DRUG RE-PROFILING

from Pharmaceutical Companies

Nobelpharma Co., Ltd.
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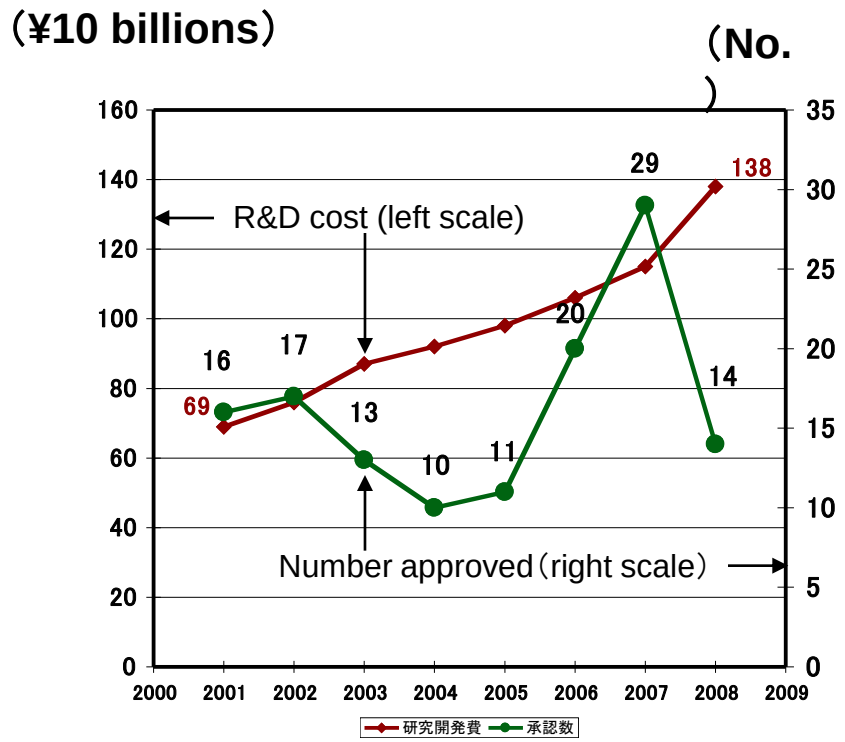
R&D cost for one new drug are about ¥60 billion



Total cost over 8 years

R&D expense ①	¥7.8 trillion
Number of approved drugs ②	130
①/②	¥60 billion

R&D expenses include those incurred overseas,
No. of approvals are just in Japan

Total for 34 companies excluding foreign companies (created by Nobelpharma from financial statements released by each company and MHLW data)

Nobelpharma's Mission

Contribute to medical treatment by providing drugs that are neglected even though they are necessary.

Re-Profiling ~ Nobelpharma's 3 products

Acquired approval and commenced sales of 3 new drugs in 2008, the 6th year after the company was founded

1. **Lunabell®: dysmenorrhea with endometriosis**
   (Tie-up: Janssen Pharmaceutical)
   - **Used for other than oral contraceptive in Japan**

2. **Nobelzin®: Wilson's Disease**
   (Tie-up: Teva Pharmaceutical)
   - **Zinc preparation**

3. **Nobelbar®: Neonatal seizures and status epilepticus**
   (Developed on own)
   - **Subcutaneous and intramuscular injection only ⇒ Intravenous**
   - **Dosage diverged from international standard**
   - **Pediatric dosage not set**
   - **Application for neonatal seizures not obtained ⇒ Physician-oriented clinical trials**

Lunabell® Compound tablets (Requested by patient group)

Product	Lunabell Compound Tablets	Ortho M-21 Tablets
Ingredients	Includes 1mg of norethisterone and 0.035mg of ethynylestradiol in one tablet	Same as at left
Efficacy	Treatment of dysmenorrhea with endometriosis	Contraception
Dosage	Repeat pattern of taking one tablet per day every day for 21 days, then take none for 7 days	Same as at left
Approved	April 2008	June 1996
Drug price	¥332.9 (1 tablet)	Not listed
Clinical trials	Pharmacological clinical trials (31 cases) Phase III comparative clinical trials (total 96 cases) Long-term dosage clinical trials (123 cases)	Open trials (504 cases)

Used Ortho M-21 data for non-clinical data (licensed)

Nobelbar® Intravenous (requested by Medical Society)

