

Analytical survey

Selectivity or specificity?

Validation of analytical methods from the perspective of an analytical chemist in the pharmaceutical industry¹

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For a number of years analytical chemists in the pharmaceutical and biomedical fields have learned how to demonstrate that their methods have a performance that can guarantee reliable results. After the advent of good laboratory practice, we know this exercise as validation of analytical methods. In the field of drug analysis, it is very clear that the definitions cover the entire field of analytical chemistry from bioanalysis to substance and product analysis. This is an important observation as the same principles should apply whatever type of sample is to be analyzed. There are a number of definitions given by several international organizations (Table 1). Most of them are congruent.

Abbreviations: IUPAC, International Union of Pure and Applied Chemistry; ILAC, International Laboratory Accreditation Conference; WELAC, Western European Laboratory Accreditation Cooperation; ICH, International Conference on Harmonization; ISO, International Organization for Standardization.

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In the last few years harmonization efforts have been rather intensive in the pharmaceutical field and also for the validation process. Unfortunately for analytical chemists, this effort from the regulatory bodies side, as exemplified by the ICH, has only focused on validation of analytical procedures used for the control of substances and formula-

Table 1
Validation of analytical methods—international definitions

Organization	Applicability	Remarks
IUPAC	Worldwide	
ILAC	Worldwide	
WELAC	Europe	
ICH	Europe, Japan, USA	Only pharmaceutical products. Why not bioanalysis?
ISO	Worldwide	Lacks definitions of selectivity and specificity

Table 2
WELAC definition of selectivity and specificity (1993)

Selectivity of a method refers to the extent to which it can determine particular analyte(s) in a complex mixture without interference from other components in the mixture

A method which is perfectly selective for an analyte or group of analytes is said to be specific

tions. Similar requirements have, however, also to be applied for analysis of drugs in body fluids. This forms the basis for pharmacokinetics and bioequivalence studies. In fact, in the USA a North American harmonization activity in this field is on-going [1].

Most of the definitions recommended by the ICH are concordant with those of other organizations such as IUPAC, ILAC and WELAC. This is good. Terms and definitions should have the same meaning all over the world, whatever kind of analysis you perform. There may be differences between languages that make some definitions confusing, but in English it is clear.

One of the key definitions for analytical chemists is, without doubt, selectivity. This can be considered as the hallmark of the analyst. If you are not clear about the effect of potential interferences in your method, all other attributes such as accuracy, precision, linearity, etc. are meaningless. Professional analytical chemists have found it difficult to understand why the IUPAC definition of specificity, as being the ultimate degree of selectivity [2], cannot be accepted by the ICH. The definition by WELAC clearly demonstrates that situation, particularly in its reference to “the extent to which it can determine ...” (Table 2) [3]. The current definition of the ICH is not clear, in that it refers to another procedure as being permissible to add to the validation exercise in order to make the method specific (Table 3) [4]. This probably has its roots in the preparatory work of the CPMP in developing this requirement (Table 4), where both quantitative and qualitative aspects are presented. It is difficult to understand why chromatographic methods are not quantitative. In any event the second statement in the ICH definition of specificity is at the very least unhelp-

Table 3
ICH definition of specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s)

ful, and at its worst confusing to the practising analyst.

Is the problem in understanding the differences between selectivity and specificity only a semantic one? It is clear that some analysts don't recognize the difference. The meaning might also differ between countries and in different languages. In some areas analysts use their own vocabulary, such as in the field of antibodies, where one often hears about monospecific and polyspecific antisera, which however, show cross-reactions. This is a typical issue that illustrates selectivity. The guiding principle should also include the fact that any definition of validation should refer to a single analytical method, not to a specification involving, perhaps, multiple analytical procedures.

So, when is a method really specific? The answer can be simply stated as: “when the analyte alone is responsible for the signal that is measured.” This has been very clearly expressed by Christian in his well-known treatise *Analytical Chemistry* (Table 5) [5]. Again the degree of inter-

Table 4
Some confusing examples from the preparatory work

Specific test procedure:

A procedure to measure quantitatively a chemical-physical parameter or functional group of one or more different analytes in the sample matrix, e.g. titration of the carboxylic group of an acid, measure of the specific absorbance, immunoassay

Selective test procedure:

A procedure to detect qualitatively the analyte in the presence of components which may be expected to be present in the sample matrix, e.g. chromatography, selective electrode

Table 5
How to distinguish between the terms specific and selective [5]

A clear distinction should be made between the terms *specific* and *selective*. A specific reaction or test is one that occurs only with the substance of interest, while a selective reaction or test is one that can occur with other substances but exhibits a degree of preference for the substance of interest. Few reactions are specific, but many exhibit selectivity

ference is shown to be the characteristic of selectivity. The phrase “exhibits a degree of preference for the substance of interest” elegantly expressed this situation.

Perhaps it is helpful to visualize the difference between specificity and selectivity graphically, as illustrated in Fig. 1. Selectivity is something that can be graded or scaled but specificity is an absolute characteristic. In this context it is unfortunate that the current ICH definition interferes with, and corrupts, already established termino-

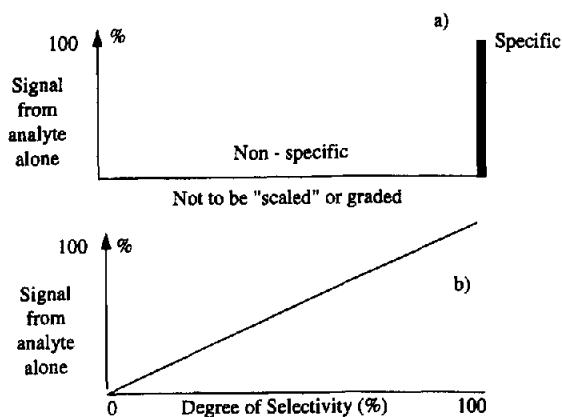


Fig. 1. Graphical demonstration of selectivity and specificity. The percentage of the measured signal attributable to the analyte alone (on the y-axis) is given as a function of the degree of selectivity (b). A perfectly selective method is said to be specific (a).

logy. The arguments that could be made against the current ICH definition are:

- (1) Only one kind of definition is required and a widely accepted definition already exists.
- (2) The definition should always refer to a single method under scrutiny.
- (3) The current proposal deals only with substances and formulations without considering the large field of bioanalysis.

The arguments in favour of the ICH definition are:

- (1) This is a regulatory issue and specificity is required.
- (2) Specifications as a whole are based on the total information from a set of methods.

Having said that, it is, however, clear to many that the ICH document reveals the surprising lack of an integrated view on analytical chemical issues in the pharmaceutical industry.

In fact, professional analytical chemists do realize that few methods are specific in the sense defined above. Many matrices are so complex that, with a degree of humility, it is only possible to talk about selectivity. This does in fact mean that there is a place for both terms, co-existing, side-by-side, but with appropriate definitions. This has clearly been expressed by both WELAC and IUPAC: “Specificity is the ultimate of selectivity”.

References

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