European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON REFLECTION PAPER ON THE USE OF (FLUORO)QUINOLONES IN FOOD-PRODUCING ANIMALS IN THE EUROPEAN UNION: DEVELOPMENT OF RESISTANCE AND IMPACT ON HUMAN AND ANIMAL HEALTH[1]

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	IFAH-Europe	EU
2	AVC	EU
3	Poultry Health Services	UK
4	BfR	DE
5	Justus-Liebig Univ Giessen	DE
6	The Soil Association	UK

[1] Currently published as "Public Statement"

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Table 2:Discussion of comments

GENERAL COMMENTS – OVERVIEW

1. **Poultry Health Services**:

This consultation document is a reasonable summary of the state of knowledge in this field.
Loss of flouroquinolones as therapeutic agents in poultry medicine would have a series of adverse effects for the practice of poultry medicine. We are happy to agree with the final conlusion of this paper that "There is a need for risk management interventions regarding the use of fluoroquinolones for humans and animals". Poultry practitioners would be keen to work with the authorities to ensure that such measures are effective and science-based. Further research may well be required to ensure that this is achieved.
Poultry Health Services conclusions: Pathogen eradication programmes and pathogen control programmes are likely to be a more effective approach to the reduction of risk relating to acquired FQ resistance in pathogens of human health significance in both the medium and long term. Attention should also be paid to the risk of transfer of resistance from treated non-food animals to human patients and also resistance acquired through human medication to animals of all sorts. Effective enforcement of existing legislation and codes of practice would also help curb any abuses which may be occurring and encourage good practice. However, as noted above, there is a real risk that a ban or even intensified regulation will divert food production to markets where such controls are not as effective and thus be counter-productive.

2. **The BfR**

The BfR points out that the point 3 and 4 of conclusions only discuss therapeutic options related to *Salmonella* and *Campylobacter* infections ignoring that the work of Helms et al. showed that patients infected with a quinolone resistant *Salmonella* or *Camplylobacter* are already at higher risk to die in comparison to patients infected with a pansusceptible strain. So BfR concludes that already the high prevalence of quinolone resistant *Salmonella* and *Camplobacter* put the public on a higher risk for morbidity and mortality.

CVMP/SAGAM comment: Being infected with a resistant strain has been reported to result in higher mortality. It is prefered not to change the text.

3. Soil Association:

The Soil Association welcomes the CVMP's reflection paper on fluoroquinolone use in farming and its potential impact on human and animal health. In commenting on the CVMP's paper we draw on international research in relation to fluoroquinolone resistance, but only the UK situation in relation to the use of fluoroquinolones, since this is the only area where we have any first hand knowledge. In general we avoid repeating points made in the CVMP's paper, but we believe that a number of the paper's findings are particularly important and worth re-emphasising. These are:

- the relative contribution to fluoroquinolone resistance in Campylobacter jejeuni from the use of fluoroquinolones in human medicine, as compared with the veterinary use, is likely to be less significant since humans, unlike poultry for example, are not asymptomatic carriers of campylobacter and therefore resistance will only be selected for during treatment for campylobacter infections [We note that this observation is consistent with the absence of fluoroquinolone resistance in Campylobacter jejeuni in Australia, where fluoroquinolones are not used in farming]
- antimicrobial-resistant Salmonellae isolated from human infections have in all probability acquired their resistance while living in food-producing animals
- antimicrobial resistance in salmonella or campylobacter infections can lead to increased severity of disease, prolonged infection and treatment failure
- while in most bacterial species, resistance to fluoroquinolones is due to genetic mutations, in the past few years plasmid-mediated resistance has emerged in the US, Asia and Europe in different bacteria including Klebsiella peumonia, e-coli and salmonella. It is to be expected that this kind of resistance will also emerge in food animals in Europe. [We note that this important development raises the possibility of more rapid and widespread evolution of resistance if, for instance, the plasmids were to be transferred to bacterial species where fluoroquinolone resistance is rarer]

While the CVMP has produced a detailed review of the resistance problem, we feel that a number of important points have been overlooked or given insufficient emphasis. In particular:

- fluoroquinolones can induce the 'SOS response' in a number of human and animal pathogens which can result in the horizontal transfer of both virulence and resistance genes. As a consequence of this, the use of fluoroquinolones not only increases resistance to fluoroquinolones, it also has the potential to promote the spread of resistance to antibiotics other than fluoroquinolones, increase the virulence of existing pathogens, and even create new pathogens. Fluoroquinolones induce the SOS response in shiga-toxin-producing e-coli, in Staphylococcus aureus and in Vibrio cholerae and in all of these cases, the farm use of fluoroquinolones could be implicated in spreading virulence and resistance genes.
- the genes coding for resistance to fluoroquinolones can become physically linked to genes conferring resistance to other antibiotics. When this occurs, fluoroquinolone use can 'co-select' for, and increase, resistance to other chemically-unrelated antibiotics. Scientific evidence exists showing that fluoroquinolone use may increase resistance to cephalosporins in Salmonella choleraesuis, to chloramphenicol in vancomycin-resistant enterococci and to extended-spectrum beta-lactams in e-coli. In all cases, there are serious implications for human medicine
- fluoroquinolone use is a risk factor for acquiring MRSA when MRSA is fluoroquinolone-resistant. Continued use of fluoroquinolones in farm animals therefore has the potential both to increase fluoroquinolone resistance in veterinary MRSA and to promote the spread of MRSA in farm animals
- Australia, which has never permitted the use of fluoroquinolones in farm animals, has very low levels of resistance to fluoroquinolones in locally acquired human campylobacter and salmonella infections. The much higher levels of resistance from similar infections acquired while travelling abroad indicates that the farm use of fluoroquinolones is promoting resistance in human infections. The international spread of resistance reinforces the need for action to restrict fluoroquinolone use at an international, as well as an EU level.

