ICORD

International Conference on
Rare Diseases and Orphan Drugs
February 16, 2005

- A Journey of Hope

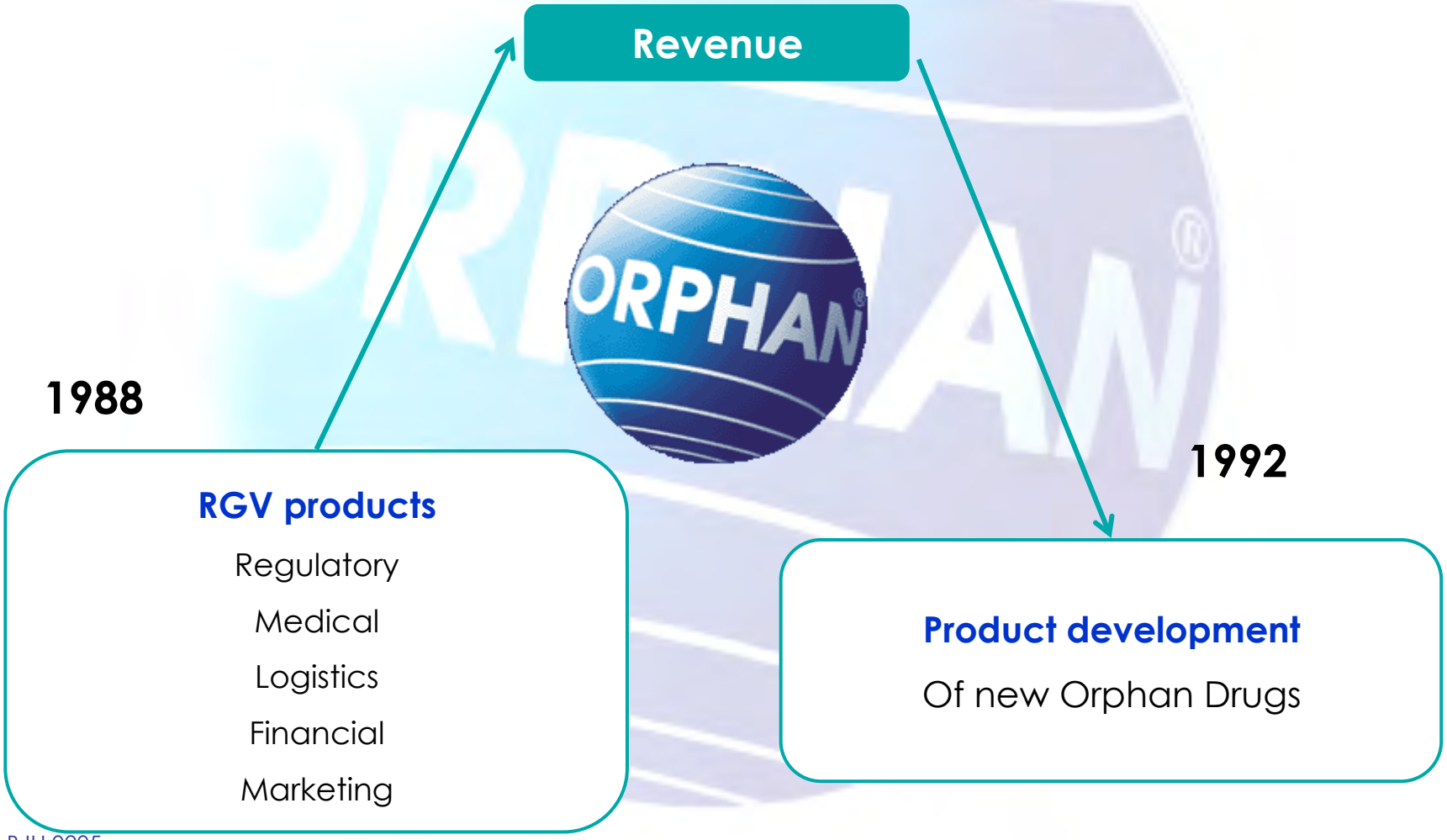
by
Bo Jesper Hansen MD PhD
President, CEO

SWEDISH ORPHAN INTERNATIONAL

Our Mission –
Our Foundation for existence

”To provide patients, healthcare personnel and the pharmaceutical industry with an independent global network, specializing in the development, marketing and distribution of orphan products for the treatment of rare disorders, and products and services to satisfy unmet medical needs where current treatment is either unavailable or unsatisfactory”

Business Concept



The NTBC Story

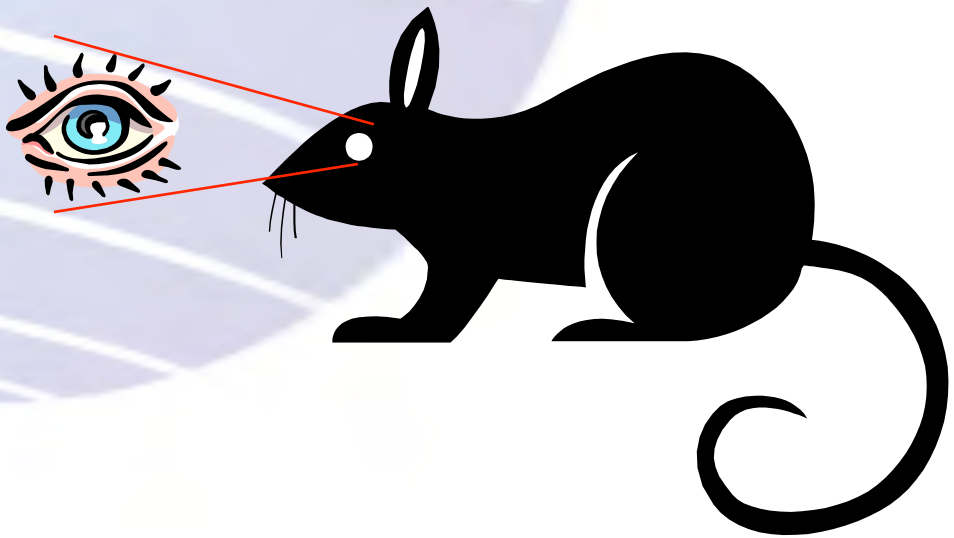
- Originally developed by ICI as a Herbicide
- ICI established contact with Prof's Holme/Lindstedt for advice on tox findings and access to a specific enzyme (4HPPD)
- 1990–91 Holme/Lindstedt treated 5 patients in Sweden
- Published in the Lancet 1992
- 1993 SOI signed a non-exclusive world wide licensing agreement for the development of NTBC in HT1 indication
- Product development by SOI 1993-
- 1995 Technology transfer agreement with Gothenburg University
- 2002, Q1 Product launch in US (via Fast Track procedure)
- 2003 SOI signed an **indefinite, exclusive world wide** licensing agreement for development of NTBC in **all Orphan Indications**
- 2005, Q2 Product launch in EU

