

# Invited Speakers

## S6.6

### Regulation of New Feed Additives

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Feed additives will obtain market authorisation in the European Union only if they have complied with and have been approved under the procedures specified in Regulation (EC) 1831/2003. Authorisations are issued for a period of ten years after which additives have to be reassessed and re-authorised. Assessment of safety and establishing whether an additive demonstrates one or more of the attributes of a feed additive listed in the Regulation is the responsibility of the European Food Safety Authority (EFSA), while the Commission and Member States, taking into account the opinion of EFSA, decide whether an additive should be authorised. The operation of Regulation (EC) 1831/2003 is critically examined in the light of the nearly 100 applications made and, from the experience gained, the implications for new additives and, particularly, truly novel additives considered. It is likely that virtually all new applications will fall within the category of zootechnical additives which carry propriety rights as opposed to other categories of additives where authorisations are made on a generic basis and so available to any manufacturer. Novel as opposed to new product may encounter particular problems because of the potentially greater demands of risk assessor faced with new issues, the difficulty of classification within the definitions introduced by Regulation (EC) 1831/2003 and because of the desire of legislators to maintain a clear distinction between feed additives and veterinary products.

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### Introduction

The European market has operated what is in effect a positive list of feed additives since the implementation of Council Directive 70/524/EEC of November 1970. This Directive incorporated a list of additives already in use in the various Member States of that time and gave authorisation for their continuing use, while requiring new additives to undergo an assessment process. This ensured that only feed additives given pre-market approval could be legally used within the European Community. The principle of pre-market approval enshrined in this Directive has operated ever since.

Directive 70/524/EEC was amended on numerous occasions over the 30 years of its life; some modification being minor in nature, others introducing major changes (see Table 1). Of particular note was the decision in 1993 to include additives based on enzymes or micro-organisms and the introduction in 1996 of a provisional authorisation procedure for additives of proven safety to allow time for efficacy data to be obtained. However, despite these many modifications, it became obvious that with the passing of time, developments within the feed industry, the need to harmonise with other legislation and the changing attitudes of consumers and other interest groups to food production in Europe had created a need for a major overhaul of the feed additive legislation. This was undertaken in the early years of the new century.

What emerged from the review of feed additive legislation was Regulation (EC)1831/2003 and its implementing rules (Regulation (EC) 429/2008). New feed additives now are authorised for use, processing or sale in the European Union only if they have complied with and have been approved under the procedures specified in this Regulation. In addition, since authorisation is now only issued for a fixed period of ten years, all additives will be required to undergo regular re-authorisation. This has implications for the many additives that were simply incorporated into the Register of Feed Additives in the 1970s and have never undergone a formal assessment of either their safety or efficacy.

Regulation (EC)1831/2003 also formally recognised the role of the European Food Safety Authority (EFSA) as the body responsible for risk assessment in all food and food-related matters (including feed additives): a role previously undertaken by the competent authorities of the Member States. However, the final decision to approve or decline a feed additives remains the responsibility of the Member States and the Commission acting as risk managers

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**Table 1.** A brief history of the regulation of feed additives

Date	Regulation	Content
1970	Council Directive 70/524/EEC	Framework for Community feed additive legislation Recognised nine categories of additives Derogations (up to five years) allowed for Member States
1993	Council Directive 93/114	One of a number of major amendments to 70/524/EEC. This incorporated micro-organisms and enzymes into the feed additive Directive
1993	Council Directive 93/113	Introduced transitional arrangements for existing enzymes and micro-organisms already in use in feeds.
1996	Council Directive 96/51	Amended 70/524/EEC to include additional categories of feed additives and to allow provisional authorisation for additives assessed as safe to provide time to develop evidence of efficacy
2002	Regulation (EC) 178/2002	The general food law, establishing principles of food The Regulation also establishes EFSA as the body responsible for risk assessments in the food chain.
2003	Regulation (EC) 1831/2003	Replaces 70/524/EEC
2008	Regulation (EC) 429/2008	Implementing rules for (EC) 1831/2003
2009	Commission Regulation (EC) 386/2009	First modification of (EC) 1831/2003 introducing mycotoxin binders as a new functional group within the category of technological additives.

## Regulation (EC)1831/2003 in practice

Despite a transition period allowing applicants to opt for an assessment under the provisions of the old Directive, the large majority of applications passed to EFSA since 2004 have been assessed under the provisions of (EC)1831/2003. At the time of writing some 98 applications have been considered, the majority falling into the zootechnical category (Table 2). To date, no applications for new technological additives have been submitted.

