Antibiotics

[Summary of antibiotics]

In 1940, when mass production of penicillin became a reality, antibiotics were defined as “substances that are produced by microorganisms and that have the capacity to inhibit the growth of and even destroy other microorganisms”, and for the following more than 60 years, they have been used as therapeutic agents for bacterial diseases. In recent years, with the advance of research on their pharmacological properties other than the antimicrobial actions, antibiotics has been also used as therapeutic agents for diseases caused by such microorganisms as viruses and protozoa, thus expanding their range of application. Further, as cases are increasing where antibiotic derivatives and artificially manufactured synthetic antimicrobial agents are included in the same category as “antibiotics”, now the definition of antibiotics as “substances that are produced by organisms, especially microorganisms, or by chemical synthesis and that has the capacity to prevent the growth and development of and even destroy other organisms” has come into mainstream.

As synthetic antibiotics are described in Chapter 8, this chapter deals with chemical substances produced by microorganisms and their derivatives as “antibiotics”.

Although antibiotics have been used for therapeutic purposes as mentioned above, the use of antibiotics as feed additives has become popular since the discovery of the effect of low concentration antibiotics to promote the growth of young domestic animals. Several theories are proposed to explain the mechanism of this effect; e.g., promoting the growth of beneficial bacteria in the gastrointestinal tract while acting bacteriostatically against harmful bacteria, thus maintaining an environment favorable to the intestinal bacterial flora. In Japan, antibiotics have been used for the purposes of promoting the growth of animals and improving feed efficiency since 1950s.

Currently, 19 types of antibiotics are designated as “feed additives” (Notification No. 750, issued by the Ministry of Agriculture and Forestry in 1976) for the purpose of “promoting the effective use of nutrients contained in feeds” stated in Article 1, Item 3 of the Regulations for Enforcement of the Law Concerning Safety Assurance and Quality Improvement of Feeds (Ordinance No. 36, issued by the Ministry of Agriculture and Forestry in 1976). The “ingredient specifications” for each type of antibiotics and for feeds that are approved to contain these antibiotics, and the “standards” for manufacture, use, storage, and labeling of these products are specified in the Ministerial Ordinance Concerning the Ingredient Specifications for Feeds and Feed Additives (Ordinance No. 35, issued by the Ministry of Agriculture and Forestry in 1976) (hereinafter referred to as “Ordinance Concerning Ingredient Specifications”). For reference, the “ingredient specifications for feeds” specified in Appended Table 1 of the Ordinance Concerning Ingredient Specifications are quoted under the «Standards and specifications in the Act on Safety Assurance and Quality Improvement of Feeds» in the summary of each monograph in Section 2 of this Chapter. Currently, only 19 types of antibiotics are permitted to be used in feeds under the Feed Safety Act (See the “List of analysis methods for antibiotics” in the following section), and the others are prohibited from being used in feeds (except for therapeutic purposes specified in Pharmaceutical Affairs Act etc.).

So far, 34 types of antibiotics have been designated as feed additives. Excluding the above 19 types of currently permitted antibiotics, the remaining 15 types, which were once designated as feed additives but now deleted from the list as a result of a re-evaluation of the safety and efficacy based on the results of subsequent

studies and newly-acquired scientific knowledge. The designation and deletion are carried out by the Minister of Agriculture, Forestry and Fisheries based on the opinions of the Agricultural Material Council. Special care is required for the use of antibiotics as they have pharmacological properties. For this reason, the Agricultural Material Council carries out a scientific examination and evaluation of the potential toxicity and efficacy of antibiotics and their demands in the livestock industry based on various study data obtained according to the evaluation criteria and methods of animal studies specified in the "Evaluation criteria for feed additives", a joint notification issued by the head of the Livestock Industry Bureau of the Ministry of Agriculture, Forestry and Fisheries and the head of the Fisheries Agency. The term "efficacy" here includes promotion of growth, improvement of feed efficiency, and prevention of reduced productivity due to specific pathogenic parasites.

Antibiotics designated as feed additives are commercially available as single or combined formulations (premix) or additives to feeds. Methods to determine the amount of antibiotics in single formulations are specified in the Ordinance Concerning Ingredient Specifications, and those in premixes and feeds are specified in the "Feed Analysis Standards. In addition to these, there are "methods for routine analysis*", specified in the ordinance issued by the head of the related Agency of the Ministry of Agriculture and Forestry.

Currently, instrumental analysis methods, such as microbiological assays (plate methods and microbioautography) and liquid chromatography, are adopted in the Feed Analysis Standards, and spectrophotometry and liquid chromatography for routine analysis methods.