The NTBC Story

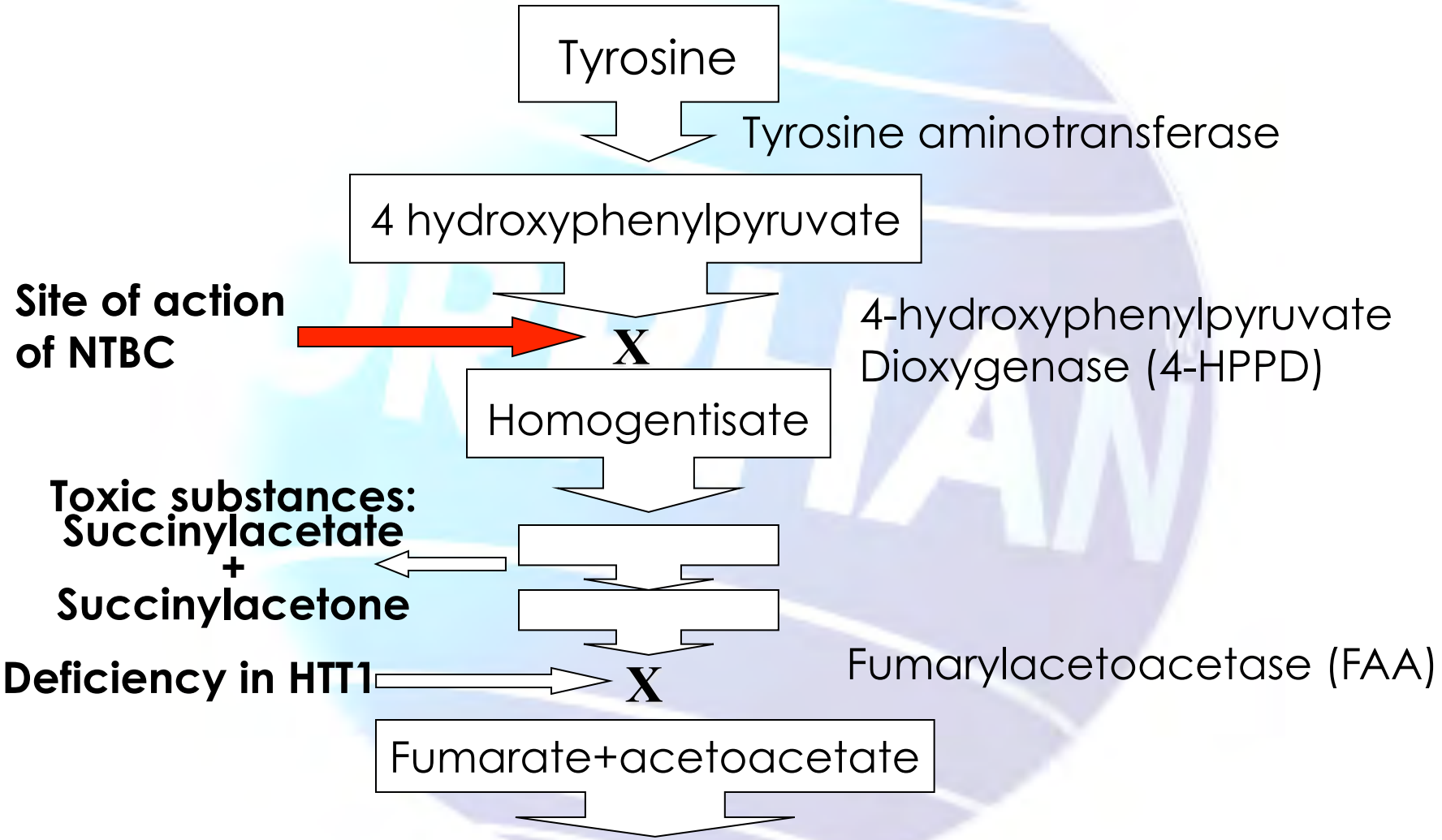
- NTBC was originally developed by ICI as a Herbicide

