

Recommendations for upper bodyweight loss limits in short-term toxicity studies

Recommendations

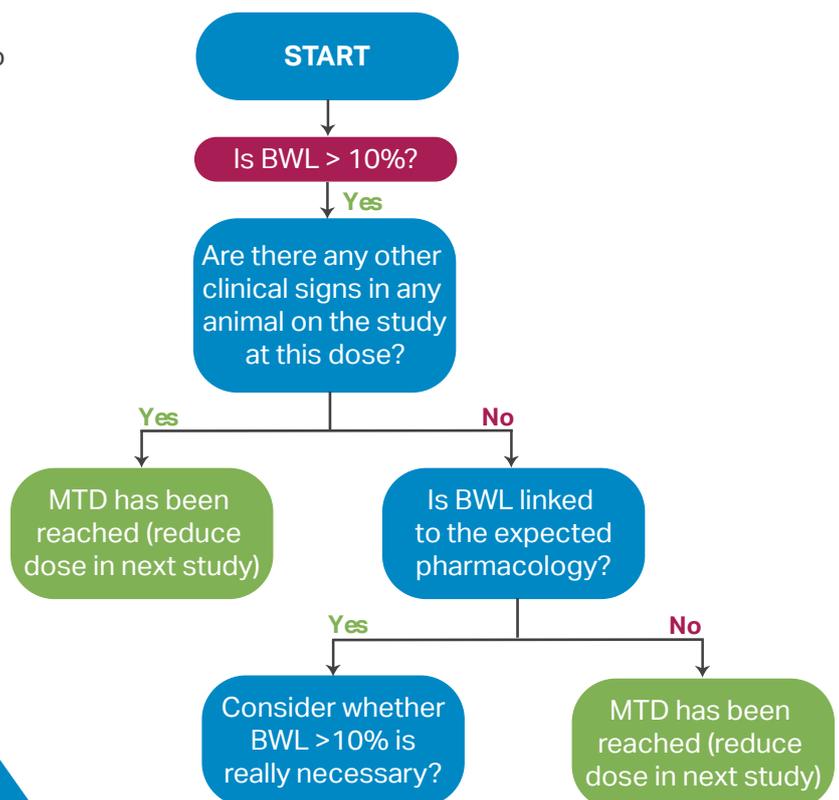
1. To use bodyweight loss as an objective measurement for determining the maximum tolerated dose (MTD) in short-term toxicity studies.
2. To set an upper limit of bodyweight loss of 10 per cent in rats and dogs. To use a decision tree as an alert system to indicate when MTD is near and to inform subsequent dosing decisions.

3Rs impact

- The upper bodyweight loss limits are less than those currently in use. Implementing these recommendations will refine the use of the thousands of animals in short-term MTD studies worldwide, as animals will experience fewer adverse effects.
- The objective approach taken to formulate these recommendations will enable more global acceptance of the definition of a MTD and has the potential to be translated to other areas such as chemical testing, pharmacology and efficacy studies.

Bodyweight loss decision tree

For use with rats and dogs only to determine the MTD in short-term toxicity studies.



**Is BWL
> 10%?**

Background

MTD studies are important from both a scientific and ethical perspective. They are used to make decisions on the progression of potential candidate drugs across a range of therapeutic areas. They also set the dose level for subsequent studies that allow for regulatory approval.

The MTD is usually determined by parameters such as bodyweight loss, clinical signs and a change in food consumption. However, such assessments are often subjective with little regulatory or cross-industry agreement on how the MTD should be defined.

Bodyweight loss is one of the few objective measurements used in short-term toxicity studies. It is used as a measure of animal welfare, with the greater the weight loss the greater the potential for suffering.

To date there has been no evidence-based guidance on the upper limit for bodyweight loss. In this NC3Rs-industry collaboration, data sharing on 151 compounds has shown the upper limit for bodyweight loss ranges from 15 to 25 per cent in practice.

Detailed analysis of the data however has shown that there is little scientific value in exceeding bodyweight loss limits of 10 per cent in rats and dogs to determine the MTD or future dosing decisions. Bodyweight loss above these limits has been found to almost always be associated with additional clinical signs.

These standardised assessment criteria will minimise the adverse effects experienced by thousands of animals used in pharmaceutical development each year.

Pioneering Better Science

International industry collaboration

The recommendations were developed by a working group of 10 pharmaceutical companies and five contract research organisations from Europe and the US, led by the NC3Rs and AstraZeneca.

Information on 151 studies, from 15 companies, has been used to develop the recommendations on upper bodyweight loss limits for rats and dogs. The evidence sets out a new upper limit of bodyweight loss to be used as a primary endpoint for selecting the highest dose of a drug that can be tolerated in animals to reduce the likelihood of major adverse effects.

Reference

Chapman K, Sewell F, Allais L, Delongeaes J-L, Donald E, Festag M, Kervyn S, Ockert D, Nogues V, Palmer H, Popovic M, Roosen W, Schoenmakers A, Somers K, Start C, Stei P, Robinson, S (2013). A global pharmaceutical company initiative: An evidence-based approach to define the upper limit of body weight loss in short term toxicity studies. *Regulatory Toxicology and Pharmacology*.

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