Potential Breakthroughs in Advanced Therapies and Biotherapeutics Medicinal Products, Sponsor Perspective

Dr. Ulrich Granzer

Granzer Regulatory Consulting & Services

www.granzer.biz

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What do we see?

- Very often rare diseases as lead conditions
- Orphan development and “orphan issues”
- Often individualized therapies based on autologous cells/tissue or on otherwise patient individualized approaches

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What needs to be done?

- **CMC**
  - **As usual?**
  - **What does it mean?**
    - GMP is a given
    - Batch sizes might be small, down to a single patient
    - Highest amount of drug use often in preclin development
    - Often very new developments – pushing the frontier
      - Gene therapies
      - Cell based therapies, CAR T, other gene manipulated cells
      - Autologous cells: Manufacture for single patients

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Preclinical

- „There is no shortage in No of test animals“
- Preclinical work as usual
  - Long term tox for chronic therapy necessary
  - All other tox testing as in ICH M3 or S6
  - But: is there a model, what happens in autologous settings?
  - Risk of autoimmune disease triggering
  - Risk of „overshooting“ activity of immune cells

A bigchallenge: Clinical development

- **Orphans have up to 10 % of living global population in clinical trial database**
  - (would be several million patients in non orphan major diseases)
- **Usually between 0.1 and 1%**
- **We need to find the patients**
  - **Rare genetic disorders: Patient interest groups (often parents)**
  - **Rare non genetic diseases (e.g. rare cancers): no patient groups – search for patients**
  - **100 centers for 50 patients not uncommon**

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Database size

- **Phase Ib/II/IIII**
  - **Usually 1,000 – 10,000 patients prior to registration for classical drugs**
  - **„Classical orphans“: 300 – 700 patients**
  - **Ultra orphans: (<10) 16 – 100 patients**
  - **Submission with lowest No of patients: 6 patients in DB (planned)**

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Meaning

- **Classical dose finding, statistics, assessment often not possible**
- **Primary endpoint at the beginning of pivotal trial often not known**
  - **Best knowledge of disease often gained during pivotal trial**
  - **Role of Guideline on small populations**
  - **Most often first chosen primary endpoint wrong**
    - Example: Friedreich‘s ataxia
      - Friedreich scale did not show clinical effects, Parkinsons disease scale did
      - Training effect of tests

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What can be done?

- Look at totality of data
- Assess trends in all endpoints
- Forest plot of all endpoints measured
- Biomarkers often important, but almost never validated

Regulators in EU and US

- **Early involvement of authority experts**
  - **Bidirectional knowledge transfer between regulators and company**
    - Understanding of disease
    - Need to leave classical pathways
  - **Discussion of clinical program**
  - **Options to be discussed and shown – use of video material**
  - **Best way for development within limited patient population**

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Role of national advice

- Early interaction in face to face meetings
  - Discussion of details
  - Pondering of ideas on development
- Direct involvement of leading experts in the EU
- Always face to face meetings
- National meeting minutes become part of EU (and FDA) briefing package)
  - Triggering direction of advice

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Protocol Assistance

- Discussion of program
- Discussion of potential endpoints and its handling
- Discussion of new initiatives:
  - Adaptive Licensing
  - PRIME

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PRIME

- **PRIority MEdicines**
- **“PRIME” is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need.**
- **PRIME builds on the existing regulatory framework and tools already available such as scientific advice and accelerated assessment”**
- **Provides the Rapporteur early on in development**

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Adaptive Licensing

- **Idea: Get an initial approval and “add” further indications to an existing licence**
- **Via “Type II variation”**
- **Upsides:**
  - **Early market entry**
  - **Early revenue stream**
- **Downside:**
  - **Early market entry triggers data exclusivity**
  - **May lead to a reduced return on investment**

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Breakthrough /RMAT designation

- On July 9, 2012 the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed. FDASIA Section 902 provides for a new designation - Breakthrough Therapy Designation. A breakthrough therapy is a drug:
- intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and
- preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.
- If a drug is designated as breakthrough therapy, FDA will expedite the development and review of such drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.

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Example: Glybera

- First ever approved gene therapy in the Western World
- Very severe metabolic disease: LPL Deficiency
- Patients must not eat fat: total of less than 15 g/day
  - Pancreatitis, death
  - Reason: LPLD is the most important enzyme for Chylomicron breakdown
  - Chylomicrons are the most important fat (triglycerid) carriers in the body
  - Blood of patients is yellow, not red, fat content in blood roughly up to 1000 times increased

Therapy

- Total of 64 i.m. injections into muscle tissue, injection point tattooed.
- Gene incorporated into muscle via viral carrier
- 2 – 4 weeks after inoculation muscle starts „manufacture“ of human LPLD

General issues following approval

- **RMP: Risk Management Plan**
  - **Registry**
    - Collection of safety (and efficacy) data post approval
    - Data to be pooled in data base and reported to regulators at defined time points
  - **Efficacy study, if possible**
  - **Dedicated Prescribing rules:**
    - Specialist prescription only
    - Training Manual for treating physicians

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And the upside:

- Chance for very small companies to get a drug to market
- Specialists of global importance to work with during development
- Sales force can be very small, but needs to be very specialized and very well trained
- Every (Ultra) orphan pushes the frontiers of science and regulatory affairs
- They can be fun!
- **Regulators usually are partners during procedure**
  - **Always direct and intense contact from start of (pre-) clinical development to approval**

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Summary

- Development pathways need to be invented on the go
- Clinical trials often small and difficult to analyse
- Regulators in authorities play a key role during development
- Overall, challenging but very rewarding as it often opens new areas of development and, thus, helps patients with severe and prior untreatable diseases

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Vielen Dank

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