- Extensive toxicology programme in 70-ties and 80-ties

  → side-effects



Mode of action NTBC



Heriditary Tyrosinemia Type 1
HTT1

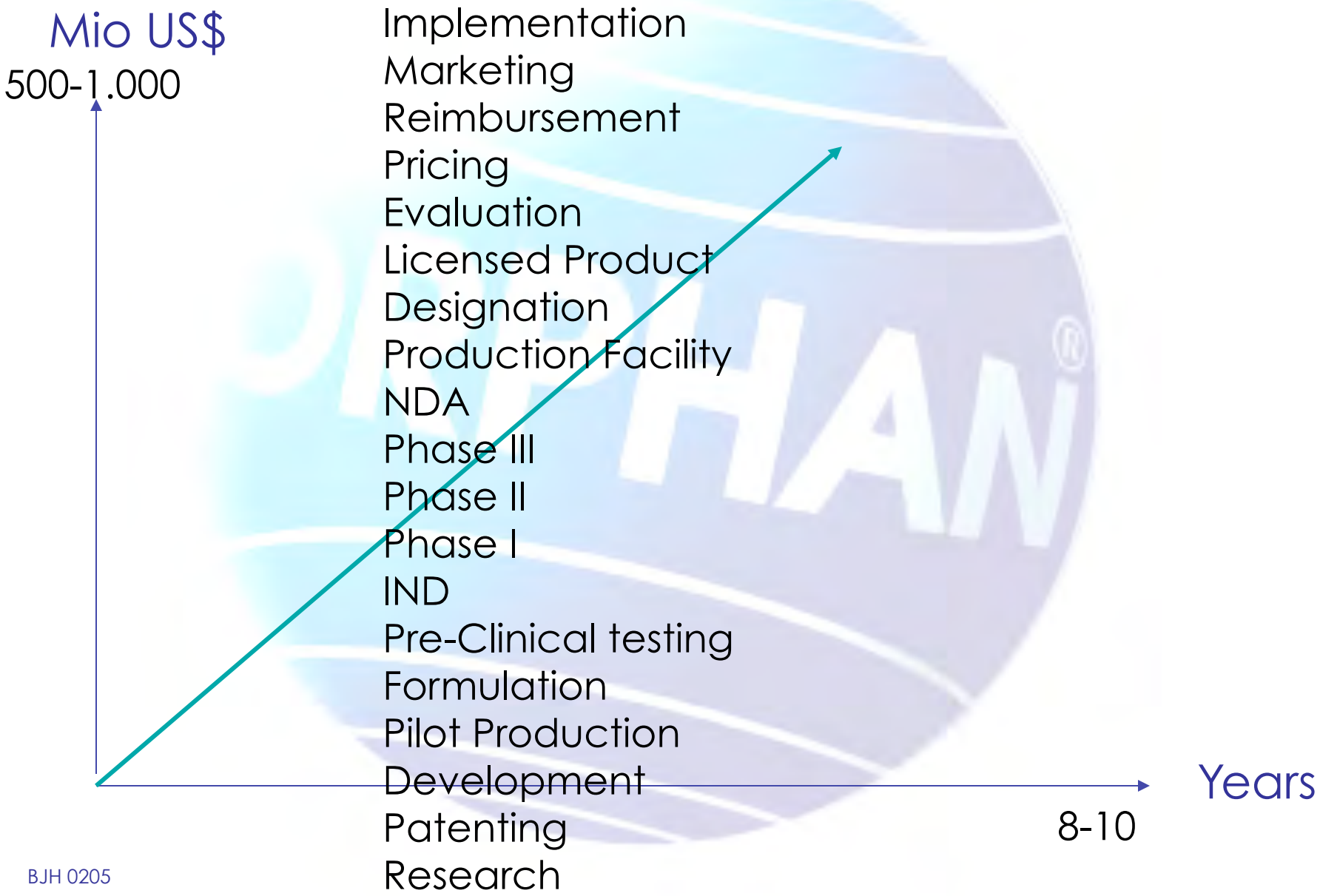
- Frequency approx. 400 worldwide
- Life threatning disease
- Two/three fenotypes:
    - Acute with liver failure in infancy <6mo
    - Subacute/chronic with a protracted course and
        * Renal tubular dysfunction
        - Rickets
        - Growth failure
        * 80-90% mortality risk in childhood or adolescence due to development of hepatocellular carcinoma.