a new fluoroquinolone resistance pattern has emerged in salmonella in South-East Asia. The salmonella bacteria have reduced susceptibility to fluoroquinolones but are fully sensitive to nalidixic acid raising the possibility that if nalidixic acid is used to determine fluoroquinolone resistance, the levels of resistance may be underestimated.

CVMP/SAGAM comment: The thorough revision of the reflection paper and the very detailed comments of the Soil Association are greatly appreciated. They address many relevant aspects of the use of (fluoro)quinolones. However, the scope of the reflection paper is limited, thus many interesting topics could not be included in this document. Some of the points addressed by the Soil Association are addressed here below when addressing comments from other interested parties, whereas others are noted but found beyond this paper.

The comments SAGAM found more appropriate to discuss in other fora are as follows:

- Fluoroquinolones and the SOS response
- Fluoroquinolones and co-selection
- Fluoroquinolones and MRSA
- Levels of fluoroquinolone resistance in different countries and how international travel can result in resistance spreading
- Resistance to fluoroquinolones and nalidixic acid
- Quantities of fluoroquinolones used in food animals
- Significance of fluoroquinolone use in different species
- Therapeutic and prophylactic doses
- Inadequacy of withdrawal periods
- The role of the veterinary profession
- The need for additional training for veterinary surgeons
- Advertising of fluoroquinolones

The comments made by the Soil Association on the limited value of nalidixic acid as markes for plasmid mediated qnr-type resistence is well taken and the text and recommendations are changed accordingly.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
IFAH-Europe		
	1. This report refers to both quinolones (e.g., nalidixic acid, oxolinic acid, flumequine) and fluoroquinolones, as is apparent from various paragraphs in the report. However, the title of the report only refers to fluoroquinolones and in this respect some sections are not always clear. **Proposal**: May we suggest adding quinolones to the title to avoid misunderstandings? Alternatively, this concern can be clarified in the text by modifying the text of page 3 or 4 or providing a definition.	Through the document the term (fluoro)quinolones will be used unless there is a need to refer to a specific molecule. An explanatory paragraph has been included at the end of the introduction.
AVC		
	2. Quinolones and fluoroquinolones are not comparable or equal in terms of their usage in the EU or their breakpoints in different species, conditions and body compartments. Therefore, we believe it is misleading and potentially damaging to use quinolones alone as the benchmarks for decisions on fluoroquinolones, except for campylobacter.	Both older and newer generations of quinolones have an impact on resistance, and therefore the term (fluoro)quinolones is used unless there is a need to refer to a specific molecule.
BfR		
	3. The BfR strongly supports the initiave on the use of fluoroquinolones, especially the final conclusion that there is a need for risk management interventions regarding the use of fluoroquinolones for humans and animals.	No modification of the document required.
Justus-Liebig Univ Giessen		
	4. Fluoroquinolones represent a class of important antimicrobials	Prices of VMP are not regulated at the EU level. We agree with this

[2] Where applicable

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	which are used against severe and invasive infecions by gram-negative and gram-positive bacteria and mycoplasma. The use of these antimicrobials by veterinarians is regulated in Germany. In agreement with these guidelines the use of these antimicrobials should be reduced in total and limited for only severe and peculiar infection diseases. The use could be regulated by the price. Any restrictive use in European countries is already counteracted by a tremendous use of fluoroquinolones in other parts of the world, e.g. in China for food producing animals. Loosing fluoroquinolones for veterinary therapy of severe infections on animals would significantly limit therapy and would encounter economic lossess by animal owners and also would be not in accordance with animal welfare.	comment in principle, but unfortunately the matter is outside the scope of the document. Although the use in some countries is not adequate, this is not a reason for not addressing the issue in the EU. There is evidence that prudent use of antimicrobials on a national level can reduce antimicrobial resistance. The CVMP/SAGAM would with pleasure support a global approach towards the prudent use of antimicrobials
IFAH-Europe		
Page 3, second full paragraph, line 2:	5. "….*and prevention of those diseases*" The reading of the second part of above sentence was slightly unclear. **Proposal**: May IFAH-Europe suggest the following wording "and <u>increases the need for</u> prevention of those diseases." In this respect, it might be appropriate to emphasise here the significance of Good Agricultural Practice (stocking density, good air quality, appropriate cleaning, HACCP, etc.). **Proposal**: May we propose to insert after the first sentence of this paragraph: "One approach should be to reduce the occurrence of food-borne pathogens as such. When the numbers of *Salmonella* and *Campylobacter* are reduced, transmission of fluoroquinolone-resistant pathogens will consequently be lowered. Hence, Good Agricultural Practice (GAP) must have a high priority. The frequent and imprudent use of antibiotics will provide favourable conditions for selection,	Agreed, changed accordingly. Agreed, changed accordingly.

