orphan drug bill and reintroduced it. Senator Nancy Kasselbaum (R, KS) introduced a similar bill in the Senate. This modified orphan drug bill proposed both tax benefits and exclusive marketing rights as incentives to the pharmaceutical industry to develop orphan drugs. In December 1982, after further modification, the Orphan Drug Act finally passed both Houses of Congress.

Celebration of the passage of the Orphan Drug Act was