Previously, liver transplantation the only option

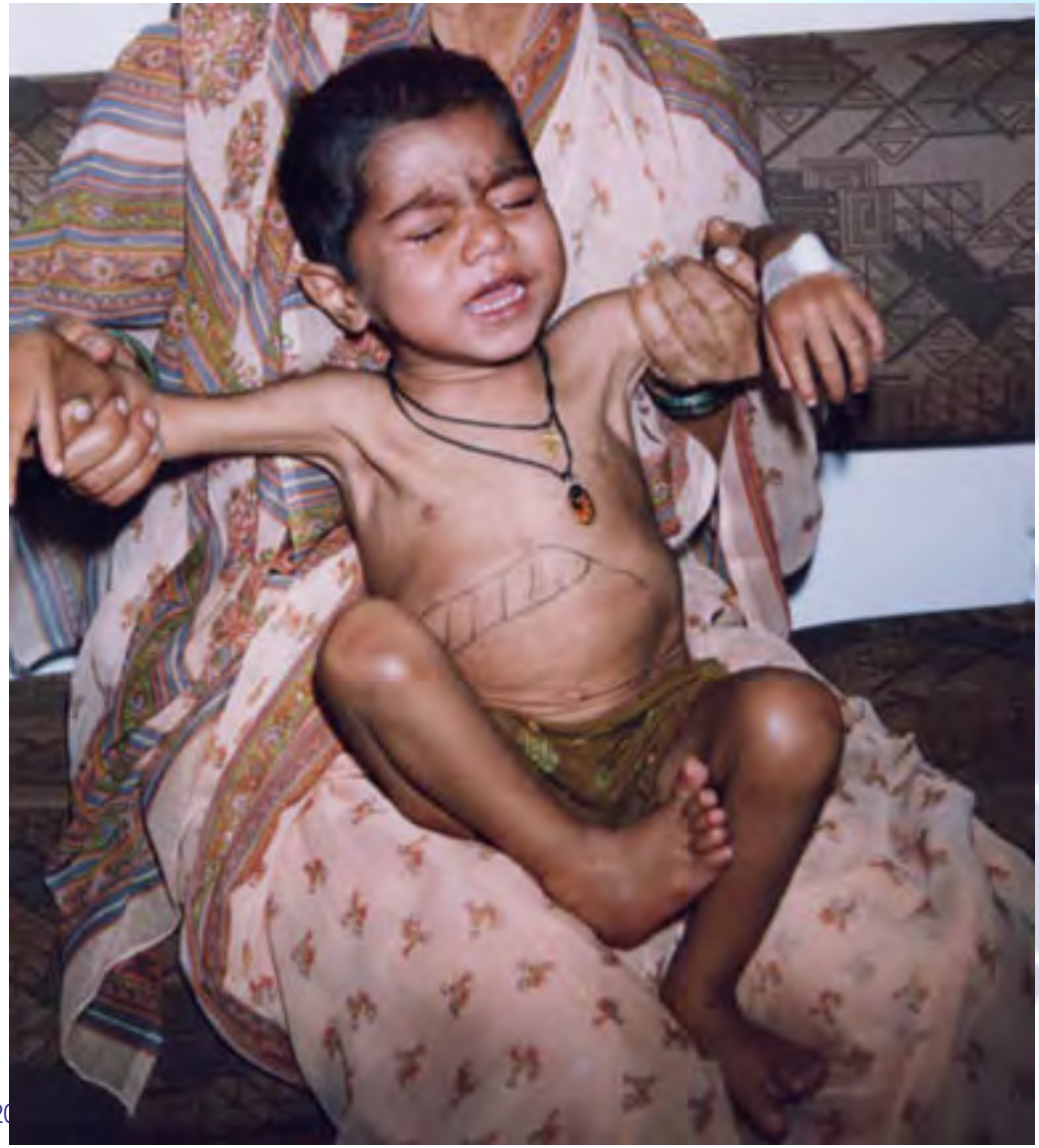
The NTBC Story

- 1990-91 Holme/Lindstedt treated 5 patients in Sweden
- Biomarkers and general patient condition improved→ The Lancet 1992
- Use of NTBC for treatment of HT-1 known to specialists
- The international uncontrolled compassionate use trial was coordinated by Holme/Lindstedt (1992→ still on-going)
- SWEDISH ORPHAN INTERNATIONAL approached for taking on responsibility for the development of NTBC in HTT1 indication

Orphan Drug Development!



Before Treatment with NTBC (Orfadin®)



The picture is taken 25 February 2004 Initially he was hypotonic, irritable, could not sit without support and had failure to thrive. He also had hepatomegaly with abnormal Liver Function Test.

After 6 mo. of Treatment with NTBC(Orfadin®)

The picture is taken 15 August 2004, after 6 months of treatment with NTBC. He has shown a remarkable recovery with improvement in general condition with weight gain of about 6 Kg, no hypotonia, he is able to play and run all over the place, irritablity has disappeared. The liver size has come to normal with normal Liver Function Test.

Dr. Anil B. Jalan

Why are Orphan Drugs for rare diseases attractive to companies?

- Definition of patient population ⇨ Market is reachable

- Development steps can be easily planned

- Clinical testing can be done cost-efficiently

- Out-sourcing of R&D can be done

- ”Soft money is easily available”?

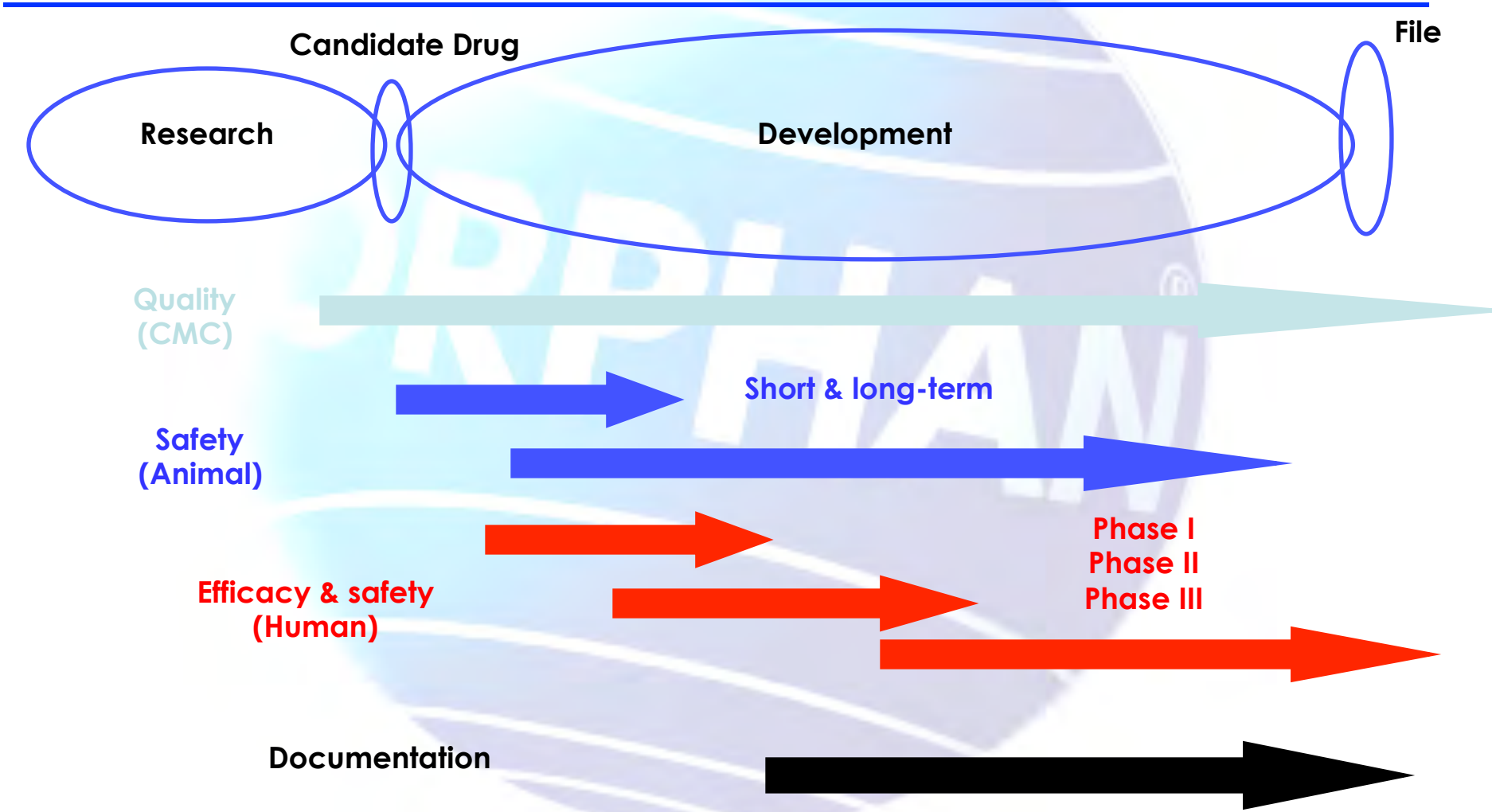
The NTBC Story

- How to finance?
    - A project consortium was formed
        - SWEDISH ORPHAN INTERNATIONAL
        - Rare Disease Therapeutics
        - Orphan Europe
- SWEDISH DEVELOPMENT FOUNDATION (ALMI)
- A Technology Transfer agreement was established between Sahlgrenska and SWEDISH ORPHAN INTERNATIONAL