Microbiological assays are the golden standard for the assay methods listed in the Feed Analysis Standards. Liquid chromatography methods may be applicable in lieu of microbiological assays for certain types of antibiotics, such as salinomycin. These liquid chromatography methods have been confirmed to have a precision equivalent to that of microbiological assays before being adopted as official methods. However, if there is a difference between the results of the both methods, the results of the microbiological assay shall be adopted for final judgment (See General Notices 13, Chapter 1).

In principle, this chapter describes each analysis method for antibiotics according to the frame of reference adopted in the Feed Analysis Standards. Where a routine analysis method is available, however, the method is included in the monographs of interest.

For reference, a total of 35 types of antibiotics (i.e., the above-mentioned 34 plus chloramphenicol, which can be carried over into feeds) are listed in Tables 9-1 and 9-2, titled as "List of analysis methods for antibiotics. The list gives information on whether the antibiotics of interest are designated as feed additives and on Item Nos. to refer to the analysis methods of interest.

*: Manufacturers of feeds that contain such monoether antibiotics as salinomycin sodium and monensin sodium are required to perform a routine analysis for these antibiotics before shipment as their safety thresholds in livestock and poultry are low.

Table 9-1 List of analysis methods for antibiotics (monographs)

Names of antibiotics [Note1]	Abbrev.	Date of designation	Date of deletion	Availability of working standards	Availability of feed analysis standards	Pure/feed grade [Note2]	Requires a routine analysis	Item Nos. in Feed Analysis Standards (Chapter 9, Section 2)					Comments [Note6]
								Microbiological test			Instrumental analysis		
								Labeled [Note3]	Identification [Note4]	Residual [Note5]	Labeled [Note3]	Residual [Note5]	
Zinc bacitracin	BC	1976.7.24		○	○	Feed		1.1.1					
								1.2.1					
Avilamycin	AVM	1992.5.14		○	○	Feed		2.1.1-2					
								2.2.1-2					
Avoparcin	AV	1985.10.15	1997.3.18	—	○			3.1.1					
								3.2.1					
Alkyl trimethyl ammonium calcium oxytetracycline	OTC	1976.7.24		○	○	Pure		4.1.1					
								4.2.1			4.2.2		4.2.2: LC
Efrontomycin	ET	1991.6.3		○	○	Pure		5.1.1					
								5.2.1					
Oxytetracycline hydrochloride	OTC	1976.7.24	1983.7.6	—	○			4.1.1					
								4.2.1			4.2.2		4.2.2: LC
Kasugamycin hydrochloride	KSM	1976.7.24	1983.7.6	—	—								
Spiramycin embonate	SP	1976.7.24	1990.3.20	—	○			6.1.1					
								6.2.1					
Enramycin	ER	1976.7.24		○	○	Feed		7.1.1					
								7.2.1					
Orienticin	OR	1994.7.18	1997.3.18	—	○								
								8.1.1					
Kitasamycin	KT	1976.7.24	2004.10.12	—	○			9.1.1	9.4.1				
								9.2.1		9.3.1			9.3.1→Multi 2
Chloramphenicol	CP	—	—	—	○								10.1.1: LC-MS, 10.1.2: LC
												10.1.1-2	
Chlortetracycline	CTC	1976.7.24		○	○	Feed		11.1.1-2					
								11.2.1-2			11.2.3		
Sodium quebemycin	QM	1976.7.24	1983.7.6	—	○			12.1.1					
Salinomycin sodium	SL	1978.9.5		○	○	Pure Feed	○	13.1.1	13.4.1		13.1.2		13.1.2→Multi 1.1, 13.2.3→Multi 1.2, 13.3.1→Multi 3, 13.3.2→Multi 4, 13.4.1→Multi 5.1, 13.5.1→Multi 5.2
								13.2.1-2	13.5.1	13.3.1	13.2.3	13.3.2	
Sedecamycin	SCM	1993.6.22		○	○	Pure		14.1.1					
								14.2.1-2					
Semduramicin sodium	SD	1994.7.18		○	○	Pure	○	15.1.1	15.4.1		15.1.2		15.1.2→Multi 1.1, 15.1.2→Multi 1.2, 15.3.1→Multi 4
								15.2.1	15.5.1		15.2.2	15.3.1	
Thiopeptin	TP	1976.7.24	2004.10.12	—	○			16.2.1					
								16.2.2					
Destomycin A	DM-A	1976.7.24		○	○	Pure							
								17.1.1					
Narasin	NR	2001.12.19		○	○	Feed	○	18.1.1			18.1.2		18.1.2→Multi 1.1, 18.2.2→Multi 1.2, 18.3.1→Multi 4
								18.2.1			18.2.2	18.3.1	
Nosiheptide	NH	1987.12.25		○	○	Pure Feed		19.1.1					
								19.2.1		19.3.1			
Hygromycin B	HM-B	1976.7.24	2004.10.12	—	○								
								20.1.1					
Virginiamycin	VM	1976.7.24		○	○	Pure		21.1.1					
								21.2.1		21.3.1			21.3.1→Multi 2
Bicozamycin	BZM	1983.7.6		○	○	Pure		22.1.1					
								22.2.1					
Flavophospholipol	FV	1976.7.24		○	○	Feed		23.1.1					
Polystyrensulfonic acid oleandomycin	OM	1976.7.24	1990.3.20	—	○			24.1.1					
								24.2.1					

