

# codex alimentarius commission



FOOD AND AGRICULTURE  
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Agenda Item 7

CX/RVDF 06/16/8  
December 2005

## JOINT FAO/WHO FOOD STANDARDS PROGRAMME CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

### Sixteenth Session

*Cancun, Quintana Roo, Mexico, 8 -12 May 2006*

### PROPOSED DRAFT REVISED GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAM FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN FOODS

(at Step 3 of the Procedure)

*Document prepared by New Zealand with the assistance of Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Costa Rica, France, Ireland, Korea, Netherlands, Thailand, United Kingdom, United States, ALA, CI, EC, FAO, IDF, IFAH, and OIE*

Governments and international organizations wishing to submit comments at Step 3 on the following subject matter are invited to do so **no later than 28 February 2006** as follows: U.S. Codex Office, Food safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th Independence Avenue, S.W., Washington DC 20250, USA (Telefax: +1 202 720 3157 ; or *preferably* E-mail: [uscodex@usda.gov](mailto:uscodex@usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: [Codex@fao.org](mailto:Codex@fao.org)).

### BACKGROUND

The 13<sup>th</sup> Session (December 2001) of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) proposed that the delegation of New Zealand prepare an updated version of the CAC/GL 16-1993: Codex Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods for consideration by the next meeting. The delegations of Australia, Belgium, Brazil, Canada, China, Colombia, Costa Rica, France, Switzerland, United Kingdom, United States offered their assistance, as did the observers from the European Commission, FAO and O.I.E. This new work was subsequently approved by the 50<sup>th</sup> session of the Executive Committee (CCEXEC) on 7 July 2002.

It was proposed that the new guide should be more reflective of the risk analysis and integrated production approach now being advocated by CAC. It should also attempt to represent the common principles and approaches that are relevant to all animal production systems supplying food for human consumption rather than potentially have such information inconsistently stated and/or duplicated in the appendices. A request was made that it should be made more relevant to and useful for developing countries to both protect their populations and to facilitate trade. The committee had also requested the generic guideline be made more relevant to the use of veterinary drugs in all animals, including fish (aquaculture) and honey-bees. Lastly, it was anticipated that this guide would better differentiate between the principles and practices applied to national residue control and verification programmes and those relevant to port of entry verification programmes.

A draft was introduced at the 14<sup>th</sup> session of CCRVDF and briefly discussed followed by a request for comments attached to the circular letter attached to the report of that meeting. At the same meeting it was agreed that New Zealand should coordinate incorporating the previously proposed milk annex into the guide. The comments received and those additionally supplied by the countries which volunteered to contribute to further drafting have been incorporated into this draft.

At the 15<sup>th</sup> session the Committee, while agreeing with the general approach of the revised document, returned the proposed draft revision of the Guidelines to Step 2 for further redrafting work by a Working Group led by New Zealand. It agreed that the Working Group would prepare a revised version of The Guidelines, based on the written comments submitted at the 15th Session, for circulation, comments and consideration at its 16th Session. The drafting group was also asked to attempt to address the recommendation from the Joint FAO/WHO Technical Workshop regarding evaluation of food consignments containing residues of veterinary drugs which should not be used in food producing animals. The Committee additionally agreed, that as appropriate, in close coordination and concurrent with the main body of the guidelines, that the Delegation of Canada, with the assistance of a Working Group would revise the outstanding sections on methods of analysis and sampling in the *Guidelines* (Part I, II and III), also for comments and consideration by the next meeting.

**PROPOSED DRAFT CODEX GUIDELINES FOR:  
THE DESIGN AND IMPLEMENTATION OF FOOD SAFETY ASSURANCE PROGRAMMES  
ASSOCIATED WITH THE USE OF VETERINARY DRUGS IN FOOD PRODUCING ANIMALS**

**SECTION 1 – INTRODUCTION**

1. The uncontrolled use of, and/or exposure to, approved and/or non-approved veterinary drugs in food production systems can result in consumers being exposed to amounts of residues in foods at frequencies which could pose a risk to their health.
2. Modern food production systems should be designed and managed to ensure that the level of exposure to contaminants<sup>1</sup> is sufficiently controlled to prevent consumers of the foods derived from these systems from being exposed to unacceptable amounts of associated hazards at frequencies likely to compromise their health.
3. The commercial entities involved in the production and marketing of food have the primary accountability for ensuring food safety. The role of competent authorities is to verify appropriate practices are being applied and sufficient controls are in place within the veterinary drug distribution and food production system as a whole to meet the appropriate level of health protection.
4. The application of a risk-based system to all food types should ensure the level of control and verification required is relative to the burden of risk that the food type contributes to consumers. The application of a risk-based approach across all food groups and hazard classes should allow a more focussed concentration of resources to those areas most likely to generate real health protection gains.
5. Risk profiles for different hazards may vary by country, region, species and/or production system. The application of a risk-based control and verification assurance system should provide the necessary basis for exporting countries to certify the safety of exported food, and for importing countries to have the confidence to accept such consignments.

**SECTION 2 - SCOPE**

6. This guide is intended to provide the overarching principles and guidance on the design and implementation of national and trade related food safety assurance programmes for residues associated with the exposure of animals to veterinary drugs in the production environment. The current and future annexes to this guide may provide a further refinement of guidance on issues which may be relevant to the control and verification programmes for products from certain species. These annexes however are subservient to the principles outlined in this guide.
7. While outside the formal scope, this guideline has been written in such a way so as to ensure that the terminology, principles and processes outlined can be readily adapted to help provide the necessary food safety assurances with respect to the residues associated with the exposure of production animals to other contaminants in their production environment.

**SECTION 3 - OBJECTIVES**

8. To provide guidance on:
  - The construct and elements of national control and verification programmes to assure that the residues associated with the use of and/or exposure to veterinary drugs are sufficiently controlled so that they are unlikely to have an adverse impact on the health of consumers of animal products.
  - The elements and operation of import assurance programmes for residues of veterinary drugs.

