Table 7: Physicochemical Methods to Replace Traditional Bioassays

SCOPE:

Bioassays provide indispensably important information but are sometimes too slow and not sufficiently reliable.

QUESTIONS FOR DISCUSSION:

1. What can be done about this? Improve the existing ones, or change?
2. What is the scope of our discussion? Which traditional bioassays do we consider?
3. What are the desirable specifications for the tasks we have in mind (e.g. for precision, sensitivity, selectivity)?
4. Which physicochemical methods have potential to replace traditional bioassays?
5. Are there experiences about these approaches we can share?

DISCUSSION NOTES:

A few reminders about the assessment of biological activity, stipulated in the ICHQ6B *Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*:

- Assessment of the biological properties constitutes an equally essential step in establishing a complete characterisation profile.
- A valid biological assay to measure the biological activity should be provided by the manufacturer (examples include: animal-based biological assays, cell culture-based biological assays, biochemical assays; other procedures such as ligand and receptor binding assays, may be acceptable).
- A biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where:
    - sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and
    - there exists a well-established manufacturing history.
- Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product which is linked to the relevant biological properties.

A bioassay plays an important role in correlating product biological activity to structure and MoA (which is the link between clinical response and activity measured in a bioassay), and thus it is an essential and valuable component of the complete analytical profile.

Bioassays are generally challenging analytical procedures, which sometimes lack precision and robustness, and require a thorough method transfer. However, approaches may be developed to

reduce assay variability, such as increasing the number of independent determinations required to report a result so that necessary accuracy and precision are achieved.

Alternative strategies to potency testing ("surrogate tests"), including binding assays and physico-chemical procedures, are being discussed and investigated: what level of correlation/body of data is necessary between the two assays (it very much depends on the complexity of the biological activity)? For future discussions, case studies would be helpful to be used as concrete examples to build on the discussion.

Current Ph. Eur. initiatives focus on the development of a general chapter on potency assays for anti-TNF-alpha products ("horizontal" standard), to be published soon for public enquiry in Pharmeuropa. This work is based on a collaborative study that had been undertaken to assess the suitability of various cell-based assay models to be applied as universal procedures for assessing the TNF-alpha inhibitory effect. Experimental data generated in the collaborative study are being used to set the basis for defining:

- system suitability parameters and criteria to be included in the general chapter;
- specific procedures to be described in the general chapter, including sufficiently descriptive conditions to facilitate successful independent analyses;
- a common set of analytical expectations and approaches.