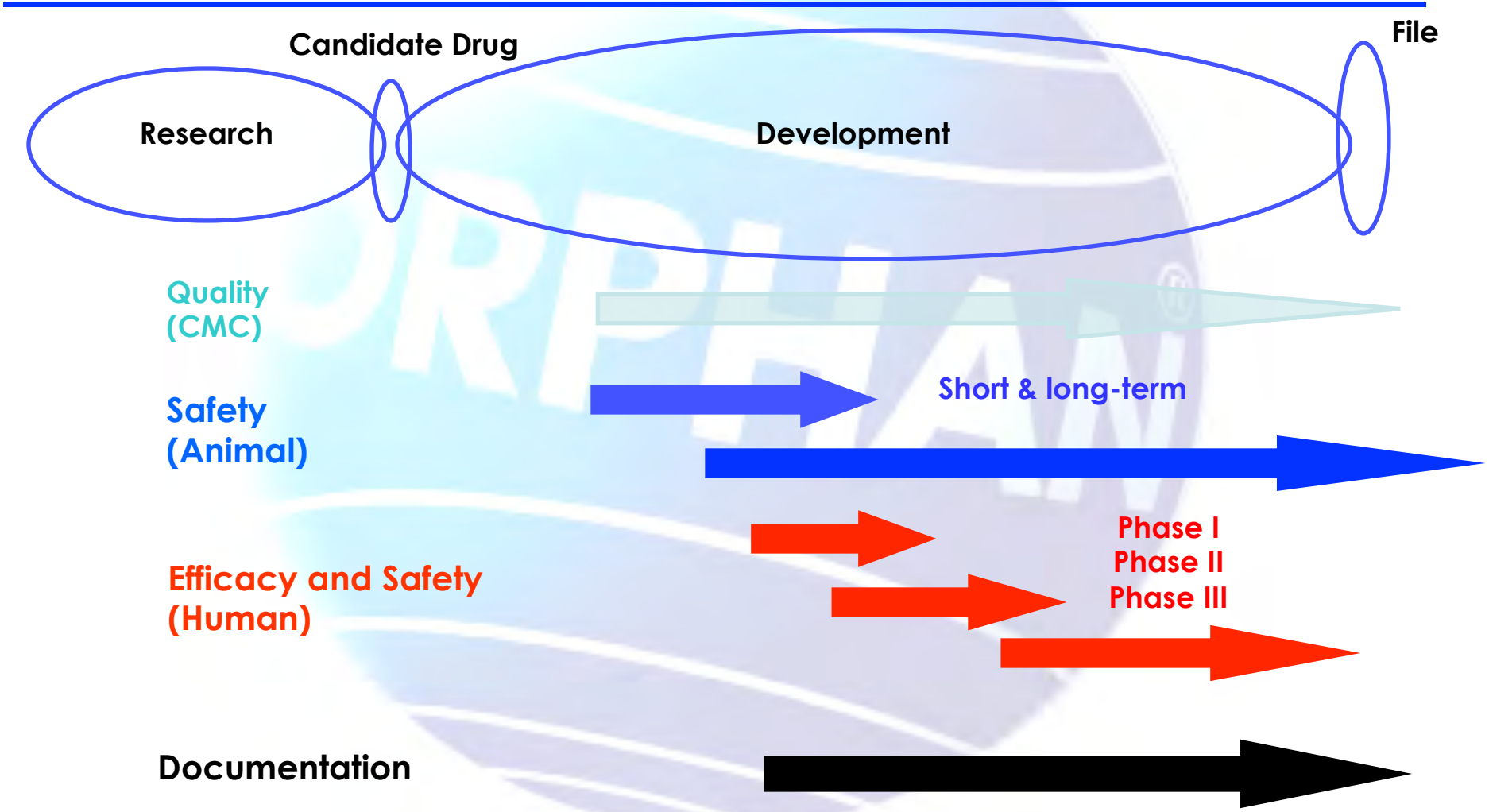
The NTBC Story

- SOI signed a non-exclusive world wide licensing agreement for the development of NTBC in HT1 indication
- ICI ”donated” 30kg of bulk substance to SOI for future development work
- NOBEL industries purified the bulk substance to clinical purity degree
- APOTEKET AB manufacturer of the finished product for clinical testing and now also the launched product
- 2001New manufacture of Drug Substance identified

Drug Development - general



Drug Development - NTBC



Scott CR et al. NTBC is an effective therapeutic agent for the treatment of children symptomatic from Tyrosinemia-1.
World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.
Aug 5-9, 2000. Boston, Massachusetts (abstract 536).