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<sup>1</sup> As defined in the CAC Procedural Manual

**SECTION 4 - DEFINITIONS**

9. For the purposes of these guidelines:

Residue:	A hazard remaining associated with the food with the potential to cause an adverse health effect as a consequence of food animals being treated with or exposed to a veterinary drug in the production system. Includes the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the drug concerned.
Veterinary drugs:	Includes both approved and non-approved veterinary drugs applied or administered to any food producing animal, or which subsequently contaminate the feed or production environment.
Approved:	Officially sanctioned or recognised by a competent authority.
Food animal(s):	Includes any food producing animal, such as meat or milk producing animals, poultry, fish and bees <sup>2</sup> .
Production system:	Unit of production for which the assurance system has been designed. Will usually be a type of production within a country (or union of countries), but may be a smaller unit within a country able to be operated as a discrete unit.
Competent Authority(ies):	For the most part this refers to the official government department(s) / agency(ies) responsible for the domestic food safety assurances associated with the use of veterinary drugs. However, this may involve other government agencies or other approved parties providing a specific market access assurance or an assurance for a specific segment of production.
Food harvest restriction / withholding period:	The recommended or mandated length of time or number of events which should occur subsequent to a defined exposure before food is harvested from the exposed animals or production system.
Risk-based	Focussed on and proportionate to an estimate of the probability and severity of an adverse effect occurring in consumers.

**PART 1: GENERAL CONSIDERATIONS****SECTION 5 - AIMS OF RESIDUE CONTROL AND VERIFICATION PROGRAMMES**

- i. To provide an appropriate level of assurance that the health of consumers of animal products will not be adversely affected by residues.
- ii. To facilitate trade.

**SECTION 6 – GENERAL PRINCIPLES**

10. Control and verification programmes for residues associated with veterinary drugs used or present on farms or feeds should:

- i. Be risk-based.
- ii. Be prevention focussed.
- iii. Focus on realistic risk profiles assessed as reasonably likely to be associated with food derived from the relevant production system(s).

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<sup>2</sup> From the CAC definition of Veterinary drug

- iv. Consider the possible risks profiles associated with both approved and non-approved veterinary drugs in the production system.
- v. Be proportionate to the relative human health risk associated with these hazards compared with other food-associated hazards.
- vi. Clearly identify the objectives of those standards or criteria which are not directly human health protection related.
- vii. Ensure all parties involved in the production, marketing and processing system of the animals and/or the food products derived from them are held accountable to make sure the inputs into and controls within their systems are appropriate to ensure that unsafe animal products will not be sold as a result of their action or inaction.
- viii. Recognise that pre-harvest controls and practices will be primarily responsible for ensuring safe food.
- ix. Recognise that the primary role of audits and sampling programmes is for the verification / validation of the efficacy of the pre-harvest controls and practices.
- x. Focus on system and population based assurances.
- xi. Be cost effective and have the support of stakeholders.

## **SECTION 7 - DESIGN TOOLS AND PUBLIC HEALTH LINKAGE**

### **7.1 Introduction**

11. The production of animal products for human consumption is an integrated process with multiple parties contributing to the control of veterinary drug related residues. The production of safe food relies on the various inputs and practices within the process being sufficiently in control.

12. It is not only necessary to have knowledge of the veterinary drugs that the animals are likely to be exposed to in the production system but also what circumstances are necessary for any of these to constitute a risk to consumers of animal products derived from these production systems (the risk profiles).

13. Assurances with respect to the safety of a food production system rely on both a confidence that appropriate practices and controls are in place which should ensure food safety, as well as some type and level of verification that these are in fact being applied at an appropriate level.

14. It is the day to day application of appropriate practices and controls that is actually responsible for producing safe food rather than any animal or end product sampling and testing regime.

15. The application of risk analysis principles and a risk management framework to national control and verification programmes can provide a level of guidance to ensure that both the design and application of control and verification programmes is risk-based and thus likely to focus on and deliver actual human health protection gains.

16. In a risk-based system, monitoring tools are predominantly about verifying that appropriate controls are in place and that these are being applied within the population as a whole at an appropriate level to ensure food safety for the specific hazard or hazard class being considered.

17. The relative importance of controls varies with the risk profile of individual hazards. Similarly the degree a system has to be out of control before public health may be compromised also varies between hazards. Accordingly, reactions to identified non-compliances will vary with the type of hazard and/or the risk profile associated.

## 7.2 Public Health Linkage

18. Veterinary drugs are regulated in many countries for a variety of reasons. Many of the objectives are not directly related to the protection of the health of consumers of animal products, or the mandate of the Codex Alimentarius Commission. The primary objective of food safety authorities and this guideline is to ensure the use or exposure to these compounds does not cause adverse health impacts in people consuming food products derived from those animals treated or exposed.

19. Hazards associated with the use or exposure to veterinary drugs can be biological, physical or chemical. Examples can include the chemical residue of the drug and/or its metabolites, physical remnants of the delivery device and biological reactions by the animal or its microflora to the veterinary drug (e.g. injection site reactions).

20. Residues can exert an adverse effect on consumers in a number of ways. Historically most control systems have focussed on the potential for chronic toxicological adverse effects. Residues can also be associated with acute pharmacological effects on consumers or their Gastrointestinal Track (GIT) microflora, and/or allergic reactions. Where the registration risk assessment identifies the likelihood and consequences of such adverse impact endpoints posing a significant risk to human health, different levels and types of controls or monitoring systems may be justified.

21. The Acceptable Daily Intake (ADI) is generally the amount of the compound and/or its metabolites that is estimated as able to be consumed on a daily basis for an entire lifetime by the most susceptible populations without adverse health affect. Where the level associated with the potential for an acute effect is less than that associated with a chronic toxicological effect then they will reflect this endpoint and will be further reduced by the appropriate safety multiples. Accordingly, the ADI concept is based on notional zero risk. Because of the high level of conservatism used in establishing ADIs, occasional ingestion of residues slightly exceeding the ADI generally should not pose a significant toxicological concern<sup>3</sup>.

22. The maintenance of average consumption of residues over time under the ADI is an expression of the objective of a residue control and verification programme.

23. Maximum Residue Limits (MRLs) are monitoring tools. Foods containing residues above an MRL are not inherently unsafe as long as any calculated acute reference dose is not exceeded. MRLs are concentrations and are food/tissue specific. They are set at levels at least low enough to ensure that even high-level consumers will not consume more than the ADI if they eat large quantities of every food type containing the residue at the MRL for that food type.