**Table 2.** Applications made in the framework of Regulation (EC) 1831/2003 and considered by EFSA

Category of additive	No of applications
Technological	0
Sensory	2
Nutritional	16
Zootechnical (micro-organisms)	37
Zootechnical (enzymes)	22
Zootechnical (others)	6
Coccidiostats	15
Total	98

A number of additives routinely used in livestock production were not required to obtain authorisation under Directive 70/524/EEC, although some form of National requirements were usually present. The new Regulation now covers the marketing of two such groups – silage additive considered as technological additives and “flavours” considered as a functional group within the category sensory additives (Table 3). Provisional arrangements were made for such additives to remain on the market for a period of seven years after the Regulation came into force. This derogation ends in 2010 and a full assessment will be required for all silage additives and flavours intended to be used after this date.

The requirements of Regulation (EC)1831/2003 are considerable and, in principle, requires all products to be assessed for their safety for the target animal(s), consumers of animal products, users of the additive such as mill workers or farmers and the impact of the additive on the wider environment. In addition the Regulation retains the requirement for an applicant to demonstrate that the additive fulfils one or more of the attributes of an additive listed in the Regulation (Article 5.3), loosely interpreted as a demonstration of efficacy. There is no doubt that if an additive had to fully satisfy all of the requirements of the Regulation an applicant would incur considerable costs. However, practice has shown that only a completely novel

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xenobiotic would suffer the full requirements. For the majority of additives considered by EFSA to date, the structure of the Regulation (and its interpretation by EFSA) makes provision for simplified procedures.

**Table 3.** Categories and functional groups as defined in Annex I of Regulation (EC) 1831/2003

<b>1 Technological additives</b>	<b>2. Sensory additives</b>
(a) preservatives (b) antioxidants (c) emulsifiers (d) stabilisers (e) thickeners (f) gelling agents (g) binders (h) substances for control of radionuclide contamination (i) anticaking agents (j) acidity regulators (k) silage additives (l) denaturants (j) mycotoxin binders	(a) Colourants (i) substances that add/restore colour to feedstuffs (ii) substances that colours food of animal origin (iii) substances that colour ornamental birds/fishes (b) flavouring substances (smell/palatability)
	<b>3. Nutritional additives</b> (a) vitamins/pro-vitamins and similar (b) compounds of trace elements (c) amino acids, their salts and analogues (d) urea and derivatives
	<b>4. Zootechnical additives</b> (a) digestibility enhancers (b) gut flora stabilisers (c) substances which favourably affect the environment (d) others

The Regulation specifies that authorisation for food use should be taken into consideration when considering consumer and user safety. Provided it can be demonstrated that human exposure via consumption of animal products or for those handling the product is not greater than direct exposure via food use, then no further assessment of consumer safety would be required and the requirements for user safety would be reduced. Similarly the Regulation makes provision for a simplified procedure for additives intended only for use with non-food producing animals and allows an element of extrapolation from what are defined as major species to other physiologically similar species. Thus data obtained with broilers can be extrapolated to ducks, quails and other poultry species not considered as a major species.

The introduction by EFSA of the Qualified Presumption of Safety (QPS) as an assessment tool (EFSA, 2005, 2007) has greatly reduced the requirements for many microbial products and, to a lesser extent, has benefited the assessment of enzymes derived from QPS organisms. Microbial additives based on one or more species considered by EFSA to qualify for QPS status are freed from the necessity to provide evidence of target animal, consumer and environmental safety. Environmental safety has also proved not to be a major issue. With the exception of the coccidiostats, virtually all of the compounds/agents considered to date have been "natural" substances or otherwise widely distributed in the environment and whose use in animal production would not result in an unusually high localised concentration in the terrestrial or aqueous environment. The Phase I assessments exempt such additives from further consideration.

The demonstration of "efficacy" can be one of the most demanding (and expensive) requirements of Regulation (EC) 1831/2003. However, this does depend on the category of additive. The attributes of technological additives which, in principle, exert their effect directly on the feed/feed ingredients, can usually be confirmed by relatively simple and cheap *in vitro* demonstrations. Even when the attribute of the additive can only be shown after ingestion by an animal the costs can be limited. Addition of colour to animal products or the demonstration of the bioavailability of a novel form of a nutritional additive for example can usually be shown by a short term study or within the course of normal production. Demonstration of efficacy is more controversial when zootechnical additives are involved. In this case and unlike other categories of additive there is only the most general link between the functional group and the attribute of the additive. As a result short term experiments may well provide evidence of credibility but not necessarily of the benefit to the user (or the environment). The Scientific Committee on Animal Nutrition (SCAN) and subsequently EFSA have chosen to interpret the requirement "to affect favourably the performance of animals" in terms of financial benefit to those purchasing the additive. In effect, unlike technological, sensory and nutritional additives where efficacy is demonstrated at the level of the functional group (see Table 2), the attributes of zootechnical additives is invariably judged at the level of the category. It is recognised that this is an imperfect solution, not the least because the requirement for three long-term animal studies in which a significant benefit to performance is

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demonstrated, is evidence only of a potential. It is well recognised that to specify when and to what extent an zootechnical additive would be effective would require many more trials. However, until the functional groups (and their definition) included under the category of zootechnical additives more closely relate to mode of action, surrogate measures able to replace the need for animal feeding studies are unlikely to be convincing.

