Introduction

As a definition of orphan drugs, for the purposes of this round table, we can select that of the FDA: “Orphan products are drugs, devices (including in vitro diagnostics), biologicals and foods for special dietary purposes which, despite potential usefulness, remain inadequately tested and/or unavailable to patients because of limited commercial interest.”

These products may be useful in uncommon conditions (rare diseases) or they may be applicable to common conditions but research investment is discouraged because the drugs are unpatentable or face impending patent expiration. Orphan products also include, on the US market, drugs that have been found to have new uses in the treatment of serious uncommon diseases. Drugs for tropical diseases may represent another important group of orphan drugs.

By “uncommon” is meant a product of limited commercial value in the USA. This encompasses any drugs with total annual drugstore and hospital sales of less than $5 million. A disease occurring with an incidence of 1% in the USA (i.e., 2 million people) is common. A disease with an incidence of 0.025% or less (50,000 or fewer patients) is certainly uncommon, and so perhaps is one with an incidence of 0.50%.

The responsibility for rejecting these orphans remains primarily with the pharmaceutical industry. However, orphan drugs have been developed by pharmaceutical firms and made available to the public and referred to as public service drugs:

- BROMOCRIPTINE
- DANTROLENE
- DIAZOXIDE
- LYPRESSIN
- METYROSINE
- PENTAGASTRIN

(*) Istituto di Farmacologia - Università Cattolica del S. Cuore, Rome. President of the Società Italiana Scienze Farmaceutiche.

(**) Presented at the International Meeting «New Strategies for Orphan Drugs» (Rome, 8-9th March 1985).
In recent years, companies have agreed to develop some orphan drugs, and some of them have been approved by the FDA (1982/1983):
- SODIUM CELLULOSE PHOSPHATE for prevention of kidney stones
- ACETOXYHROXAMIC ACID for kidney infections
- INJECTABLE HEMIN for hepatic porphyrias
- CHENODIOL (for dissolving gallstones in some high surgical risk patients)
- I-PEPTOPROTEIN, a diagnostic kit for the management and therapy of testicular cancer
- ETOPOSIDE for refractory testicular cancer
(L-5-HYDROXYTRYPTOPHAN was made available for investigational use in the treatment of postanoxic myoclonus)

Other orphan drug companies have agreed to develop the following (from Finkel, 1978 and Groft, 1983).

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SPONSOR</th>
<th>INTENDED USE</th>
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<tbody>
<tr>
<td>AMIODARONE</td>
<td>Ives</td>
<td>Cardiac arrhythmias</td>
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<tr>
<td>BACTITRACIN</td>
<td>A.L. Laboratories</td>
<td>Pseudomembranous enterocolitis</td>
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<tr>
<td>CARNTINE</td>
<td>McGaw</td>
<td>Primary carnitine deficiency</td>
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<tr>
<td>CITRIC ACID, GLUCONIC ACID, MAGNESIUM HYDROXY-CARBONATE, MAGNESIUM ACID CITRATE, CALCIUM CARBONATE SOLUTION</td>
<td>Guardian Chemical</td>
<td>Dissolution of urinary tract calculus and prevention and treatment of encrusted indwelling urinary tract catheter</td>
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<td>DEPRENYL</td>
<td>(1)</td>
<td>Certain patients with Parkinson's disease</td>
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<td>ETHANOLAMINE OLEATE</td>
<td>Glaxo</td>
<td>Bleeding esophageal varices</td>
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<tr>
<td>HEMATIN</td>
<td>Abbott</td>
<td>Hepatic porphyria</td>
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<td>HYDROXY-ETHYL STARCH (HETASTARCH)</td>
<td>American Critical Care</td>
<td>White blood cell harvesting</td>
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<tr>
<td>L-5-HYDROXY-TRYPTOPHAN</td>
<td>Bolar Pharmaceuticals</td>
<td>Postanoxic myoclonus</td>
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<tr>
<td>INDIUMII Oxine</td>
<td>Amersshon</td>
<td>White blood cells and platelet imaging</td>
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<tr>
<td>METHACHOLINE C1</td>
<td>Roche</td>
<td>Diagnosis of occult bronchial asthma</td>
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<tr>
<td>I131-M-iodobenzyl-guanidine (131-MIBG)</td>
<td>Mallinckrodt</td>
<td>Adrenal medullary imaging agent</td>
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<tr>
<td>MONOOCANONIN</td>
<td>Ascot</td>
<td>Cholesterol gallstone dissolution</td>
</tr>
<tr>
<td>NP-59 (6-BETA-19-iodonorcholesterol)</td>
<td>Mallinckrodt</td>
<td>Adrenal cortical imaging</td>
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<tr>
<td>PENTAMIDINE</td>
<td>Zenith</td>
<td>P. carinii pneumonia</td>
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<tr>
<td>PIMOZIDE</td>
<td>McNeil</td>
<td>Tourette's syndrome</td>
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<tr>
<td>TRIENTINE (TRIETHYLENE TETRAMINE DIHYDRO-CHLORIDE)</td>
<td>Merck Sharp and Dohme</td>
<td>Wilson's disease</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Roche</td>
<td>Neuromuscular disorders secondary to cholestatic disease in vitamin E deficient patients</td>
</tr>
</tbody>
</table>

(1) Confidential.
The recent Orphan Drug Act has overcome many of the previous obstacles to the study and approval by the FDA of so-called orphan drugs. The important provisions furnished by the above act are here reported:


- Tax credit of 50 percent for the expenses of the clinical trials performed prior to marketing approval (+ normal deduction for the remainder of the clinical expenses, 75%)
- 7-year exclusive marketing license for unpatentable drugs
- Protocol assistance
- Grants and contract ($4 million per year)

Important orphan drugs are being developed thanks to the activities of the National Institutes of Health.

Orphan drugs developed by the activities of NIH

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DISEASE/S</th>
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<tbody>
<tr>
<td>Vaccine for respiratory syncytial virus</td>
<td>Infant croup</td>
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<tr>
<td>Rimantadine</td>
<td>Influenza</td>
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<tr>
<td>Phosphonoformate</td>
<td>Herpes</td>
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<tr>
<td>Bromovinyldeoxouridine</td>
<td>Herpes</td>
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<tr>
<td>Benzylesters and small peptide derivatives</td>
<td>To prevent sickling</td>
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<td>Antagonistics to the hormone LH RH</td>
<td>Hormone-dependent cancers</td>
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<tr>
<td>Perfluorochemical emulsions</td>
<td>Blood substitutes</td>
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<tr>
<td>Siroxane-free hemoglobin, modified hemoglobin</td>
<td>Blood substitutes</td>
</tr>
<tr>
<td>Oxygen binding chelates</td>
<td>Blood substitutes</td>
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An important problem now arising concerning orphan drugs is whether drugs intended for limited use in select populations may not require the same amount of preclinical and clinical testing as drugs intended for larger patient populations or broader indications. Standards for the establishment of safety and effectiveness are undoubtedly to be maintained. But certain tests could be waived (e.g., carcinogenicity; may long-term human exposure substitute long-term toxicity studies in animals?). This and other relevant questions our round table will face; we hope to receive reliable answers to them.
REFERENCES