24. Generally, most MRLs are actually set even lower than required to achieve the ADI in high level consumers. Instead they reflect the level of residue that should be achievable in the majority<sup>4</sup> of the various edible tissues of treated animals if the veterinary drug is used as per the veterinary drug's label and foods are harvested from the animal production system after the recommended withdrawal period has expired.

25. Different countries have different types and intensities of challenge of animal disease. Accordingly, Good Practice in the Use of the Veterinary Drugs (GPVD) may also vary between countries and different MRLs may be set to reflect the use conditions associated with the local disease challenge profile within the production systems. From a public health point of view, higher MRLs in the exporting country do not pose a particular toxicological health concern as long as the frequency distribution of residues in the exported product, combined with an estimation of the volume of imports relative to the domestic production, allows it to be concluded that it is unlikely that the ADI will be regularly exceeded in the importing country<sup>5</sup>.

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<sup>3</sup> International Programme on Chemical Safety (IPCS) toxicological assessment monograph for food additives

<sup>4</sup> The way MRLs are derived means that statistically, it is possible that a small percentage of animal tissues will contain residues in excess of the MRL when treated according to label and slaughtered or milked at the minimum recommended withholding period.

<sup>5</sup> IPCS toxicological assessment monograph for food additives

### 7.3 Types of Verification Programme

26. Generally verification programmes can fall into three broad categories depending upon the criteria applied to the sample selection and/or their objectives; (a) system verification programmes, (b) risk-targeted verification programmes or (c) surveys.

#### (a) System Verification Programmes

27. The objective of system verification programmes is to provide information on the level of application of the practices and controls overall. As such they normally involve non-biased sampling of a specified population with broadly similar attributes so that the results can be used to derive a statistical confidence as to the level of control present in that population as a whole. They can focus on the level of application of specific controls in the process or can focus on monitoring the levels of hazard in the animals / products at or close to the point of harvest.

28. A combination of point of harvest testing coupled with direct audits of the various control points in the system can be used to reduce the amount of and reliance on chemical analysis while providing a higher level of assurance than point of harvest testing alone.

#### (b) Targeted Programmes

29. Targeted verification programmes involve the directed sampling of specific suppliers or products considered to pose a greater likelihood of not complying with one of the controls and/or having been found to have non-compliant residues detected.

30. Their objective is to place a greater intensity of inspection / audit on suppliers or product considered to possibly have a greater potential than the general population of being non-compliant. Suppliers and/or product may be targeted due to for example:

- previous poor performance,
- breakdowns or absence of one of the quality system components usually relied on,
- other intelligence information,
- potential risk factors which may be correlated with an increased use of veterinary drugs such as high somatic cell counts, or
- as a result of ante or post-mortem findings e.g. injection site lesions or resolving pathology.

31. While it is hard to derive general population based conclusions from targeted programmes, the operation of statistically based system verification programmes involving unbiased sampling in parallel with targeted verification programmes provides a greater level of assurance than the operation of either programme alone.

#### (c) Surveys

32. Surveys are differentiated from system verification programmes mainly by their objectives and that they tend to be applied to sub-populations which may be linked by a common variable. Objectives of surveys may include the collection of base-line data for trend analysis or the collection of new data for consideration as to whether the development of additional controls and verification programmes may be appropriate. They are an appropriate tool to look more intensely at whether certain variables such as geographical position, season, or age may have an effect on the presence, absence or level of a residue.

#### (d) Other Verification Programmes

33. Domestic residue control and verification programmes may have other objectives not directly related to assuring food safety but these are outside the scope of this guideline.

## PART 2: RECOMMENDATIONS

### SECTION 8 – REVIEW AND RANKING OF HAZARDS

#### 8.1 Introduction

34. Animals and/or production systems can be exposed to a variety of sources and types of chemicals that can potentially lead to residues in the products derived from them. However, not every one of these chemical inputs has the same potential to lead to a risk to the consumers of animal products derived from the production system. Hazard control is not the same as risk management.

35. In designing national control and verification programmes an understanding of the circumstances necessary for each chemical input to actually constitute a threat to consumers of animal products, along with a relative estimate of the likelihood of this occurring, are essential parts of the process of determining what controls and verification systems may be appropriate.

#### 8.2 Types and Sources of Chemicals and Exposure Pathways

36. When reviewing and ranking the residues associated with the chemical inputs likely to be present at some stage in the production system it is firstly necessary to describe the potential sources and exposure pathways. For veterinary drugs, the type of residue and the pathways considered should not just be restricted to those sanctioned by the national regulatory authority but should also consider potential use of drugs in non-sanctioned ways or use of non-sanctioned drugs.

37. Types, sources and exposure pathways of chemicals may include:

##### Types and sources:

- |     |                        |                                                                                                           |
|-----|------------------------|-----------------------------------------------------------------------------------------------------------|
| (a) | Veterinary drugs e.g.: | Approved / recognised drugs and uses<br>Non-approved / recognised uses<br>Illegal or non-recognised drugs |
|-----|------------------------|-----------------------------------------------------------------------------------------------------------|

##### Exposure pathways:

- |     |                  |                                                                                                                   |
|-----|------------------|-------------------------------------------------------------------------------------------------------------------|
| (a) | Intended e.g.:   | Direct administration to the animals<br>Indirect administration to the animals through addition to feed or water. |
| (b) | Unintended e.g.: | Feed or water contamination<br>Environmental contamination                                                        |

#### 8.2 Risk Profile Considerations

38. After the potential types, sources and exposure pathways of chemical inputs into the production system have been identified, it is then necessary to consider what are the circumstances required for each of these to cause an adverse health impact on consumers, as well as the likelihood of such circumstances occurring in the absence of a control.

39. Such considerations will include:

- What type of residue is associated with the chemical input e.g. chemical residue, biological residue or pathology, greater chance of resistant bacteria or physical remnant.
- The class and severity of the adverse health effect associated with it e.g. chronic toxicity, acute pharmacological, allergic reaction, or microbiological disturbance.



- What use and/or production circumstances are necessary, and what is the likelihood of these occurring, for the residue to be in foods derived from the production system at levels and frequencies approaching those which could pose an actual risk to human health.
- What consumption circumstances are necessary for the residue to actually constitute a risk to consumers of animal products.