GUIDELINE SECTION TITLE		
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	spread……"etc.	
Page 3, second paragraph, fifth sentence:	6. "*Antimicrobial resistant bacteria can have human health consequences due to the increased occurrence of infections with resistant bacteria during and after treatment with antibiotics these bacteria are resistant to.*" Note that above slightly difficult-to-read sentence is applied in a general context whereas the cited Barza and Travers reference specifically relates to *Salmonella* infections.	Agreed, changed accordingly.
AVC		
	7. It can also be said the amount of fluoroquinolones used in man is also not readily available but is considered substantially higher than in animals. As reported in Danmap 2004, 58kgs were used in animals and over 12 times as much, 722 kgs of active, were used in man.	Not agreed, as the amount of fluoroquinolones used in humans is known in the EU at present (ESAC). The text has been modified to provide clarification that only use in animals is addressed in this section.
	8. To give a complete overview, quinolones have been included as well as the fluoroquinolones. Although these two classes are related, reference to quinolones confuses the antimicrobial resistance picture, because in most cases, fluoroquinolone resistance is considerably lower. AVC does not believe that these two classes should be considered as identical or data on the two combined. In particular, data, hypotheses and conclusions based on findings with quinolones should not be transposed directly to fluoroquinolones.	See the comments above.
IFAH-Europe		
Page 4, first	9. "*The first…..on the market*". IFAH-Europe believes the current wording can be improved as follows:	IFAH proposal can be agreed to and the text has been revised

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paragraph:	" ……. and the first fluoroquinolone (enrofloxacin) during the late 1980's and early 1990's. Since then additional ~~new~~ fluoroquinolones…"	accordingly.
AVC		
	10. In fact, in certain cases they may be the only effective class of drugs e.g. for the treatment of colisepticaemia in turkeys following a Mycoplasma and/or turkey rhinotracheitis virus infection, for neonatal calf colisepticaemia and for acute *E. coli* mastitis in cows. Tissue distribution and penetration may also have a significant impact, as these may not be adequate with the alternative agents to achieve a satisfactory clinical response.	Addressed in page 24 of original document.
IFAH-Europe		
Page 4; Table 1:	11. **Questions**: Should "*All quinolones*" be read as "All fluoroquinolones plus all quinolones"? As to UK: *"no information"*: are any quinolones approved for the food animals included in the table (cattle, pigs, poultry)? If not, the figure of 1.4 tonnes should be identical for both columns.	Agreed, and the term (fluoro)quinolones as described in the introduction is used. Agreed.
	12. **Comment**: It might be valuable to link the sales of fluoroquinolones and the production of meat by calculation of a ratio. By applying this, it appears that Portugal deviates strongly. As you already indicated on page 5, the data are difficult to interpret. It seems that the value of 3.6 metric tonnes of fluoroquinolones for Portugal is inconsistent.	We prefer not to change the text. This was discussed in the SAGAM and rejected originally (biased due to animal imports/exports). The sales from Portugal have been modified following the information provided by Portuguese authorities.
AVC		
	13. There is discussion of use of fluoroquinolones and quinolones on a quantity and meat production basis (Table 1 of the document). Where there are figures, usually they are not broken down by species. In AVC's knowledge and experience, the most extensive oral	CVMP/SAGAM is aware that there is only limited data on consumption, but as no exact figures have been provided, no changes can be made in the text.

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	fluoroquinolone use is in poultry, especially turkeys, followed by companion animals and calves. Injectables are mainly used in cattle and to a lesser extent in pigs. There are no drinking water or in-feed fluoroquinolone formulations approved for pigs in the EU, although there is a piglet doser formulation. Quinolones are not so widely used; flumequine has a limited registration in the EU outside France and oxolinic acid is mainly used in farmed fish, which are not mentioned in this document. More accurate figures may be obtainable in confidence from IFAH Europe. There are a large number of oral fluoroquinolone products available for companion animals, mainly dogs, which live much more intimately with the human population than farm animals generally. AVC believes that quinolone use is not relevant to the broad use of fluoroquinolones in farm animals, and that farm animal use of fluoroquinolones may not be the only relevant source of resistance in terms of impact on humans, and the use in companion animals should also be considered. AVC suggests that this part of the text should be improved and the volume usage of fluoroquinolones in animals compared with human usage.	From the data available we cannot consider that older quinolones are not widely used. Objectives have been clarified to exclude the use of (fluoro)quinolones in aquaculture. Although many products are available for companion animals, the main reservoir of food borne pathogens resistant to (fluoro)quinolones are food producing species. IFAH has not provided such figures, consequently no change is proposed.
	14. In some countries, such as Spain, fluoroquinolones have been extensively used. Including generic enrofloxacin there were 13 companies selling 32 formulations in 2000 (Veterindustria, 2000). In other parts of the world, notably Asia, entire drums of active substance, produced in China, can be found on farms. This highlights the international scope of the situation and suggests that action taken unilaterally in the EU is unlikely to have the desired effect. See also comments later on foreign-acquired food poisoning or disease. AVC, as a matter of policy, believes that the use of fluoroquinolones should be under veterinary supervision, following veterinary diagnosis, and the products should not be available as bulk or foreign-sourced generics for routine on-farm use.	A summary of the number of Marketing Authorisations for (fluoro)quinolones is available at the EMEA web page (http://www.emea.europa.eu/postconference.htm). It is agreed that the issue should also be addressed at international forums (e.g Codex, OIE).

