Home Office

Naming of products and substances in project licences for batch quality control and regulatory toxicology

Summary:

1. Inspectors assessing project licence applications for work involving the quality control (QC) testing of batches of products for release must ensure that, where an alternative non- animal test exists, the product to be tested is named in the licence and a valid scientific or regulatory reason for testing in animals is given. The reasons for this are set out below.

2. Currently the commonly used tests which fall into this category are the Rabbit Pyrogen Test (RPT), the Abnormal Toxicity Test (ATT) and the General Safety Test (GST). At this time the RPT has validated non-animal alternatives, although the validation has been completed only for some substances. The alternatives comprise the bacterial endotoxin test (or BET) and the monocyte activation test (MAT). (The BET was formerly known as the limulus amebocyte lysate test or LAL). For some products alternative tests have been shown not to work: for example, where pyrogens other than lipopolysacchride (LPS) are involved. It is acceptable to allow the use of RPT for these substances.

3. For some older products the current Marketing Authorisation (MA) may specify the use of the RPT although the validated alternative could now be used. It is acceptable to allow the ongoing use of the RPT for these substances provided licensees can demonstrate either that genuine efforts are being made to validate the alternative or that an appropriate amendment to the MA is in train.

4. Similarly, the requirement for the use of the ATT or GST in current MAs should be reviewed. Their ongoing use is acceptable only if licensees can demonstrate that genuine efforts are being made to validate alternative assays, or that an appropriate amendment to the MA is in train.

5. The use of the RPT, GST or ATT may be accepted only if it is required by the MA and there is demonstrable evidence that non-animal alternatives are not scientifically valid. The evidence relating to an individual product or substance should be assessed prospectively, either at the time the licence is granted if

all the products/substances are known, or via amendment during the course of the licence.

6. All QC licences and all regulatory toxicology licences must specify the testing guidelines and/or monographs to be used in the programme of work. Inspectors must consider the requirements of Article 13 of Directive 2010/63 EC with respect to the 3Rs in their assessment. Where doubt exists as to whether this can be satisfied, advice should be taken from the relevant specialist inspector.

7. For new product development work, before the market authorisation stage, the project licence must contain sufficient assurances that a robust decision-making process in the selection of tests will be followed before live animal testing takes place. From July 2013, the MHRA has been actively seeking alternatives to animal tests to be used when reviewing proposals for a testing protocol for the MA of a new product or variation of an existing product.

8. The principles set out above should be applied to both new project licence applications and to existing licence authorities, where these are identified. An additional condition (see paragraph 22 below) should be applied to all such licences.

Background:

Legal background

Section 2A (1) of the Animals (Scientific Procedures) Act requires that the Secretary of State must exercise his or her functions under this Act with a view to ensuring compliance with the principles of replacement, reduction and refinement. Section 2A (2) (a) indicates that "the principle of replacement is the principle that, wherever possible, a scientifically satisfactory method or testing strategy not entailing the use of protected animals must be used instead of a regulated procedure".

In addition Project Licence standard conditions 2 and 3 require:

"The licence holder shall ensure that the specified programme of work does not involve the application of any regulated procedure to which there is a scientifically satisfactory alternative method or testing strategy not entailing the use of a protected animal.

The licence holder shall ensure that regulated procedures are not applied to an animal as part of the specified programme of work if the data to be obtained from the application of those procedures is already available in a Member State and has been obtained there by procedures which satisfy any relevant regulatory requirements of the EU."

Article 13 of EU Directive 2010/63 states:
Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

Considerations and conclusions:

9. Members of the ASRU Inspectorate have discussed these issues in detail and their conclusions are summarised as follows:

10. It was noted that in Article 38 of EU Directive 2010/63 and in s5B(2)(a) of the revised Animals (Scientific Procedures) Act, one of the criteria by which a programme of work can be judged 'favourable' (i.e. allowable) is if it 'is required by law'. However, Article 13.1 of the Directive also requires a method not entailing the use of a live animal to be used if it 'is recognised under the legislation of the Union'.

11. Each type of project licence in which substances or products are tested for safety, efficacy and other reasons (e.g. pharmacokinetics) was considered. It was considered that the area of primary concern was the QC testing for batch testing required by the Market Authorisation for the substance or product.

12. Project licences held by pharmaceutical companies, contract research organisations (CROs) and academic institutions for the development of new

chemical and biological entities before they are authorised are controlled by testing guidelines for example:

- ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) ;
- VICH (Veterinary International Conference on Harmonisation);
- EudraLax (collection of rules and regulations governing medicinal products in the European Union).