## **SECTION 9 – CONTROL POINTS**

### **9.1 Introduction**

40. Most controls available tend to attempt to mediate what and how animals or production systems are exposed to chemicals, or the time between a known exposure and subsequent harvest of animal products.

41. Accordingly, restricting both what formulations of veterinary drugs can be used, how they can be used and by whom is a key control point. Similarly, imposition of time or event based harvest restrictions subsequent to the last exposure can also be used to mitigate potential risks. For some contaminants, environmental restrictions may be the most relevant control point.

42. Restrictions and recommendations however are only part of the control system. These are only as good as the knowledge, practices, skills and motivation of those administering the compounds, or those of the feed compounders, and how effectively any harvest restriction stays identified with the exposed animals or product and is communicated to subsequent purchasers.

43. The shutting off of both the avenues and motivation for extensive off-label use or alternative import and/or manufacture of non-sanctioned veterinary drugs, including non-endorsed alternative distribution and sales networks, are also potentially key control points.

### **9.2 Regulatory Controls over Veterinary Drugs**

44. Restrictions on what formulations can be used and how they can be used is a key control point. Similarly, imposition of time or event based harvest food restrictions subsequent to the last exposure can also be used to mitigate potential risks.

45. For veterinary drugs it is important that the competent authority tasked with providing consumer assurances for foods has a sufficient level of control over and knowledge of what veterinary drugs are being sold and used within the production systems.

46. All formulations of veterinary drugs manufactured or imported into the country should be required to be recorded on a national register before being able to be used.

47. Appropriate approval criteria should be established for such formulations to be added to this list. These approval criteria may accept the assessments of other recognised competent authorities where use patterns are likely to be similar.

48. Those formulations not on these lists should not be allowed to be used and sufficient sanctions need to be in place to act as a deterrent. Ideally national regulations should be established to enforce what veterinary drugs may be sold domestically and how these may be used.

49. It is important that the approval and registration systems are both efficient and as far as possible meet the needs of the producers so as to reduce the motivation for alternative product sourcing networks to develop.

50. Information and/or education programmes regarding the suitable use for both efficacy and the protection of consumers need to be supplied and/or provided for each formulation.

51. For certain drugs it may also be appropriate, where justified by an appropriate risk assessment, to have further sale and use conditions mandated to help ensure appropriate use and to prevent misuses or abuses. Such additional controls should be targeted at managing specifically identified risks and should be regularly checked as appropriate to the risk posed for both their efficacy and necessity. They may include for example:

- Requiring all sales to be subject to a prescription from a regulatory or professional body/person,
- Restricting administration to individuals or professions with prescribed competencies,
- Requiring all treated animals / production systems to be identified in specified ways,
- Requiring all uses to be recorded and/or notified to (a) central database(s).

52. Both the continued efficacy and the necessity of any such additional controls should be reviewed against the local risk profile to ensure they don't act in a counterproductive fashion by motivating alternative product sourcing and use to develop.

53. In a risk-based system it is also desirable that the competent authority(ies) be able to derive estimates of both the level and most common types of uses of each veterinary drug.

### **9.3 On-farm Recommendations**

#### **(a) Use of Veterinary drugs**

54. Producers should only use veterinary drugs which have been approved for use in food producing animals. Non-approved veterinary drugs should not be used (except as provided for in the next paragraph). Veterinary drugs should be used strictly in accordance with the officially approved / recognised instructions.

55. Veterinary drugs should only be used off-label in accordance with direct and written veterinary advice. Such advice should be consistent with national and/or international guidance documents and technical information on this issue.

56. Excepting situations covered by the above paragraph, only those veterinary drugs specifically approved for use in lactating animals should be used in animals being milked for human consumption.

#### **(b) Assurance Systems**

57. Producers should have appropriate on-farm food safety assurance measures in place with respect to the use of and/or exposure to veterinary drugs. All workers directly involved with the animals should be familiar with the system used.

58. All treated or exposed animals, or lots of animals, need to be positively identified as being subject to food harvest restrictions for the period for which they apply (slaughter/harvest/milk withholding period).

59. Records should be kept of all details of the treatment and the length of time and/or number of milkings required before the animal or product from the animal can be harvested for human consumption.

#### **(c) Additional advice for lactating animals:**

60. The food safety assurance measures need to be structured to be responsive enough to be able to provide sustainable assurances on a daily basis that milk is harvested only from those animals considered to have an acceptable residue status.

61. Discarded milk should not be fed to other animals unless appropriate controls are in place to assure product from these animals will not be harvested before any transferred residues have fallen to acceptable levels.

62. Ideally, treated or exposed animals in large herds should be kept separate from those animals not under restrictions to help reduce the potential for mistakes. Animals under harvest restrictions should ideally be milked after the rest of the herd.

63. Animals under milk harvest restrictions should be milked in such a way that ensures their milk does not mix with milk being harvested for human consumption. Any equipment used needs to be able to be adequately cleaned prior to being used on other animals.

#### **9.4 Communications with subsequent purchasers**

64. It is important that any food harvesting restrictions still in place on the animal or animal product at the time of sale be communicated to subsequent purchasers of the animal(s) or products derived from them.

65. Processors should be held accountable for ensuring that they only purchase and/or process animals and/or animal products from suppliers who can credibly attest to the suitability/safety of the animal or animal product for the purpose intended.

66. Where animals or animal products are supplied to processors by other than the primary producer then these suppliers should be held accountable by processors to show that they have due knowledge that the animal or animal product is no longer under any relevant restriction.

### **SECTION 10 – VERIFICATION**

#### **10.1 Principles and the Role of Verification Programmes**

67. The overall objective of the implementation of verification programmes is: To provide an appropriate level of confidence that the practices and controls in place are appropriate and being applied to the extent necessary to ensure that the health of consumers of animal products will not be adversely affected by any chemical inputs into production systems.

68. It needs to be remembered that in risk-based prevention focused systems it should be the pre-harvest practices and controls, not post-harvest testing, which are primarily responsible for delivering safe food.

69. The frequency and intensity of verification / audit should depend on the performance of the sector and the level of non-compliance that may lead to a significant human health risk.

70. The objectives and consequent actions emanating out of specific verification programmes will vary depending on whether they are looking at the generic efficacy of the whole, or parts of, of the control system or whether they are targeted to assess the compliance of selected individuals or groups of individuals.