## **Generic versus holder specific authorisations**

Most new applications for additives are likely to continue to fall within the zootechnical category and to a much lesser extent within the sensory and nutritional categories. There are several reasons for this. Virtually all technological additives and most nutritional additives are historical entries in the Register of Feed Additives and have never been associated with an applicant or group of applicants. Additives in these categories are considered generic and thus do not offer proprietary benefits. Far from seeing additions to these categories it is likely that the process of re-authorisation will see losses from the existing list of additives. Already, some additives have taken on the aspects of "orphans", akin to orphan drugs, where it is difficult to see who will champion their cause. Feed use may represent a very small market for the manufacturer and so taking responsibility for re-authorisation may hold few attractions, while distributor Companies may be too small to individually carry the costs of applications. In contrast authorisations for zootechnical additives are holder-specific and so provide disproportionately affect SMEs protection for innovation.

## **The future for new and for novel feed additives**

The majority of "new" additives are variants of those already existing and, generally, seek holder-specific authorisation as zootechnical additives. Regulation (EC) 1831/2003 has been in operation for a sufficient period for applicants to be aware of the practical requirements for authorisation and thus to be in a position to make the judgement whether the size of the market would support the cost of registration. The introduction of an additive with novel properties or mode of action presents greater problems. There is inevitably a greater uncertainty surrounding the requirements of the risk assessor who, in the absence of previous similar cases, may opt for a very conservative position including extensive toxicological requirements. This has considerable cost implications which may disproportionately affect SMEs.

The Regulation itself may introduce additional issues. It may, for example, be difficult meet the requirement to classify the additive in terms of the existing categories and functional groups as defined in the Annex I of the Regulation (Table 3). This is not helped by the fact that there is already a partial mismatch between the definition of what constitutes an additive and categories to which an additive has to be assigned. While most additives fit comfortably within one of the five categories, two properties recognised by the Regulation - favourably affecting the characteristics of animal products and favourably affecting animal welfare - are not found in any of the definitions of categories and so are, in effect, excluded. Although provision is made in the legislation for the addition of new categories/functional group as consequence of "technological progress or scientific development", this is always retrospective and of little help to an applicant with a novel product. The single instance of the introduction of a new functional group (mycotoxin binders) resulted from requests to the Commission to find a "home" for a range of pre-existing products from an industry concerned that they would be otherwise excluded from the additive market. Flexibility for classification is available only for zootechnical additives with includes the functional group "other" which allows the applicant to propose a definition. Such an option is not included for the other four categories of additives.

A significant factor influencing the structure and language used in Regulation (EC) 1831/2003 is the desire of legislators to establish clear water between the descriptions of feed additives and those of veterinary products. This distinction is essentially based on the requirement for zootechnical additives to "affect favourably the performance in good health" unlike veterinary products used to treat a specific disorder. This distinction is not as fundamental as may first appear. Therapeutic agents are used as prophylactics for animals at risk but not displaying clinical signs at the time of application. Conversely, many additives show their greatest effects in animals in less than good health. The legislation tacitly acknowledges this, since reduction of morbidity is considered a legitimate attribute of a feed additive as it "favourably affects" animal welfare. With the possible exception of enzymes, most zootechnical additives that produce a performance response show their greatest effects in animals with a "poor" health status and have a lesser effect in healthier animals; a response recognised since the early use of antibiotics as growth promoters. Novel additives, particularly those which claim an action on the host (e.g. immune modulators) may be seen by the Commission to fall outside the definitions of the Regulation and thus will not be considered as a feed additive. To date, at least one additive on

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the borders of an additive/veterinary product has failed to gain authorisation because of the constraints imposed by Regulation (EC) 1831/2003.

## Conclusions

An increased range of and improved definitions of the categories/functional groups in Regulation (EC) 1831/2003, particularly in the zootechnical category, would better reflect current science, provide more meaningful data for labelling purposes and make it easier for applicants to classify novel products within the boundaries of the existing legislation.. Equally importantly, definitions which more closely accord with scientific understanding would encourage and, ultimately allow, efficacy to be demonstrated without the need for extensive animal trials while still providing evidence of potential effectiveness. In the meantime it is the responsibility of risk assessors and managers to ensure that the application of the legislation does not disproportionately affect smaller enterprises and does not stifle enterprise.

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