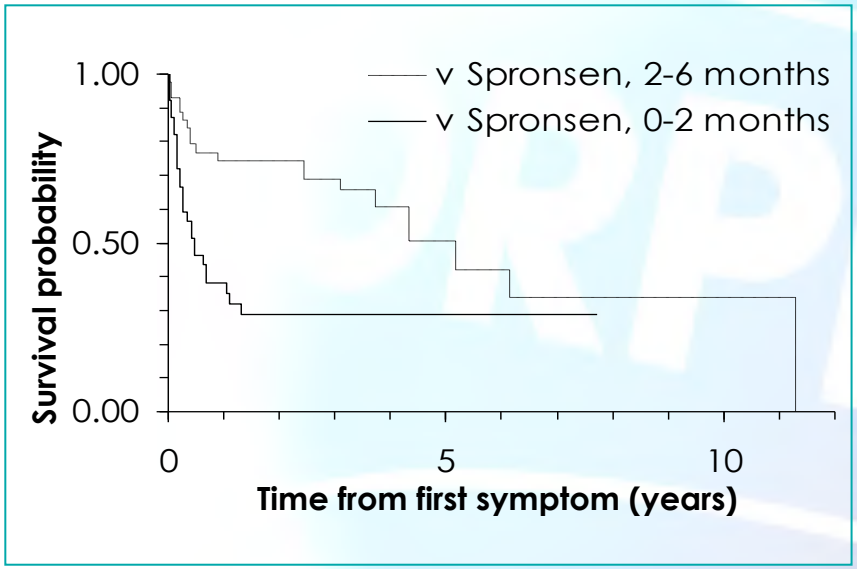
In Conclusion

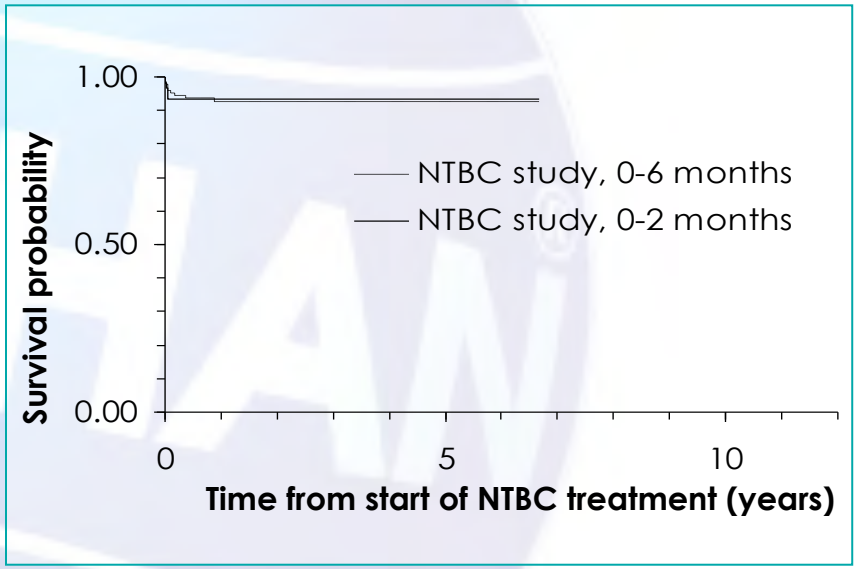
NTBC is an effective therapy for Tyrosinemia Type 1.

NTBC will:

- reverse the acute symptoms of liver failure
- allow for normal growth
- reverse and prevent renal dysfunction
- prevent rickets
- prevent acute neurologic crisis
- prevent or delay the need for liver transplantation

Survival Rate +/- NTBC





Source: Van Spronsen et.al. Hepatology 1994; 20: 1187

T02-04 Media Inquiries: 301-827-6242

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

January 22, 2002 Consumer Inquiries: 888-INFO-FDA

FDA approves drug to treat rare pediatric liver disease

FDA today approved a new drug, nitisinone capsules, to treat hereditary tyrosinemia type I (HT-1), a rare pediatric disease causing progressive liver failure and liver cancer in young children. Fewer than 100 children in the United States are affected by HT-1.

Nitisinone is an orphan drug. Orphan products are developed to treat rare diseases, or conditions that affect fewer than 200,000 people in the U.S. The Orphan Drug Act provides a seven-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan drug.

Because of liver failure or liver cancer, children with hereditary tyrosinemia type I rarely survive into their twenties without a liver transplant. However, for children treated early enough with nitisinone, liver failure and liver cancer occur at much-reduced rates.

Nitisinone was studied in more than 180 patients with a median age of 9 months when therapy started. When the drug was combined with a restricted diet, the 4-year survival rate of children under 2 months of age at the time of diagnosis was 88 per cent. Historical data for children treated with dietary restrictions alone shows a survival rate of 29 per cent for the same time period.

Nitisinone must be used in conjunction with a diet restricted in the amino acids tyrosine and phenylalanine. High tyrosine levels may be toxic to eyes, skin and the nervous system.

The most common side effects of the drug were related to high tyrosine levels due to patients not eating the appropriate foods as well as rare cases of mild reductions in platelet and white blood cell counts.

Nitisinone should be prescribed by physicians experienced in treating hereditary tyrosinemia type I, as the correct dose must be adjusted for each patient according to specific biochemical tests. Access to a nutritionist skilled in managing children with inborn errors of metabolism requiring a low protein diet is an important part of therapy. Blood tests should be monitored regularly to maintain the correct dose for that patient and to monitor for potential adverse events.

Nitisinone is a product of Swedish Orphan International AB, of Stockholm, Sweden and distributed in the U.S. by Rare Disease Therapeutics Inc., of Nashville, Tennessee. Nitisinone will be marketed under the name, Orfadin.

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BJH 0205

The NTBC Story

- **Orfadin® (NTBC) – HT1**
  - USA **– approved and launched with orphan drug status**
  - EU **– approved**
  - Named patient sales in almost 50 countries outside US
  - 8 years of logistic services for NTBC in almost 50 countries on a named patient basis
  - Designations in Europe and USA for Tyrosinemia and other indications

- **NTBC – other indications**

  In exploration stage via investigator lead studies
  - Alcaptonuria (NIH)
  - Rare cancers (CHLA)

The NTBC Story
or

”How an **unsuccessful herbicide**

became a **successful life saving drug** for ~400 kids world wide”