71. A combination of direct audits of the various control points in the system coupled with point of harvest testing will provide a higher level of assurance than point of harvest testing alone. Such combinations can be used to reduce both the amount of and reliance on chemical analyses.

72. Similarly, the operation of statistically based system verification programmes involving non-biased sampling in parallel with verification programmes targeted at specific suppliers or product will provide a greater level of assurance than the operation of either programme alone.

73. While the sample sizes for system verification programmes can be statistically pre-determined (see Part One for additional guidance), the number of risk-targeted samples will vary according to the frequency at which the profiling attributes present themselves.

#### **10.2 Examples of design considerations for verification programmes**

74. As appropriate to the pre-determined risk profiles in the country and/or production system, verification programmes may be used to help evaluate the:

- validity of the assumptions used during the registration process
- existence or non-existence of alternative unacceptable production, marketing and/or advice chains;
- effectiveness of veterinary drug and pesticide label information (Good Practice in the use of Veterinary Drugs [GPVD], Good Agricultural Practices [GAP]) as a human health risk mitigation tool, and how well the use recommendations correlate with actual uses of, or needs for, the product;
- effectiveness of other education or risk mitigation programmes;
- efficacy of any feed medicating quality systems;

- effectiveness of animal production and animal sales quality systems as they relate to animal identity and information transfer on any food harvest restrictions;
- application and effectiveness of corrective actions;
- significance of environmental and/or natural contaminants.

### **10.3 Audit of Pre-Harvest Control Points**

75. Pre-harvest and/or pre-processing quality assurance and verification programmes may be used to reduce the reliance on post-harvest verification programmes such as chemical analysis.

76. On-farm sampling may also be used where the risk profile assessment has identified that there are specific concerns associated with the use of substances prohibited by the competent authority.

77. As appropriate to the pre-determined risk profiles in the country and/or production system, the following potential pre-harvest control points may be considered for a level of audit in the verification programme.

- The sellers and purchasers of veterinary drugs to verify what is being sold and how they are being marketed.
- The users of veterinary drugs (including farmers, veterinarians and feed compounders) to verify how drugs are actually being used in the production systems, e.g. according to label, what records are being kept and how the treatment status of animals is identified.
- The animal and animal product sale systems to verify whether and how any food harvest restrictions associated with the animal or product is being communicated.
- The assurance systems used by processors and/or producers to ensure the suitability of the animals or product they are being supplied with for the purposes they intend using it for.

### **10.4 Point of Harvest Verification Programmes**

#### **(a) General Considerations**

78. Post-harvest verification programmes of the actual levels and frequency distributions of residues present in animals or products at the point of harvest should be established in addition to one or more of the aforementioned pre-harvest verification programmes. Both system and risk-targeted verification programmes should be used in parallel.

79. The frequency and intensity of verification / audit of each hazard chosen to be monitored under the system verification programme should depend on its risk profile, the previous performance of the sector and the level of non-compliance that may lead to a significant human health risk.

80. Where non-biased samples are selected from the general population it should not be necessary to retain lots of production associated with randomly selected samples while the results are awaited as the results will be reflective of a wider proportion of the general population. Similarly, recall action is only justified on health grounds if the results indicate an acute risk to human health.

81. For targeted verification programmes, where it is considered that both the likelihood and human health significance of a potential non-compliance poses an unacceptable risk then all associated product should be retained until sufficient information can be generated to provide the required level of assurance.

#### **(b) Sample Taking**

82. Appropriate mechanisms to prevent possible bias occurring in both the selection and taking of samples need to be put in place.

83. Samples should ideally be taken before animals and/or products are commingled with animals or product from other suppliers. For lactating animals samples should ideally be taken at the time the milk is collected from the farm.

84. Each sample needs to be clearly identified with the unit of production and the supplier that it represents so that appropriate trace-back and follow-on actions can be applied should a non-compliant result be found.

85. The identity and integrity of what the sample is meant to represent also needs to be maintained throughout the sampling, storing, shipping, analysis and reporting process.

**(c) Laboratories**

86. The laboratories used should have in place a suitable quality assurance programme and they should have validated all methodologies used to an appropriate level relative to their role within the monitoring programme.

87. The performance characteristics of each of the methods used by the laboratories should be pre-agreed with the competent authority requiring the testing and should be set to reflect the objectives of the specific part of the programme. Regulatory reporting levels for laboratories should be pre-agreed with the competent authority and should only be set as low as that specifically determined as being required to meet public health objectives.

## **10.5 Analytical Results**

**(a) Reporting of results**

88. Laboratory results should be interpreted in conjunction with the performance characteristics of the method and the analysts. Laboratories should be required to provide this information when reporting potentially non-compliant results.

89. Analytical results at or above the MRL should not be stated as discrete numbers but as a range of values that the laboratory is confident the true result falls within (the confidence interval). Where the range reported falls both above and below the MRL then it is not possible to definitively conclude the result was non-compliant. Such results may never-the-less warrant further investigation.

90. Laboratories should also report all incidences where unusual extraneous substances were detected but for which the identity was unable to be confirmed.

**(b) Analysis of results**

91. Each non-compliant result should be analysed to ascertain what contributing factors lead to its occurrence, the systemic significance of the identified case and what associated factors are necessary for it to constitute a potential human health risk.

92. All detections of unidentified substances should also be considered for possible further follow-up.

93. Depending on the results of this analysis, a consideration of whether and what local and/or systemic corrective actions are appropriate to prevent an unacceptable frequency of reoccurrence and/or to remove product considered to pose a direct threat to the health of consumers should be undertaken.

94. When an animal tissue has a residue in excess of the relevant MRL at the point of harvest it can mean one of a number of things, not all of which are in the direct control of the producer or supplier. These include:

- The veterinary drug was not used according to label or prescription instructions.
- A non-authorized veterinary drug or formulation was used.
- The minimum post-treatment food / feed harvest restriction / withdrawal period was not observed (failure to maintain the identity of restricted animals or animal products is often a factor here).
- An unintended feed, water or environmental exposure occurred.
- The food / feed harvest withholding period recommendation on the label is not fully appropriate.
- The food / feed came from one of the small percentage of animals that statistically are predicted will have residues in excess of the MRL even after the food harvest restriction / withdrawal period has elapsed.