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IFAH-Europe		
Page 5, third paragraph:	15. IFAH-Europe strongly endorses the proposal: 1. to include prudent use wording to the SPCs, 2. to harmonise the prudent use wording in all Member States for all products containing (fluoro)quinolones.	Agreed.
Page 5, sixth paragraph, last line:	16. "……..*of a patient acquiring a nosocomial infection with* ….." Should the last sentence read as "……..acquiring a <u>fluoroquinolone-resistant</u> nosocomial infection with…."?	Agreed. Text modified according to reference.
Page 5, seventh paragraph, last sentence:	17. (*But resistance is also …*) The emphatic statement in the last sentence is inconsistent with the first sentence of paragraph 2, page 7 *(The relation between usage of fluoroquinolones and development of resistance is complex,…*). Whilst it is tempting to correlate different observations a general caution is required, as rightly indicated on page 7, second paragraph; a temporal relationship is not in itself proof. The epidemiology of enteric diseases is complex and there are many possible sources other than food animals and many routes of transmission other than food of animal origin.	The word "clear" has been changed to "well documented".
	18. We are concerned about the general use of the term "breakpoints". IFAH-Europe would like to stress the importance of the appropriate use of this term and would like to highlight the difference between clinical and microbiological breakpoints. We consider it very important to work together with CVMP regarding this issue.	Headline has been modified. Definitions are needed for breakpoints (EUCAST); text has been revised accordingly.

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Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
AVC		
	19. The entire topic of breakpoints is one that deserves separate discussion. AVC is happy to organise a seminar on behalf of the EMEA, subject to appropriate financial support from the EU, to discuss this topic, which is of importance to large companies and to SMEs producing antibiotics and to public health and laboratory specialists.	See also IFAH Europe concerns about breakpoints (comment 18). Organising a seminar on this issue is outside of the scope of this FQ reflection paper.
IFAH-Europe		
Page 6, first paragraph, first sentence:	20. "*(Fluoro)quinolones….. genes*." In order to more fully explain resistance (e.g., inclusion the contribution of efflux mechanisms, topoisomerase IV, *parC* and *parE*), IFAH-Europe proposes to replace the first paragraph by: **Proposal**: "(Fluoro)quinolones inhibit the activity of the type II topoisomerase family that control bacterial DNA topology. In most bacterial species resistance is due to mutations in the DNA gyrase, encoded by *gyrA* and *gyrB,* and topoisomerase IV, encoded by *parC* and *parE* genes. The primary target of fluoroquinolones can be attributed mainly, although not exclusively, to mutations in the g*yrA* gene and the *parC* gene in Enterobacteriaceae. Furthermore, decreased uptake or increased efflux of fluoroquinolones contribute to fluoroquinolone resistance. In Enterobacteriaceae resistance to quinolones is most commonly acquired by mutations in two steps. One mutation in the *gyrA* gene mediates full resistance to first generation quinolones such as nalidixic acid and flumequine and reduced susceptibility to fluoroquinolones. A second mutation in either *gyrA, gyrB* or *parC* genes mediates clinical resistance to fluoroquinolones."	Not agreed, for the reason of keeping the text on the *gyrA* as concise as possible.
Page 6, third paragraph, fourth	21. "*However, reports (reviewed in Aarestrup et al. 2003) have shown that isolates with a single mutation in gyrA to some extent are refractory to the bactericidal effect of fluoroquinolones*"	Not agreed. CLSI and EUCAST have footnotes indicating that caution is needed. The text is not based on the review from Aarestrup only, but has

