The challenge of developing drugs to treat rare diseases:
The example of Sanfilippo Syndrome Type A

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Typical Drug Development

- Identify the drug target
- Make a pure, stable and target-specific drug
- Ascertain acceptable toxicity profile before giving the drug to people
- Perform initial human studies examining safety across a wide range of doses (Phase I clinical trials)
  - Usually 20 to 40 patients or healthy volunteers
  - May be one or more trials
- Test efficacy, exploring different dosing regimens (Phase II)
  - Usually 50 – 200 patients
  - May be one or more trials
- Formally test efficacy, comparing to standard treatment if it exists (Phase III, or “pivotal” trial)
  - Typically 300 – 1000 patients
  - Typically 2 trials
- Drug registration and further clinical research (Phase IV)

Rare disease challenges:

- Limited detailed knowledge about the natural progression of the disease:
  - Frequency of clinical manifestations
  - Rate of disease progression (and variability thereof)
- Limited knowledge about what laboratory measures correspond to the variety of clinical expression of disease – “biomarkers”
- Relatively few patients in whom to carry out the necessary stages of drug development
- Often devastating, progressive diseases, often affecting children, where the urgency of developing a new treatment must be balanced against the responsibility of doing so safely, and the need to demonstrate efficacy conclusively

Shire's approach to these challenges in Sanfilippo Syndrome, Type A

- Extensive pre-clinical characterization of the drug
- "Natural History" or "Surrogate Endpoint Trial" – an observational study with no investigational treatment
  - Up to 20 children enrolled in a trial and comprehensively evaluated every 6 months for one year
    - Neurodevelopmental assessments
    - Brain imaging
    - Analysis of "biomarkers" in cerebrospinal fluid and other biological specimens
- Relatively small scale initial treatment trial in which safety and preliminary indicators of efficacy are studied (Combined Phase I/II)
  - Up to 15 children to be enrolled in 3 dose groups
  - Extensive analyses, similar to those in "Surrogate Endpoint Trial"
- Relatively small scale pivotal trial expected (Combined Phase II/III)
- Long-term safety follow up of all treated patients (including Phase IV)

Drug development – ancient principles, modern challenges

From Avicenna's 11th Century Canon of Medicine:

- The drug must be free from any extraneous accidental quality.
- It must be used on a simple, not a composite, disease.
- The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by Its essential qualities and another by its accidental ones.
- The quality of the drug must correspond to the strength of the disease…..
- The time of action must be observed, so that essence and accident are not confused.
- The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
- The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.