- Analytical method problems.

95. Some results may reflect an issue more appropriately addressed by the veterinary drug / pesticide registration or recognition system.

## **10.6 Regulatory responses to identified non-compliances**

96. Where the analysis indicates a significant local or systemic control failure, this should elicit an appropriate corrective reaction from the entire segment of the population potentially similarly affected or motivated. Sufficient restrictions and targeted verification should then be put in place so as to be able to assure appropriate corrective actions have been put in place and are being applied. The time scale for taking such actions and the intensity of any reaction will vary according to the health significance of any unacceptable level and frequency of non-compliance found.

97. In many cases a determination as to whether the incident(s) are the result of isolated mistakes or whether they represent an unacceptable level of negligence or wilful non-observance of the recommended / mandated conditions of use will influence the regulatory or commercial reaction. Similarly the identification of the failure of a control point outside the direct control of the producer or supplier (such as registration issues) may also necessitate a different reaction if long-term solutions are to be found.

98. For isolated mistakes the provision of appropriate advice and motivation for the relevant sector to make the necessary improvements to the controls and practices may be an appropriate response. This should of course be coupled with a level of follow-up verification that appropriate corrective actions have been put in place and are being applied e.g. through heightened analytical surveillance activity.

99. Where an unacceptable level of negligence or wilful non-observance of the recommended / mandated conditions of use is determined as being the cause, publicly promoted punitive reactions (e.g. condemnations, fines, movement controls etc) may also be appropriate and have some wider deterrent value. This is in addition to the provision of appropriate advice and/or motivation for the sector to make the necessary changes along with an appropriate level of subsequent verification that sufficient corrective actions have been put in place and are being applied.

100. Where the analysis identified a significant contribution due to a control point failure outside the producer's / supplier's direct control (e.g. registration / label issues) then appropriate actions should be taken to ensure the sector responsible for the control takes the necessary corrective actions to prevent an unacceptable level and/or frequency of recurrence.

101. For farm targeted verification programmes: Where the results from the sampled portion of the lot does not provide the necessary confidence that the rest of the lot has been produced with a sufficient application of appropriate practices and controls, the lot should be not passed for human consumption until sufficient information can be generated to provide the required level of assurance as to its safety.

102. For non-biased sampling programmes: Where the results indicate there is a direct risk to public health, an attempt should be made to trace and remove all similarly affected product. In making such judgements it needs to be acknowledged that the non-compliant result represents only a small proportion of the total production likely to be similarly affected and not as yet identified. The unidentified proportion likely represents a much greater potential threat to consumers than the identified "lot". Accordingly, any actions taken with respect to the identified non-compliant lot are less significant than the actions taken on the system as a whole.

103. Where pre-harvest controls cannot be relied upon due to their non-existence or an unacceptably high level of non-compliance by animal food producers, a higher level of post harvest verification may be appropriate in order to attempt to be able to provide the required level of consumer assurance. This should be regarded as an interim measure only until the appropriate corrective actions to the control system have been put in place and subsequently demonstrated to be effective.

104. The results of non-biased sampling of the general population are a measure of the effectiveness and appropriateness of the controls and practices within a wider segment of the production system. Accordingly they should be used for an assessment as to whether one of the controls may need adjusting, and should not be routinely used or relied upon for product disposition judgements. Where non-compliant results are returned, recalls are not necessary unless an assessment is made that the result indicates a direct risk to human health e.g. where it has been calculated that an acute reference dose is likely to be exceeded. Except in such situations, occasional incidences of results in excess of the relevant MRL should not be considered to constitute an imminent health threat.

105. Control and verification programmes should be regularly reviewed to ensure their continued efficacy and/or necessity as well as to review the potential impact of changes to the risk profiles. Where a significant level of non-compliance is identified in any one year and consequent changes to the control programme implemented, a higher level of verification should be considered for the subsequent year to help assure the appropriateness of the changes to the resolution of the problem. Some of the selected lower risk profile compounds should be considered for rotation in and out of the programme based on performance to ensure as wide as possible scope is covered.

### **PART THREE:**

#### **SECTION 11 – INTERNATIONAL ASSURANCES**

106. As with national programmes, it is the practices and controls in place in the exporting country rather than port of entry testing that best ensures safe food. Communication and co-operation between the relevant competent authorities can be used to deliver higher-level assurances than sole reliance on port of entry inspection programmes. To help facilitate trade from developing nations, the potential for longer phase-in times and increased cooperation, and possible technical assistance across all aspects of programme development and operation, should be considered as long as it has been assessed that there is no direct risk to human health or where assurances can be obtained using other mechanisms.

##### **(a) Exchange and review of control and verification programmes**

107. The application of a risk-based control and verification assurance system should provide the necessary basis for exporting countries to certify the safety of exported food, and for importing countries to have the confidence to accept such consignments.

108. Trading countries should be encouraged to exchange copies of their control and verification programmes along with the results of the preceding year. In any review, it needs to be noted that risk profiles and management options may vary substantially between countries. The appropriateness of the control and verification assurance system to the risk profiles and circumstances existing in the exporting country relevant to the level of human health protection required by the importing country is the relevant consideration, not how closely it may or may not mirror the control and verification system in the importing country.

109. Where either the risk profile of the exporting country, and/or the level of health protection of the importing country, is significantly higher (e.g. where one country has a substantially lower ADI) additional controls and verification may be required. Estimation of the relative proportion that imports are likely to contribute to the total consumption by the importing country's population may be useful to determine whether any identified differences in the level of hazard control are actually likely to be significant in the absence of further controls.

110. The same risk-based principles should apply to export assurance programmes as have been applied to the design and implementation of national assurance programmes. Where deemed appropriate, targeted quality assurance programs may be used to deliver the higher level of assurance required for the specific segment of production.

**(b) Port of entry testing programmes**

111. The assurances able to be gained from countries providing copies of their control and verification programmes and the subsequent certification that product has been produced in accordance with the programmes is much greater than able to be gained from port of entry inspection programmes. In such cases the role of port of entry testing programmes, should they be considered necessary, changes from being a primary measure of product acceptability to that of being a secondary system verification tool.