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sentence:	IFAH-Europe assumes that this sentence refers to *Salmonella*. Generally we and others (CLSI, EUCAST; see the respective web sites) believe that the statements (Aarestrup et al 2003) are not sufficiently supported by the literature. This view is based on conflicting evidence with respect to infections with clinically ciprofloxacin-susceptible, nalidixic acid-resistant *Salmonella* strains (see pages 6 and 7 of this response).	other sources as well.
Page 6, fourth paragraph, second line:	22. IFAH-Europe assumes that this paragraph relates strictly to *Salmonella*, as is being appropriately confirmed on page 14 in the 7th paragraph of the EMEA consultation paper. It is suggested that this point is indeed clarified. Nalidixic acid is not a good marker for all Enterobactericeae. For *E. coli* there is no literature available reporting clinical failures in infections caused by low-level fluoroquinolone resistance. Hence, we suggest to replace "Enterobactericeae" by "S*almonella*". As regards *Salmonella*, all antimicrobial resistance surveys should include both nalidixic acid (to detect the population with decreased susceptibility to ciprofloxacin; MICs from 0.12 to 2 mg/l) and ciprofloxacin (to detect high-level resistance; MICs ≥4 mg/l). Many surveys have already adopted this concept.	Not agreed. Acquisition of resistance is addressed here and not necessarily the clinical resistance. Nalidixic acid is an accepted marker for acquired resistance due to chromosomal mutations. Breakpoints have been substituted by epidemiological cut of values. For ciprofloxacin, agreed in principle. Nevertheless, we consider the current text as correct, please see also table 3. In order to detect qnr-genes cipro and nal should be used. The text has been changed accordingly
AVC		
	23. Resistance in Enterobacteriaceae: AVC believes that nalidixic acid, as a quinolone, is not a valid marker for fluoroquinolones. Resistance tests for fluoroquinolones must either be run using fluoroquinolones alongside nalidixic acid or preferably instead of nalidixic acid, as the main interest is fluoroquinolone resistance itself. In addition, the breakpoints are at least 8-fold different and, consequently, decisions on resistance based upon findings with nalidixic acid cannot be directly extrapolated to fluoroquinolones (see	Please see the comments above.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	Table B of AVC comments)	
	24. There are marked differences seen between the resistance data for quinolones and fluoroquinolones and reliance on the quinolone data is misleading, suggesting there is greater fluoroquinolone resistance than in reality. Moreover, AVC believes that decisions made on the basis of clinical case submissions for diagnostic purposes, often submitted after exposure to antimicrobials and treatment failures, cannot be taken to represent the status of resistance in the general population, which is revealed by slaughter animals surveyed. This reasoning also applies to *Salmonella*.	Nalidixic acid resistance is the most sensitive indicator of acquired resistance to (fluoro)quinolones related to gyrA-mutations only. We agree. There are differences, but no other data on the prevalence of resistance are available in the monitoring of resistance in clinical isolates.
	25. There are marked differences seen between the resistance data for quinolones and fluoroquinolones and reliance on the quinolone data is misleading, suggesting there is greater fluoroquinolone resistance than in reality. Moreover, AVC believes that decisions made on the basis of clinical case submissions for diagnostic purposes, often submitted after exposure to antimicrobials and treatment failures, cannot be taken to represent the status of resistance in the general population, which is revealed by slaughter animals surveyed. This reasoning also applies to *Salmonella*.	Nalidixic acid resistance is the most sensitive indicator of acquired resistance to (fluoro)quinolones. Agreed, there are differences, but no other data on the prevalence of resistance are available in the monitoring of resistance in clinical isolates.
IFAH-Europe		
Page 6, fourth paragraph, third line:	26. The general use of the term "*breakpoints*" in different contexts can be misleading and may result in confusion. The issue of the breakpoints has not been addressed in the current document. However, IFAH-Europe would like to stress the importance of this subject and would like to highlight the difference between clinical and microbiological breakpoints. We endorse the use of appropriate *clinical* breakpoints for everyday use in the clinical laboratory to advise on therapy, and *microbiological* breakpoints to perform resistance monitoring in order to detect the development of resistance. We consider it very important	Agreed, please see the modifications in the text.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	to work together with CVMP with regard to this issue in order to avoid confusion with the breakpoint concept. As described by EUCAST, there should be a strict differentation between clinical breakpoints and microbiological breakpoints (perhaps better referred to as "*epidemiological cut-off values*"). IFAH-Europe proposes that the term "*low breakpoints*" should be replaced by "epidemiological cut-off values" or "microbiological breakpoints".	
Page 6, fifth paragraph:	27. Please note that clinical breakpoints for *Campylobacter* have not yet been universally established.	Clarified on the text; there are no universally accepted breakpoints for any bacterial species. In Europe the EUCAST cut off values are used for *Campylobacter*.
	28. Appropriate application of microbiological and clinical breakpoints for *Salmonella* spp. (page 6 of the Consultation Report).	The text has been revised to make the terminology more stringent.
Page 7, first paragraph:	29. IFAH-Europe suggests that the reflection paper takes note of the significant impact of foreign travel in North America and Europe on the prevalence of fluoroquinolone-resistant *Campylobacter*. This exceeds the resistance rates of *Campylobacter* from domestic patients. For instance, in Sweden resistance to ciprofloxacin was virtually absent in domestically acquired strains yet in *Campylobacter* from Swedish patients contracted outside Sweden the rate of ciprofloxacin resistance exceeded 60 % (Osterlund et al. 2003). Similarly, in Denmark the resistance rate to ciprofloxacin in patients who travelled abroad amounted to 64 %; for *C. jejuni* strains from domestic patients the figure was 17 %; and for *C. jejuni* of Danish broiler meat this figure was 1 % (DANMAP 2003). In Canada *C. jejuni* of Canadian patients acquired abroad were significantly more resistant to ciprofloxacin than *C. jejuni* acquired locally (59 % versus 11 %) (Gaudreau and Gilbert, 2005). These examples from countries where fluoroquinolones are administered more strictly than in some other countries demonstrate that the usage of fluoroquinolones in a prudent manner in avian medicine only contributes a minor extent, if at all, to the overall ciprofloxacin	Although we agree in that travel contributes to the prevalence of fluoroquinolone resistant *Campylobacter* infections in humans, this is here out of scope. This reflection paper focuses on the use of (fluoro)quinolones in the EU in food-producing animals. Need for international co-operation is recognised.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	resistance in human *Campylobacter*.	
	30. The reference to Butzler, 2005 appears to be incorrect. Either it should be Butzler, 2004 (Clin. Microbiol. Infect.10:868-876) or an original reference.	Corrected
Page 7, second paragraph, 9th line:	31. **Proposal:** change into: „……transmission is rare <u>though possible by indirect routes of transmission</u>."	We cannot agree. The word rare includes indirect routes of transmission.
Page 8; Table 2:	32. It is striking that in Denmark, characterized by a very limited use of fluoroquinolones (see Table 1), a relatively high figure of quinolone resistance was neverthless encountered in *Salmonella enteritidis* (DANMAP 2002). Note that the usage of fluoroquinolones decreased strongly during 2002, suggesting the observations are not related to the national use of fluoroquinolones. Clinical resistance to ciprofloxacin (based on breakpoints defined by EUCAST or CLSI) has never been observed.	The current data prove that there are difference in resistances rates. The number of isolated tested may have affected the data. ARBAO database does not use standardised breakpoints so the results may be affected by differences in the interpretation criteria between countries.
Pages 8 and 12; Tables 2 and 4:	33. Neither table includes the number of strains investigated per species and per country. We understand that it is difficult to include all details in such a summary overview, though it might be important information. **Proposal**: Could you consider putting such information in a footnote? Similarly, without interpretive criteria % resistance is not objective; is it possible to include the definition of a resistant isolate within a footnote? Would it be possible to add to the legend of Table 2 "sampled at slaughter" or to insert in the text on page 7 "healthy" (first line of last paragraph)? Do the data in Table 4 refer to enrofloxacin with breakpoint 2 mg/L?	Variable information available has been addressed in the text before the table 2. More information is now available on the EFSA's Zoonosis Report (http://www.efsa.europa.eu/en/science/monitoring_zoonoses/reports.htm)
AVC		
	34. Table 2 of the document uses quinolones as its marker (either nalidixic acid or flumequine). Danish data (Danmap 2002) shows 23%	Please see the previous comments. Explanatory text has been introduced.