Table 9-1 List of analysis methods for antibiotics (monographs) (cont.)

Names of antibiotics [Note1]	Abbrev.	Date of designation	Date of deletion	Availability of working standards	Availability of feed analysis standards	Pure/feed grade [Note2]	Require a routine analysis	Item Nos. in Feed Analysis Standards (Chapter 9, Section 2)					Comments [Note6]
								Microbiological test method			Instrumental analysis		
								Labeled [Note3]	Identification [Note4]	Residual [Note5]	Labeled [Note3]	Residual [Note5]	
Polynactin	PN	1990.3.20	2004.10.12	—	○								
								25.1.1					
Macarbomycin	MC	1976.7.24	1985.10.15	—	○								
								26.1.1					
								26.2.1					
Bacitracin manganese	BC	1976.7.24	1985.10.15	—	○								
								1.1.1					
								1.2.1					
Monensin sodium	MN	1978.9.5		○	○	Pure	○	27.1.1	27.4.1		27.1.2		27.1.2→Multi 1.1, 27.2.3→Multi 1.2, 27.3.1→Multi 3, 27.3.2→Multi 4, 27.4.1→Multi 5.1, 27.5.1→Multi 5.2
								27.2.1~2	27.5.1	27.3.1	27.2.3	27.3.2	
Lasalocid sodium	LS	1983.7.6		○	○	Pure	○	28.1.1	28.4.1		28.1.2		28.3.1→Multi 3, 28.3.2→Multi 4, 28.4.1→Multi 5.1, 28.5.1→Multi 5.2
								28.2.1~2	28.5.1	28.3.1	28.2.3	28.3.2	
Kanamycin sulfate	KM	1976.7.24	1983.7.6	—	○			29.1.1					
Colistin sulfate	CL	1976.7.24		○	○	Pure		30.1.1					
								30.2.1					
Fradiomycin sulfate	FM	1976.7.24	1985.10.15	—	○			31.1.1					
Tylosin phosphate	TS	1976.7.24		○	○	Pure		32.1.1	32.4.1				32.3.1→Multi 2
								32.2.1	32.5.1	32.3.1			

Upper row: premix; lower row: feeds

Note 1: The names of the antibiotics in gothic letters are those designated as feed additives as of November 2009.

2: Antibiotic formulations for feed additives are divided into pure grade and feed grade based on the method of manufacture. The former is prepared by removing microorganisms, culture media, etc. by filtration, and the latter is prepared without removing these materials.

3: “Labeled” means a quantitative test to estimate the recovery rate of the labeled potency of feeds etc.

4: “Identification” means a quantitative test to identify the presence or absence of antibiotics labeled on feeds etc.

5: “Residual” means a quantitative test to determine the amount of antibiotics carried over into feeds that are supposed to be free of antibiotics (trace quantitative test).

6: Numbers with “Multi” correspond to the Item Nos. for multicomponent analyses listed in Table 9-2.

Table 9-2 List of analysis methods for antibiotics (multicomponent analysis)

Item Nos. in the Feed Analysis Standards (Chapter 9, Section 3)	Range of application	Objective [Note1]	Method	Abbreviations of antibiotics to be analyzed							
				KT	VM	TS	SL	SD	NR	MN	LS
1.1 1.2	Premix Feed	Labeled	Liquid chromatography				○	○	○	○	
2	Feed	Residual	Microbioautography	○	○	○					
3	Feed	Residual	Microbioautography				○			○	○
4	Mixed feed	Resdual	Method using LCMS				○	○	○	○	○
5.1 5.2	Premix Feed	Identification	Microbioautography				○			○	○

Note 1: For the “Objective” column, see Notes 3 to 5 under Table 9-1.