112. It is worthy to note that the tissue / fluid matrices used for national verification programmes may vary from those used in port of entry programmes e.g. milk versus processed dairy products. The process, processing aids and/or other additives may on occasion introduce confounding variables. It is important that any methodology used is fully validated for the specific matrix analysed and any “regulatory action levels” are set at levels which are determined to pose a significant risk to human health as opposed to just reflecting the level of determination of quantification of the method.

113. Except where a direct risk to health is suspected or detected, certified product should be subjected to non-biased sampling and release programmes at a frequency determined by the exporting country’s performance. Consignments of animal products tend to be heterogeneous by nature and will often be made up of commingled product from a variety of animals and sources. Results will reflect the performance of the production system as a whole and should not be extrapolated to specific judgements on other units within the consignment except where a common pre-harvest risk factor is shared and a direct health threat is indicated.

114. Samples need to be clearly identified with both the consignment and the sub-unit of the consignment actually sampled to allow exporting countries to be able to fully trace their origin back should a non-compliant result be found. The recording of commercial information such as bar codes can often help this process. The identity, integrity and security of the sample need to be maintained throughout the sampling, storing, shipping, analysis and reporting process. Unprocessed proportions of the sample need to be maintained sufficient to allow possible independent confirmation of the finding should a dispute result. When non-compliant results are reported appropriate information as to the confidence interval of the result, a description of the method used and the performance characteristics of the method of analysis should be provided to all parties affected by the result (e.g. the owner of the consignment and the certifying competent authority).

115. The results of port of entry testing programmes should broadly correlate with the findings of the exporting country’s own verification programmes. Except where a higher level of protection has been determined as necessary by an appropriate risk assessment, Codex MRLs, or the MRLs applied in the exporting country should be used as the monitoring tools. Where occasional incidents of non-compliance are found these should not be treated with undue concern unless the type, level or frequency varies substantially from what the exporting country is finding itself. All results should be reported back to the competent or certifying authority of the exporting country as both the potential problem and potential solutions rest there.

116. Where the type, level and/or frequency of non-compliance detected raises concerns as to whether the imports are meeting the level of human health protection required by the importing country, then additional assurances may be requested. The importing country may also choose to increase the level of port of entry verification to confirm that the assurances given are in fact addressing the problem. Targeted sample and hold programmes should be reserved for those situations where it is assessed that a direct risk to human health exists and where such a risk is considered also likely to be in consignments already produced and not able to be subjected to further control by the competent authority of the exporting country.



117. Where residues of prohibited substances are found, the competent authorities of both the importing and exporting country should cooperate to work towards resolving the problem. Resolution of such problems will require an analysis in the originating country of exactly where, how and why such residues are finding their way into the production system, what may have gone wrong within the country's own control and monitoring system, and subsequent application of appropriate additional controls to address the situation. It needs to be acknowledged that the ultimate resolution of such problems may take some time. Where an appropriate level of cooperation is occurring, the level of regulatory reaction by the importing party should be only that deemed essential to prevent a direct risk to public health. Especially in cases where the exporting country is a less developed nation, consideration should be given by the importing country to the provision of an appropriate level of technical assistance to help resolve the issue.

118. The application of new sampling and testing methodologies can also on occasion reveal types and levels of residues previously unknown to exist by one or both parties. The determination of where, how and why such residues are finding their way into the production system and their significance again may take some time. Where the presence of such residues is associated with previously accepted production practices, the implementation of changes, should these be deemed necessary, may need to be implemented over an extended period of time. Again, where an appropriate level of cooperation is occurring, the level of regulatory reaction by the importing party should be only that deemed essential to prevent a direct risk to public health. Especially in cases where the exporting country is a less developed nation, consideration should be given by the importing country to the provision of an appropriate level of technical assistance to help resolve the issue.

120. In all cases the competent authorities should co-operate to ensure the health of consumers of both countries is protected.

## **PART FOUR**

### **11.0 Sampling Protocol Design and Planning: Statistical Considerations**

#### **11.1 Introduction**

121. The Codex Alimentarius Commission has decided that recommended sampling procedures for food additives, pesticide residues and residues of veterinary drugs in food are exempted from the general sampling procedures of food commodities developed by the Codex Committee on Methods of Analysis and Sampling - Normal Practice. Accordingly the following guidelines have been written. It is important to note that this section does not just apply to the sampling associated with laboratory analyses but is also broadly relevant to all verification and auditing programmes contributing to the assurance programme.

#### **11.2 Principles**

- The purpose of the verification programme needs to be clearly defined.
- The population being sampled and to which the results apply needs to be defined.
- Whether the sampling is non-biased or targeted (directed), and the criteria to be applied to the analysis of the results need to be pre-determined.
- Sample sizes for non-biased sampling protocols should be statistically based
- The targeting criteria applied to directed sampling need to be pre-determined.
- Each sample needs to be clearly identified with the unit of production and the supplier it represents
- The identity, security and integrity of the sample needs to be maintained throughout the sampling, storing, shipping, analysis and reporting process.
- Unprocessed proportions of the sample need to be maintained to allow possible independent confirmation of the finding should a dispute result.

### 11.3 General design considerations

122. In designing a sampling protocol it is essential to define both the purpose of the programme and the population of interest. It is also important to define the criteria to be applied when analysing the results with respect to the need / desirability for any further action, and especially how such criteria and reactions directly relate to the protection of human health. Generally sampling protocols have a low efficacy to be able to detect low levels of non-compliance so where such levels are considered potentially a significant risk to human health other assurance programmes are far more important.

### 11.4 Populations of Interest

123. Ultimately “a population” made up of “units of food consumed” is the most relevant to human health. However as it is the application of appropriate pre-harvest practices and controls which ensures food safety, a sampling strategy which verifies both the appropriateness and level of compliance of these pre-harvest practices and controls can be used to provide appropriate assurances that the health of consumers is unlikely to be negatively affected. Generally the population of interest for targeting pre-harvest compliance / appropriateness verification information will be those population units to which common practices and controls should be applied e.g.

- the seller of the chemical input into the production system,
- the producer,
- the supplier of the animals or animal product to the processor, or
- the processor .

124. However, because the potential consequences to human health are much larger when large production units (farms) are out of control, the usual pre-harvest population randomly sampled is a standardised unit of production sold at any one time e.g. individual animal, vat of milk, barrel of honey, or defined weight of aquaculture product. In this way the larger producers / suppliers should effectively have a greater probability of being sampled while still maintaining the randomness of the sampling protocol.