13. There is a mandatory requirement for new medicines to be tested according to such guidelines and so there is no benefit for the Secretary of State to know the name of the substance to be tested as it is highly unlikely that there would be grounds for disallowing such testing. For these licences, effective controls and protection of animals can be achieved through application of the earliest clear and unambiguous end-points and staged dosing regimens, etc. Adherence to the legal requirements to use non-animal alternatives can be effected by using the wording in paragraph 22 either in the text of Section D of the project or as an additional condition. Licence controls through end-points should be used to effect refinements.

14. Testing of industrial chemicals pre- or post- authorisation is a legal requirement and controlled by OECD guidelines. The harm- benefit assessment would not be influenced by the substances being named in the project licence. Ongoing requirement to consider the use of non-animal alternatives should be effected by using the wording in paragraph 22(ii) either in the text of Section D of the project or as an additional condition. Licence controls through end-points should be used to effect refinements.

15. Post-authorisation QC testing of vaccines and other biologicals for potency, efficacy and safety for release are mandated in specific testing monographs and for these the substance is already named in the monograph. The project licence should refer to the named substance and/or the monograph.

16. Post-authorisation QC testing of non-biological pharmaceuticals is limited to the ATT and the RPT. Such testing can only be allowed if the MA specifies that the test is required and this should be stated in the licence. For the RPT, alternatives exist, but there may be scientific reasons for continuing to use animals. For these licences the Secretary of State must be aware of the product being used and must consider the validity of the reason for that testing. Licensees must be encouraged to validate a non-animal alternative test for each listed substance or product. There should be clear instruction via an additional condition on the licence (see paragraph 22 below) to notify the Home Office if an alternative non-animal test for a substance or product becomes validated and accepted. The animal test should then be removed from the licence. They must also apply to us for an amendment for any additional product they may wish to test under the licence.

17. For some older products the current Marketing Authorisation (MA) may specify the use of the RPT although the validated alternative could now be used. It is acceptable to allow the ongoing use of the RPT for these substances provided licensees can demonstrate either that genuine efforts are being made to validate the alternative or that an appropriate amendment to the MA is in train.

Substances vs. products:

18. There are instances where the BET has been validated and accepted for a particular substance but RPT can be allowed for products containing this substance. For example, an older MA may specify that the RPT is required in which case the licensee should be encouraged to validate a non-animal alternative and amend the MA. Alternatively there may be some factor in the formulation of the product that interferes with the alternative test – e.g. silicone in the vial stopper. In such cases, it is essential that project licences allowing the RPT specify the product and not just the substance to be tested.

Actions to be taken

Inspectors

19. The ASRU licence database does not provide information to readily identify all potentially relevant existing licence authorities. The following is a pragmatic approach to immediately identify the majority of cases.

20. All inspectors should identify any new licences authorising QC or batch testing using live animals. They should also consider what existing licences they are aware of which may be relevant to these instructions. The existence of other relevant licences may be identified through inspection, assessment of amendment requests, or brought to the attention of inspectors in other ways.

21. Licensees should be invited by the assigned inspector to request amendment of existing licences by using the wording in paragraph 22 either in the text of Section D of the project or as an additional condition. If the relevant changes have not been achieved within 6 months of the request, formal powers for amending licences under Section 12 should be considered.

22. Additional conditions to be applied *to all project licences* authorising batch quality control tests:

    (i) For all batch quality control testing using live animals, the substance or product to be tested must be named in the licence providing scientific justification for such a test.
    (ii) You must notify the Home Office when an alternative non-animal test for a substance or product becomes validated and accepted in order that the authorisation for the ongoing use of the live animal test can be withdrawn for the particular substance or product.

Licensing team

23. A list of all such licences will be maintained by the Licensing team.

Animals in Science Regulation Unit
6 February 2014

Directive 2010/63 EU, Article 13

Choice of methods

1. Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

2. In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected:

(a) use the minimum number of animals;

(b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm;

(c) cause the least pain, suffering, distress or lasting harm;

and are most likely to provide satisfactory results.

3. Death as the end-point of a procedure shall be avoided as far as possible and replaced by early and humane end-points. Where death as the end-point is unavoidable, the procedure shall be designed so as to:

(a) result in the deaths of as few animals as possible; and

(b) reduce the duration and intensity of suffering to the animal to the minimum possible and, as far as possible, ensure a painless death.