Product	Nobelbar Intravenous 250mg	Phenobar injection solution 100mg
Ingredients	Phenobarbital sodium 274 mg (Phenobarbital 250mg)	Japanese Pharmacopoeia Phenobarbital 100mg
Efficacy	Neonatal seizures and status epilepticus	Calming down from nervous state (when urgently needed) When seizures occur Autonomic seizure, psychomotor seizure
Dosage	Neonatal seizures: initially 20mg/kg intravenous dosage (can be supplemented) Maintenance dosage 2.5 to 5mg once daily intravenously Status epilepticus: 15 to 20mg/kg once daily intravenously	Subcutaneous or intramuscular injection of 50 to 200mg each time, once or twice daily. Increase or reduce according to age and health condition.
Approved	October 2008	1948
Drug price	¥2,060/bottle	¥80/tube
Clinical	Physician-oriented clinical trials for	There are clinical trial results for

Used public documents for non-clinical data and for status epilepticus data

Nobelzin® Capsule (Requested by patient's group and Medical Society)

Ingredients	1 capsule contains 83.92mg zinc acetate hydrate (25mg zinc) 1 capsule contains 167.84mgmg zinc acetate hydrate (50mg zinc)
Applications	Wilson's Disease (hepatolenticular degeneration)
Background	Existing drugs (penicillamine, trientine hydrochloride) promote excretion of copper, and have strong side effects This drug does not have critical side effects of preventing copper absorption, and does not require strict dietary restrictions Approval obtained in the US based on only physician-oriented clinical trials (1997) Approved and marketed in a total of 28 countries including in Europe (2004) based only on US clinical trial results
Development history	September 2004: Phase III clinical trial started in Japan, 37 cases (including 17 pediatric cases) January 2008: approved in Japan

Non-clinical data was from the US (licensed) and from public documents

Re-profiling Nobelzin®: Clinical research

(Requested by Medical Society)

Purpose	Double blind clinical trial for hepatic cirrhosis with hyperammonemia 150mg per day, or placebo (3 part) taken for 12 weeks
Medical institutions	Iwate Medical University and 11 other facilities
Background	Many reports of results indicating efficacy of zinc sulfate preparation Not much experience using it in Japan, and there are no results from a double blind test
Action mechanism	Supplies zinc which is insufficient in hepatic cirrhosis, increases activity of the metabolic enzyme for ammonia* *Ornithine transcarbamylase, glutamine synthase
Major evaluations	Ammonia in blood before and after dosage Side effects while dosed
Supplementary evaluations	BTR (branched chain amino acid to tyrosine ratio) in blood before and after drug dose, survey psychoneurotic functions, hepatic level
Case target	50 (25 cases all groups)
Registration period	September 2009 to September 2010

Clinical research objectives: Improved medical treatment and true research

- The primary objective of clinical research is to improve medical preventive methods, diagnostic methods, and treatment methods, to understand causes of illness and illnesses, and to improve patients' lives…(the rest omitted)
- Researchers that respect the human rights and individual dignity of the trail participants will be able to conduct trials more smoothly…(the rest omitted)

(From the preface to the ethical guidelines for clinical research)

- POC
- Innovative drugs, medical devices
- Innovative uses for existing drugs(Re-profiling)
- Rare diseases, intractable diseases
- With no prospective marketability, pharmaceutical companies will not try to make them generally
- If data obtained is left as it is, it cannot be used as material for application evaluations

「Clinical research」: Cannot be used as data for application evaluation

	Clinical research	Clinical trials
GCP correspondence	no	yes
IND (Investigational New Drug Application)	no	yes
Quality assurance (monitoring, DM, audit)	no	yes

・If ethical guidelines for clinical research are observed, it can in effect correspond to GCP.
・It is possible to submit IND even if not the company, even now.
・Take care of quality assurance.

Clinical research」: Is it possible to use it for application evaluation material?

1. （IND）
2. Data quality assurance
3. Observe ethical guidelines

⇒ Wouldn't it be alright to be subject to examination?

Only Japan has a double standard for clinical research and clinical trials.

・IND can also be used for clinical research.

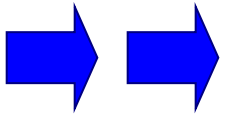
・ Quality assurance (monitoring, DM, audit).

Clinical research/clinical trial environment: from "preparation" to "practice"

(5-year strategy to create innovative drugs & medical devices)

1. Clarifying causes of disease, and understanding illness = true research
2. Improving medical technology = making use of its results (improved technologies)
   - If it doesn't get approval, it can't be "useful"
   - Promote clinical research

Clinical research
・Large increases in budget
・Revise system



Creating innovative drugs including Re-profiling

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