125. Generally, conclusions will be drawn from the prevalence, or lack thereof, of non-complying results in the units sampled during the production season or calendar year. However, where problems are found during the course of the production season, corrective actions may have already been applied and have started to have a positive effect well before the end of the production season or calendar year. For small populations, or for either low risk or reasonably stable exposure scenarios, then several production seasons or calendar years may be used / needed to collect the number of samples statistically determined to give the required level of confidence.

126. Where it is possible to further refine and describe the affected population associated with defined risk factors such as season, region or specific type of production, then a correlation of the sampling protocol to such a co-variable may be justified.

### 11.5 Point of Sampling

127. The point at which a sample is taken depends on the objective of the specific programme. Where the objective is to verify the effectiveness of controls at the supplier level, generally samples are taken at the point of sale / harvest where it is still possible to correlate the unit sampled with a supplier or producer.

128. On-farm sampling may also be used as part of an ante-mortem quality assurance programme or where there are concerns associated with the possible use of substances prohibited by the competent authority.

129. Where the objective is to verify the overall effectiveness of a system at ensuring the general population's exposure is less than the ADI then multiple sample units can be combined before analysis, or commingled product sampled and analysed.

130. Where the objective is to verify the credibility and effectiveness of the control and verification programmes present in an exporting country, samples may be taken from standardised units of export at the port of entry. Such secondary verification programmes have quite different design considerations with respect to their objective, the population of interest and the type of response to any identified level of non-compliance.

131. For port of entry testing programs the population of interest is all like product produced under a common control and verification system. While units of product may be sampled from selected consignments, the results attained are only reflective of the discrete unit (package) sampled and the performance of the national control and verification system as a whole. For consignments of non-homogenous products, except where there is a commonality of pre-harvest source, the results attained from the sampled unit are no more reflective of the rest of the consignment from which the sampled unit came than other similar product produced under the same national control and verification system.

#### **11.6 Non-biased versus targeted sampling: sample size considerations**

132. Non-biased sampling is designed to provide profile information, especially as to the level of application or performance of a control or control system for a specified animal / food population over a defined period (usually annual).

133. Sample sizes for non-biased sampling protocols should be statistically based and may be influenced by the size of the population (where less than 5000), the prevalence of non-compliance determined to be significant, the level of confidence to be placed in the results as well as economic considerations.

134. If the size of the population is small then the effect of sampling without replacement should not be ignored and the sampling distribution should be based on the hypergeometric distribution. However most populations sampled using non-biased sampling will tend to have larger than 5000 units and the effect of sampling without replacement (hypergeometric) and sampling with replacement (binomial) becomes small and the binomial distribution can be used to determine an appropriate sample size. Regardless of the size of the population sampled, the required sample size based on the binomial distribution will always be equal to or greater than the required sample size based on the hypergeometric distribution.

135. The sample size for a defined confidence will be effectively constant for populations exceeding 5000 units.

136. Where non-compliant results are detected it is possible to derive a crude estimate of the likely prevalence in the general population. However, where no non-compliant results are found then any statements about prevalence need to be stated as a confidence level that the prevalence of non-compliant results does not exceed a specified percentage. The sample size required to give the required level of statistical assurance can be read from Table 1.

**Table 1:** Number of samples required to detect at least one non-compliant result with pre-defined probabilities (e.g. 90, 95, and 99 percent) in a population having a known non-compliance prevalence.

Non-compliant prevalence (% in a population)	Minimum number of samples required to detect a non-compliant result with a confidence level of:		
	90%	95%	99%
35	6	7	11
30	7	9	13
25	9	11	17
20	11	14	21
15	15	19	29
10	22	29	44
5	45	59	90
1	230	299	459
0.5	460	598	919
0.1	2302	2995	4603

137. The probability of failing to detect a specified prevalence of non-compliant results associated with a specified targeting mechanism can be read off table 2 below. Because of the low efficacy of sampling protocols to detect low prevalences of non-compliance, other assurance mechanisms are more important where a low prevalence of non-compliance is expected and can exert a significant adverse health effect on the consuming public at these levels.

**Table 2:** Probability of failing to detect a non-compliance

Prevalence (%)	Number of animals in sample tested									
	5	10	25	50	75	100	200	250	500	1000
1	0.951	0.904	0.779	0.605	0.471	0.366	0.134	0.081	0.007	0.000
2	0.904	0.817	0.603	0.364	0.220	0.133	0.018	0.006	0.000	
3	0.859	0.737	0.467	0.218	0.102	0.048	0.002	0.000		
4	0.815	0.665	0.360	0.130	0.047	0.017	0.000			
5	0.774	0.599	0.277	0.077	0.021	0.006				
6	0.734	0.539	0.213	0.045	0.010	0.002				
7	0.696	0.484	0.163	0.027	0.004	0.001				
8	0.659	0.434	0.124	0.015	0.002	0.000				
9	0.590	0.389	0.095	0.009	0.001					
10	0.528	0.349	0.072	0.005	0.000					
12	0.470	0.279	0.041	0.002						
14	0.418	0.221	0.023	0.001						
16	0.371	0.175	0.013	0.000						
18	0.328	0.137	0.007							
20	0.254	0.107	0.004							
24	0.193	0.064	0.001							
28	0.193	0.037	0.000							
32	0.145	0.021								
36	0.107	0.012								
40	0.078	0.006								
50	0.031	0.001								
60	0.010	0.000								

138. Directed or targeted sampling protocols are designed to place a greater intensity of inspection / audit on suppliers or product considered to possibly have a greater potential than the general population of being non-compliant. As it is just a sub-population which is considered to have greater chance of non-compliance is being sampled it is not possible to extrapolate any non-compliant results to make conclusions about the general population. However, where compliant results are found these results in conjunction with non-biased program results provide a higher level of assurance that the residue control system is working at an appropriate level of control.

139. The application of directed or targeted sampling in port of entry sampling programmes is only appropriate where product is known to or suspected of sharing the same exposure profile. As animals are exposed to veterinary drugs prior to any product being harvested, any directed sampling at port of entry should be reserved for situations where sub-populations of product likely to have shared a similar pre-harvest exposure profile can be identified.