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Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	resistance to quinolones in *S.* Enteritidis from poultry, however if the breakpoint of >2µg/ml is used for ciprofloxacin there is no resistance, only when the breakpoint is reduced to >0.06µg/ml does the resistance figure increase to 23%. Similarly, in the UK's *S.* Typhimurium figures for pigs, there was no ciprofloxacin resistance at >2µg/ml breakpoint. This highlights the necessity to standardise both clinical and microbiological breakpoints with the fluoroquinolones. This should be relatively easy to achieve using pharmacokinetic and pharmacodynamic relationships and by taking account of which infection is being treated and where, whether systemically or in the intestinal tract.	
IFAH-Europe		
Page 9; Table 3:	35. In the Italian monitoring programme ITAVARM 2003 the *E. coli* resistance rate to enrofloxacin was reported to be 11 %. It should be noted that this figure is based on the disk diffusion method.	Agreed, and the text modified to provide more clarification.
Page 10, third paragraph:	36. It might be a useful addition to add a comment to the susceptibility of the *Salmonella* isolates of Delsol et al. after the last sentence of this paragraph. **Proposal**: "It is significant to note that the 5-day enrofloxacin treatment did not result in any change of the MICs of nalidixic acid or ciprofloxacin and, hence, the treatment did not induce a decreased susceptibility to fluoroquinolones. In addition, the experimental conditions did not reflect the practice of the pig industry (Silley and Froyman, 2004)".	We think that this change is not necessary, and thus no changes are made.
AVC		
	37. AVC is critical of the Delsol et al (2004) study on *Campylobacter coli* described in the document, in that it was monitored for only 5 weeks after treatment and not followed through to slaughter. There was quite a variation in recovery of fluoroquinolone resistant	Agreed, and changes made in the text.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	isolates in the relatively short observation period but given the above linear projection, the resistance level would have probably returned to normal by 90 days post treatment. AVC stresses that care needs to be taken in relating experimental studies such as this to practical situations.	
IFAH-Europe		
Page 10, fourth paragraph, first and second sentence:	38. "*In the developed countries most human infections with Campylobacter and Salmonella are food-borne. It is generally agreed that the main reservoir of these bacteria are food-producing animals and that the main source of infections are animal products.*". **Proposal**: "……*Campylobacter* and non-typhoid *Salmonella* are food-borne". **Comment**: Note that many reservoirs and routes of transmission of *Salmonella* spp. have been described other than food animals and animal products (e.g., vegetables, environment, sewage, human to animal transmission; for references see, e.g., Kinde et al. 1996; Santamaria and Toranzos, 2003; Sivapalasingam et al. 2004).	Agreed. The word "Non-typhoidal" has been added to the text. Most of these sources are contaminated with animal faeces and therefore they are of animal origin.
AVC		
	39. AVC disagrees with the statement that 'In the developed countries most human infections with Campylobacter and Salmonella are food borne' (More details in the AVC document p. 5-6)	Not agreed. Please refer to the previous comment.
	40. AVC believes that it is more appropriate to consider *C. jejuni* and *C. coli* separately as they have different epidemiologies of infection and quinolone susceptibility patterns. Valid breakpoints need to be established for the individual *Campylobacter* spp. (More details in the AVC document on p. 6)	We cannot agree. Epidemiology is not different, as is animal derived for both. EUCAST cut off values have been established for *Campylobacter* spp.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
IFAH-Europe		
Page 10, fifth paragraph, first sentence:	41. "Antimicrobial *resistant Salmonellas isolated from human infections most likely have acquired resistances while living in the food producing animals*". It has also been widely reported that treatment of *Salmonella* spp. in humans with fluoroquinolones may also result in *Salmonella* with decreased susceptibility to fluoroquinolones (Quabdesselam et al. 1996; Piddock 2002; Melau Kristiansen et al. 2003). In many other studies this possibility has not been investigated because a sample prior to medication wasn't collected. **Proposal**: IFAH-Europe suggests that this possibility is added to the text.	Partially agreed, text has been revised.
Page 10, fifth paragraph: last sentence:	42. "*Epidemiological and microbiological studies have also demonstrated that nalidixic acid resistant Salmonella were selected in the animal production and subsequently spread to and cause infections in humans*." In this respect it is of extreme importance to underline the significance of the spread of resistant strains including strains with decreased susceptibility to fluoroquinolones in the environment (for review see Davis et al. 2002). Antimicrobial-resistant isolates of *Salmonella* including nalidixic acid-resistant isolates, are frequently isolated in the EU, without any antimicrobial treatment of the given animal (e.g., Mölbak et al. 1999). Similar, striking experiences have been made in other continents in remote communities where inhabitants have had little or no use of antimicrobial agents (Bartoloni et al. 2004; Davis et al 2004). Clonal dissemination of *Salmonella* resistance may be the most important factor regionally, nationally and globally. Not only human travel from areas with heavy, indiscriminate antibiotic consumption, but also international trade of food, feed and live animals will contribute to the emergence of antimicrobial resistance in any part of the world (Hakanen et al. 2001). This phenomenom deserves attention.	Partially agreed, see changes on the text.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
Page 10, sixth paragraph:	43. Several reservoirs of *Campylobacter* have been described. There is increasing evidence that poultry is only one of the sources of human *Campylobacter* (Michaud et al. 2004; Wassenaar, 2005). Recently Champion et al. (2005) demonstrated that less 50 % of the *C. jejuni* human isolates investigated were not found in animals, suggesting that most *C. jejuni* infections may be from non-agricultural sources. As these researchers used the robust comparative phylogenomics approach, these findings may have much weight.	SAGAM agrees that many reservoirs exists but considers that for fluoroquinolone resistance for *Campylobacter*, poultry is the main reservoir.
Page 11, first paragraph:	44. **Question**: It may be useful to include the evidence that fluoroquinolone-resistant *E. coli* are less virulent than fluoroquinolone-susceptible *E. coli* strains (e.g., Vila et al. 2002; Moreno et al. 2006).	General analysis of literature does not support this statement.
Page 11: epidemiology section	45. Would it be feasible to include a sentence in this epidemiological section about the possible impact of co-resistance? For instance, more strict, prudent use of older molecules (e.g., tetracyclines, sulfonamides) could be very important because usage of these molecules may affect the susceptibility of several bacterial species to valuable classes such as fluoroquinolones or cephalosporins due to co-resistance mechanisms. Similarly, as mentioned above, clonal spread of resistance can be very important.	Although we agree in that co-resistance is highly relevant, it was initially decided not to address the issue in detail in the reflection paper. However, new data on co-resistance are available, and these will be addressed separately.
Page 11, second and third paragraph:	46. Please note that the theory of Barza and Travers (2002) has not been generally accepted. For a general criticism see Wassenaar (2005).	The mentioned paper is noted, but no change in the text is proposed. The estimated number of cases relays on evidence from a number of publications.
Page 11,	47. **Question**: A large body of evidence suggests that the disturbance of faecal flora following ingestion of therapeutic fluoroquinolone doses, is	In principle we agree that disturbance of faecal flora is transient. The text