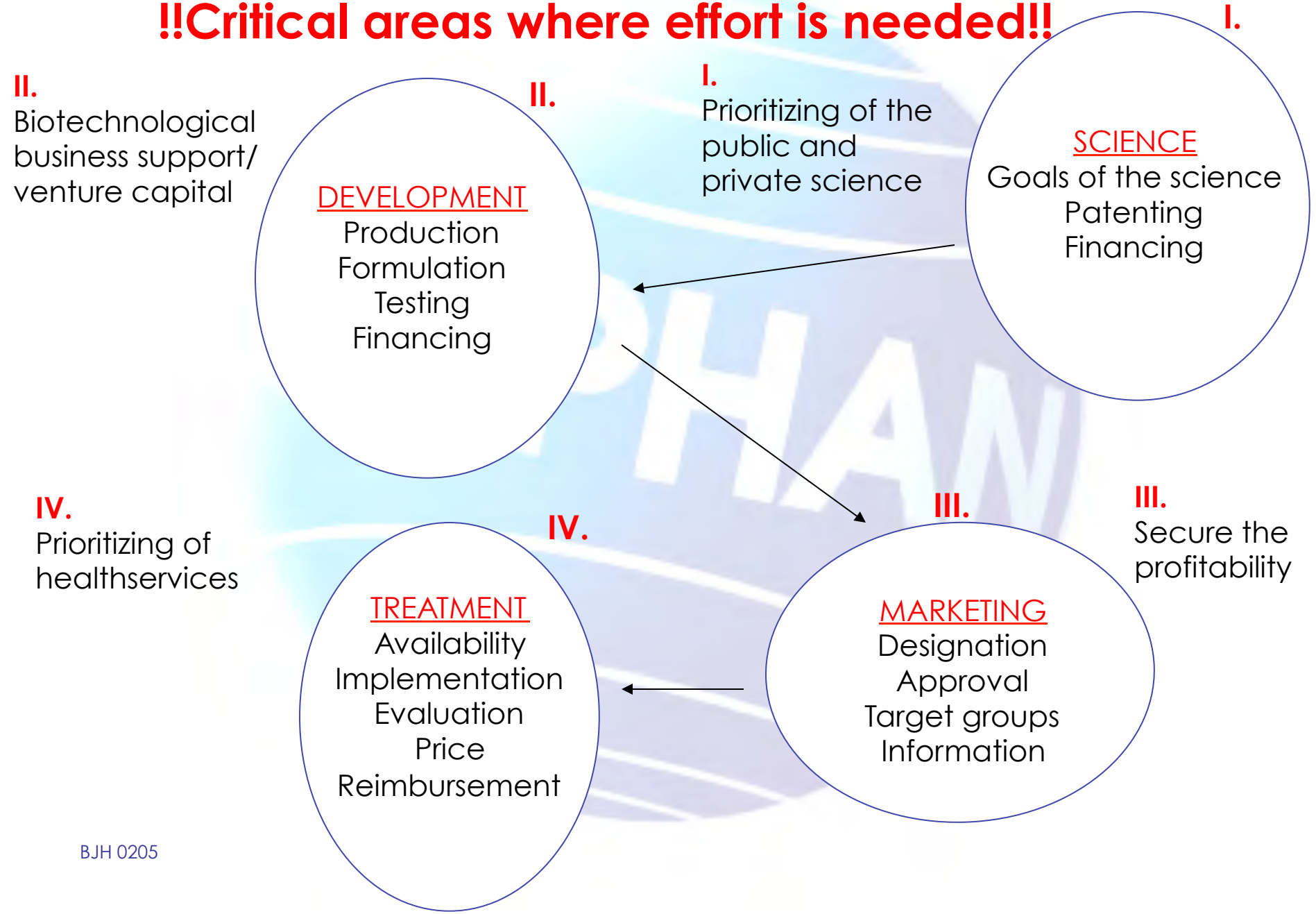
Commited physicians

Commited orphan drug focused companies

Orphan drug Legislation/Regulation

Development of Orphan Drugs.

!!Critical areas where effort is needed!!



We have:

- rare diseases on the political agenda
- active, organised patient groups
- active organised industry
- patients involved for first time in EU decision making
- public funding

