# How to define high-risk medicinal products?

- Difficulty: Find the balance!
  - Definitions should be suitable to classify products like TGN1412 as high-risk
  - Definitions should on the other hand not classify conventional products as high-risk

=> Matter of extensive debate!

# How to define „high risk“?

- „Medicinal products are potential high-risk medicinal products when there are concerns that serious adverse reactions in first-in-man trials may occur.“

- Operational definition: Concerns may arise from knowledge or also lack of knowledge regarding …
  1. **… the mode of action**
  2. **… the nature of the target**
  3. **… the relevance of the animal model(s)**

- Regulatory consequence:
  Classification according to the definition criteria to be put to the IMPD / protocol by the Sponsor.

# How to define „high risk“?

- Important:
  **Guideline repeatedly states that not every novel medicinal product is high-risk, and clearly states that for many new medicinal products the conventional non-clinical programme provides an acceptable safety estimate.**

# How to define „high risk“?

(1) MODE OF ACTION

- **Novelty, plausibility, extent of knowledge**
  (again: either particular knowledge that there is a higher risk, or particular lack of knowledge)
  (e.g., newly discovered signalling pathways)

- **Nature and intensity of the effect**
  (extent, amplification, duration (!), reversibility (!))

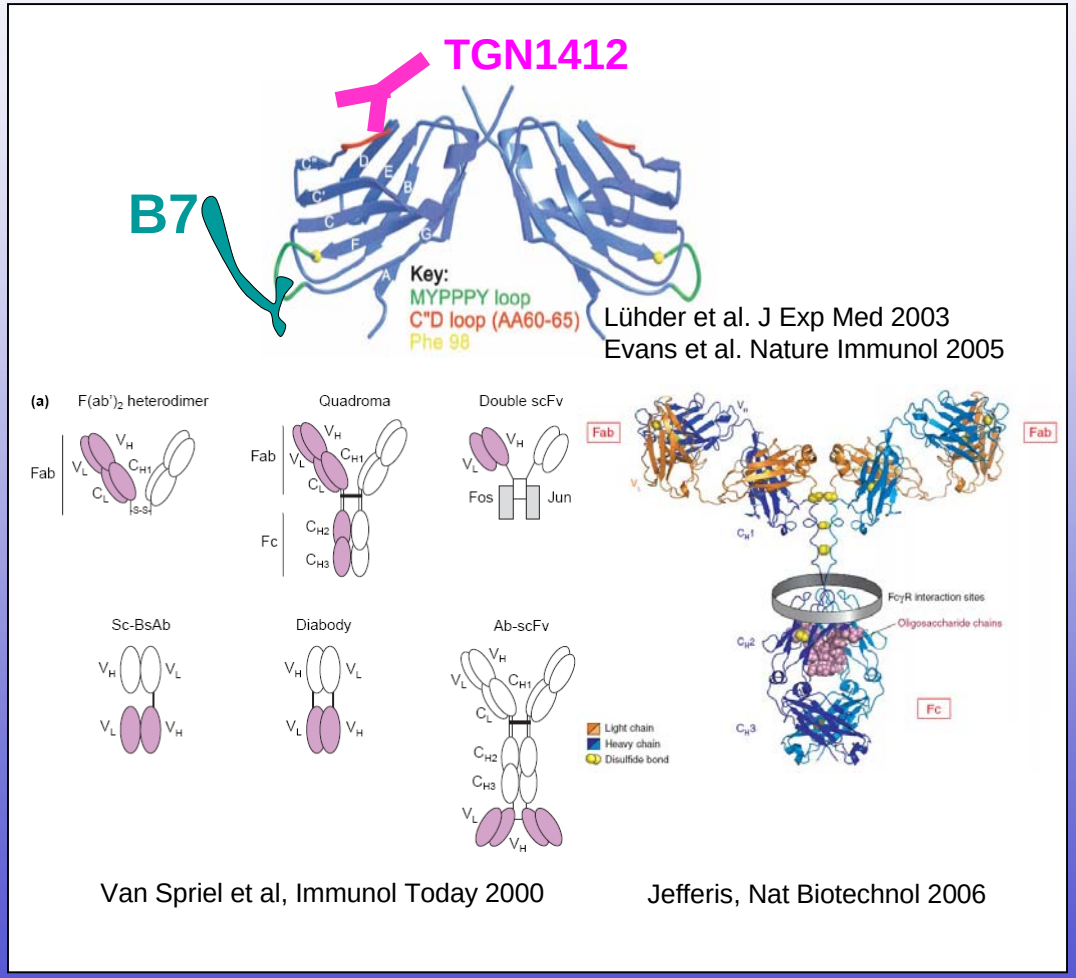
- **Type of dose response**
  (linear, non-linear, U-shaped, bell-shaped)

# How to define „high risk“?

- *(Mode of action, continued)*

  **=> More special reference to the following aspects:**

  – **Pleiotropic** mechanism, including the immune system
  – **Bypass** of physiological control, e.g. (super-) agonists
  – **Novelty** of structure, e.g. engineered mAbs or fusion proteins



# How to define „high risk“?

(2) NATURE OF THE TARGET,
irrespective of the mode of action

- **Nature of the target itself might pose a higher risk, even if there is extensive knowledge on the mechanism of action**
  (example: Mechanism is an enhanced cytotoxic effect in tumour cells expressing the target. However, target is expressed in physiological tissues.)
- **Extent of knowledge on structure, tissue distribution, cell specificity,…**

# How to define „high risk“?

(3) RELEVANCE OF ANIMAL MODEL

- **Central: How reliable is the target species for non-clinical toxicology testing?**
- **Comparison should include functional data** (binding alone not sufficient, see talk Prof. Silva-Lima).
- **Limited relevance might lead to „high risk“ classification.**

# Comments on section 4.1 of the guideline

- **Repeatedly stated that section is too broad**
  - virtually every new compound would be considered a potential high-risk compound
  - Fear of non-harmonized interpretation by NCAs
- **Various proposals to narrow to more specific classes**, e.g.
  - Monoclonal antibodies or even only full-length mAbs
  - Agonistic compounds

  (as suggested by Duff Report, which appears more specific)
- **Request for specific examples**
- **Define „non-high risk“ in addition**
- **Request to re-define the focus on „serious adverse reactions“ as basis for the „general“ definition**
- **Proposal to change the scope from a definition to criteria for risk mitigation strategy**
  including the request to avoid „black and white“ („high-risk“ vs. „non-high-risk“)