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
third paragraph, first sentence:	transient. Would it be possible to include some references? (e.g., Pecquet et al. 1986; Pecquet et al. 1990; Edlund and Nord, 1999).	has been modified accordingly.
Page 11, fourth paragraph, last sentence:	48. *"For infections with (fluoro)quinolone resistant Salmonellas alternative antimicrobials are cephalosporins (3rd and 4th generation)."* **Proposal**: It should be emphasised that the occurrence of fluoroquinolone-resistant *Salmonella* is very rare.	CVMP/SAGAM does not agree.
	49. Conflicting evidence regarding the effect on public health of *Salmonella* infections with reduced susceptibility to fluoroquinolones (page 11).	CVMP/SAGAM does not consider the evidence provided conflicting.
Page 11, fifth paragraph:	50. IFAH-Europe would like to make a general comment regarding fluoroquinolones and therapy of human salmonellosis. An analysis of the available literature concerning patients infected with *Salmonella* strains showing decreased susceptibility to fluoroquinolones, mainly case reports with one or a few patients, shows that treatment failures may occur (Aarestrup et al. 2003; Crump et al. 2003). Detailed analysis of these studies reveals that therapy failures were not necessarily related to decreased fluoroquinolone susceptibility. The majority of the case reports actually refer to *S. typhi* and as humans are the only reservoir for *S. typhi*, the presence of *S. typhi* isolates with reduced susceptibility to fluoroquinolones seems a consequence of fluoroquinolone treatment of patients with typhoid fever. Regrettably, in many of the anecdotal communications a pre-treatment isolate was not available, in a few cases it was indeed demonstrated that reduced susceptibility developed during fluoroquinolone therapy of the patient (Umasakar et al. 1992). Similarly, in non-typhoid *Salmonella* development of reduced ciprofloxacin susceptibility during therapy has	SAGAM considers this comments not relevant for this reflection paper. Treatment failures might be the result of a variety of reasons. Data on Salmonella Typhi infections are considered predictive for the expected therapeutic effect of treatment of fluroquinolone resistant, non typhoidal Salmonellas. Invasive infections are among the high priority indications for the use of fluoroquinolones. These infections also occur with food borne Salmonella.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	been frequently reported (e.g., Piddock et al. 1990, Quabdesselam et al. 1996; Brown et al. 1996; Pers et al. 1996; Workman et al. 1996; Melau Kristiansen et al., 2003). In many studies patients were not treated according to the label indication, which may explain the treatment failures. Unfortunately, very few, if any, controlled studies are available. It should also be realised that treatment failures may occur for other reasons, irrespective of whether the organism is resistant or susceptible; treatment failures also occur with isolates fully susceptible to nalidixic acid and ciprofloxacin. This applies especially to seriously-ill, immunocompromised patients (AIDS, cancer, etc.), as is detailed in the reports referred to by Aarestrup et al. and Crump et al. Conversely, it is not surprising that no relapses occurred in cases where the full ciprofloxacin dosage over the entire prescribed time course was applied (unpublished results Bayer HealthCare). Hence, the treatment failures Aarestrup et al. and Crump et al. refer to, deliver no evidence for inadequacy of the current clinical breakpoints of CLSI and EUCAST. In cases where the recommended treatment regimen, was properly followed, normal cure was frequently achieved. The conclusions of the recent work regarding the impact of drug resistance in *Salmonella* on mortality and hospitalisation (Helms et al. 2002; 2004) were limited by the absence of medical treatment information, as indicated in the Consultation Report. Consequently the researchers state that *"We had no data on treatment with antimicrobial drugs.Therefore, exploring the extent to which the excess mortality of patients infected with quinolone-resistant strains was caused by reduced efficacy of drugs was impossible."*. The relative risks were based on study periods from 3 months (Helms et al. 2004) up to 24 months (Helms et al. 2002) post-treatment. In such a long time span several unrelated complications may occur. It should also be emphasised that for the seriously-ill patients with several underlying diseases the cause of death was not available. In the study of Helms et al. (2004) the clinical outcome for multiple-resistant isolates was not	

