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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

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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
— ACETOHYDROXAMIC ACID for kidney infections
— INJECTABLE HEMIN for hepatic porphyrias
— CHENODIOL (for dissolving gallstones in some high surgical risk patients)
— 1-FETOPROTEIN, 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).

DRUG	SPONSOR	INTENDED USE
AMIODARONE	Ives	Cardiac arrhythmias
BACITRACIN	A.L. Laboratories	Pseudomembranous enterocolitis
CARNITINE	McGaw	Primary carnitine deficiency
CITRIC ACID, GLUCONIC ACID, MAGNESIUM HYDROXY-CARBONATE, MAGNESIUM ACID CITRATE, CALCIUM CARBONATE SOLUTION	Guardian Chemical	Dissolution of urinary tract calculi and prevention and treatment of encrusted indwelling urinary tract catheter
DEPRENYL	(1)	Certain patients with Parkinson's disease
ETHANOLAMINE OLEATE	Glaxo	Bleeding esophageal varices
HEMATIN	Abbott	Hepatic porphyria
HYDROXY-ETHYL STARCH (HETASTARCH)	American Critical Care	White blood cell harvesting
L-5-HYDROXY-TRYPTOPHAN	Bolar Pharmaceuticals	Postanoxic myoclonus
INDIUM[111] OXINE	Amersham	White blood cells and platelet imaging
METHACHOLINE Cl	Roche	Diagnosis of occult bronchial asthma
I[131]-M-IODOBENZYL-GUANIDINE ([131]-MIBG)	Mallinckrodt	Adrenal medullary imaging agent
MONOOCTANOIN	Ascot	Cholesterol gallstone dissolution
NP-59 (6-BETA-19-IODONORCHOLESTEROL)	Mallinckrodt	Adrenal cortical imaging
PENTAMIDINE	Zenith	P. *carinii pneumonia*
PIMOZIDE	McNeil	Tourette's syndrome
TRIENTINE (TRIETHYLENE TETRAMINE DIHYDRO-CHLORIDE)	Merck Sharp and Dohme	Wilson's disease
Vitamin E	Roche	Neuromuscular disorders secondary to cholestatic disease in vitamin E deficient patients

(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:

Provisions of the Orphan Drug Act (PL-97-414, Jan 4, 1983)

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, 73%)
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

DRUG	DISEASE/S
Vaccine for respiratory syncytial virus	Infant croup
Rimantadine	Influenza
Phosphonoophormate	Herpes
Bromovinyldeoxyuridine	Herpes
Benzylesters and small peptide derivatives	To prevent sickling
Antagonistics to the hormone LH RH	Hormone-dependent cancers
Perfluorochemical emulsions	Blood substitutes
Stroma-free hemoglobin, modified hemoglobin	Blood substitutes
Oxygen binding chelates	Blood substitutes

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.

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