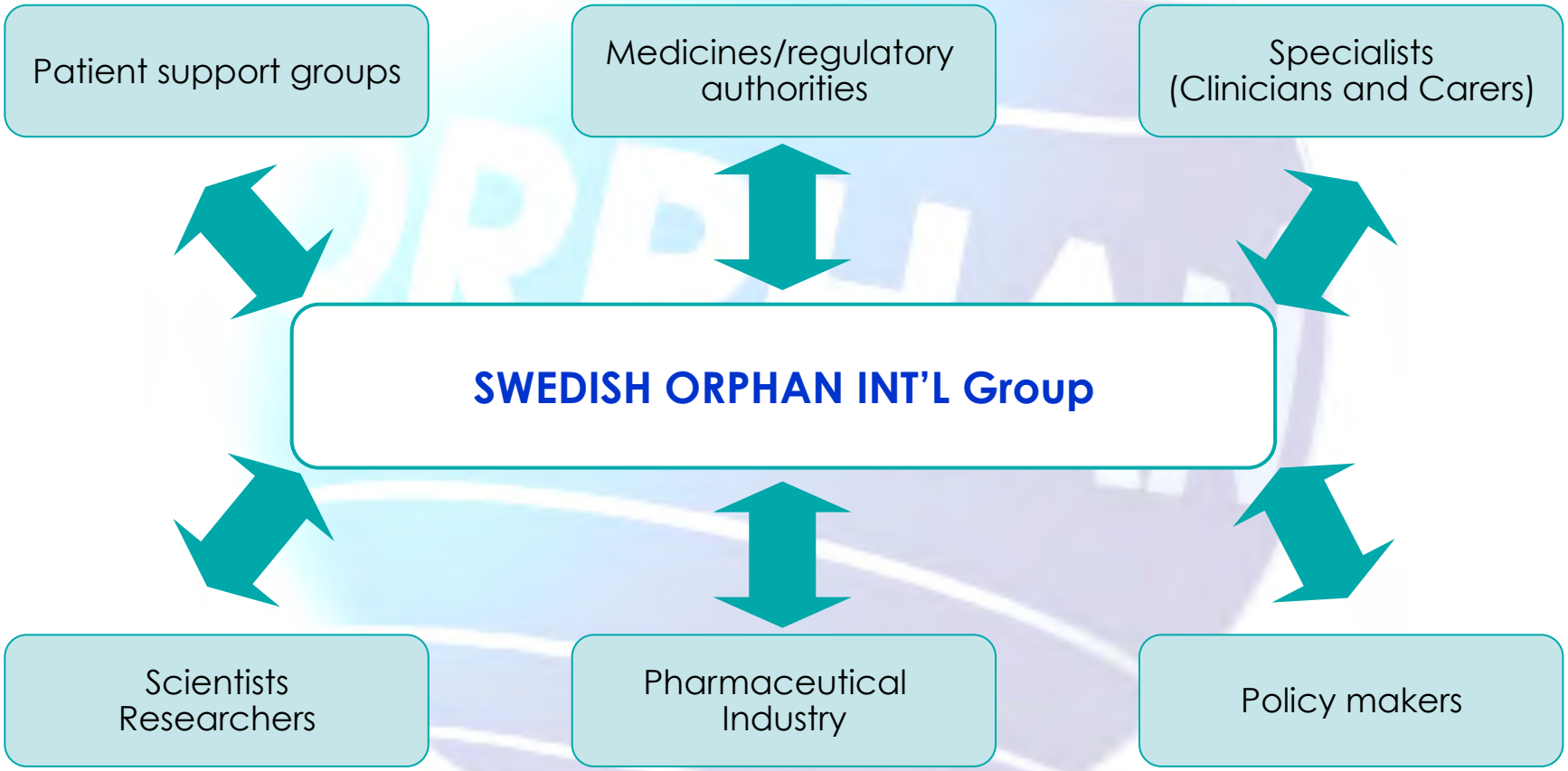
The EU Orphan Drug Policy

- G10
  - High level group on innovation and provision of medicines
  - Under the aegis of EC
  - Guidelines/recommendations for the European commission
    - No.9: Commission and member states to put in place an effective policy in terms of incentives to research and support the development and marketing of orphan and paediatric medicines
- 6th framework programme
- Member states incentives

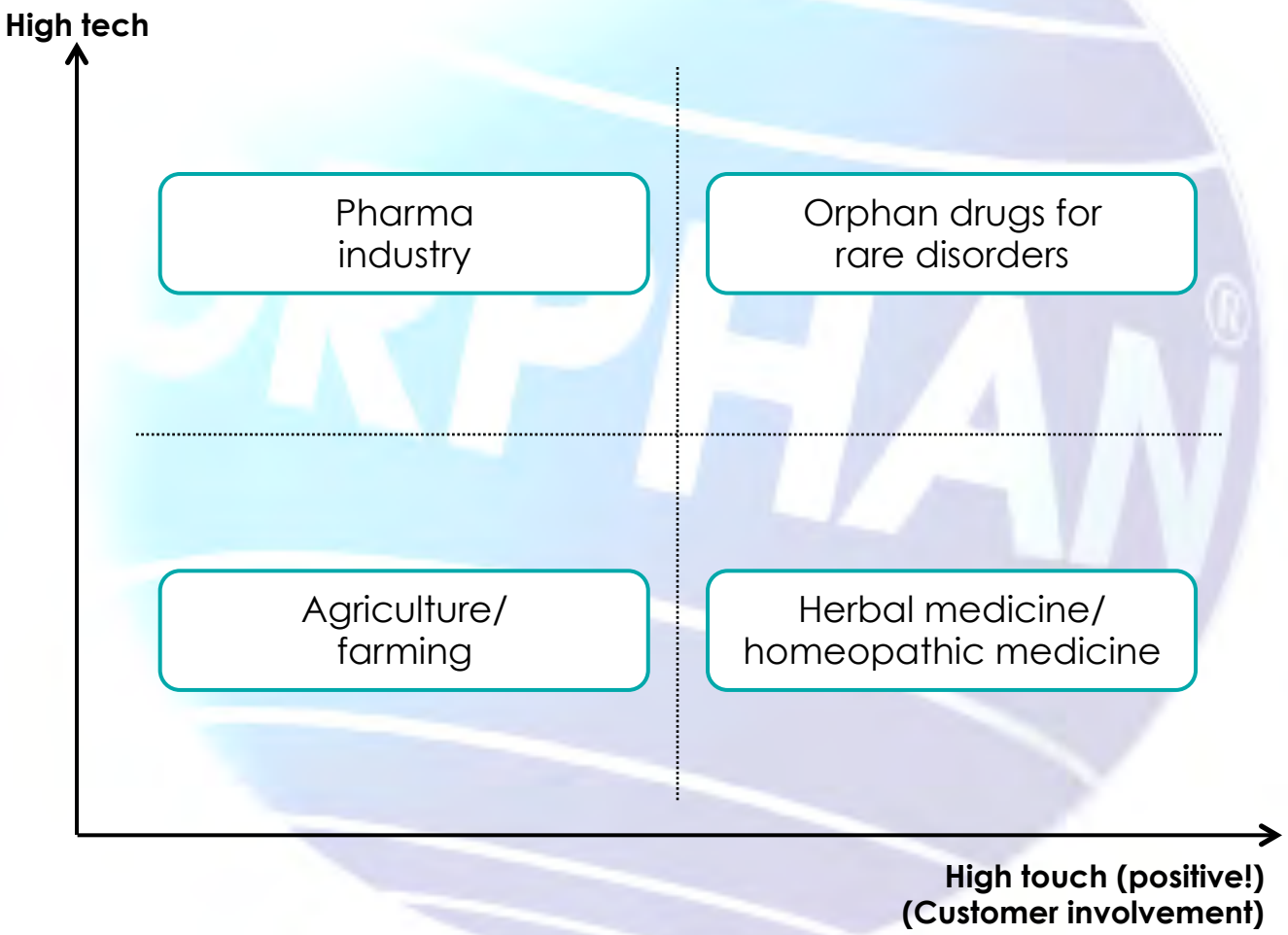
We need:

- community policy on rare diseases
- national governments to become committed
- equable access to marketed drugs
- co-ordinated training and qualification programmes

A Community with Active Partners



Added Value


High tech
Pharma industry
Orphan drugs for rare disorders
Agriculture/ farming
Herbal medicine/ homeopathic medicine
High touch (positive!)
(Customer involvement)

Acknowledgements:

- Prof's Holme and Lindstedt
- The patients and their families
- The team at SWEDISH ORPHAN INTERNATIONAL
- Rare Disease Therapeutics, Inc
- Orphan Europe

SWEDISH ORPHAN INTERNATIONAL