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	reported, which hampers attribution of the detrimental effects to fluoroquinolone resistance per se´. Indeed, the studies of Holmberg et al. (1987) and Lee et al. (1994), who reported increased mortality, increased hospitalisation rates and longer illness after infection with multi-resistant strains, albeit quinolone susceptible, suggest that the observations of Helms et al. have to be attributed to the multiple-resistance rather than to quinolone resistance. Unfortunately, Helms et al. (2004) did not disclose the frequency of antimicrobial resistance to other antimicrobial agents, which hampers further interpretation. Moreover, information on foreign travel is lacking and the time point of sampling has not been defined (important because of resistance development during therapy). Finally, we should be aware that the origin of the infective *Salmonella* strains is unknown. Thus, pending further data, these studies have to be interpreted with extreme caution. **Proposal**: IFAH-Europe encourages adding several limits of these studies to the 5th paragraph (after the last sentence "Information on treatment regimens in these cohorts are missing.").	
	51. Conflicting evidence regarding the impact of quinolone-resistant *Campylobacter* on human health (page 11).	Agreed that the evidence might to some extent be conflicting. Nevertheless the body of evidence shows impact of resistance on therapy.
Page 11, sixth paragraph:	52. At the start of this paragraph it might be appropriate to mention that most cases of campylobacteriosis are self-resolving and do not require antimicrobial treatment. It might also be included that the vast majority of *Campylobacter* cases occur in children who are not treated with fluoroquinolones. Consideration also needs to be given to adding after the second sentence of this paragraph "The large majority of human *Campylobacter* infections are due to *C. jejuni",* as only about 5 % of human campylobacteriosis can be attributed to *C. coli* infections. Generally we consider that insufficient detail is presented in the sixth paragraph of the Report, as discussed in the next paragraphs. (More details in the IFAH Europe comments).	Agreed that evidence might be conflicting, and text is slightly modified. Please see the comment above.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	In summary, two extensive, apparently conflicting, studies are presented. One study, comprising detailed observational work with 740 patients, failed to convincingly demonstrate an impact on public health related to fluoroquinolone resistance. It did, incidentally, demonstrate an ineffectiveness of ciprofloxacin treatment for susceptible infections. The second study comprised 3489 (later 11597) cases, for which fewer details on history or treatment were available. Nevertheless, this study clearly demonstrated that duration of disease did not differ between ciprofloxacin-resistant and -susceptible infections. This largest study thus far clearly shows that fluoroquinolone resistant infections do not affect the duration of illness and convincingly rejects the hypothesis that fluoroquinolone resistant *Campylobacter* display an increase in virulence. The above examples (not all the literature is quoted) demonstrate clear evidence that fluoroquinolone-resistant *Campylobacter* infections do not affect human health more so than infections caused by susceptible *Campylobacter*. The recent study of Helms et al. (2005) provides insufficient data to alter this conclusion.	
Page 11, last paragraph, last line:	53. *"….treatments like azithromycin….."* **Proposal**: insert "erythromycin" to keep in line with the conclusions (page 14; third paragraph).	Agreed; text has been revised.
AVC		
	54. **AVC completely disagrees with the statement referring to 'Their potential of relatively rapid selection of resistance'**. Fluoroquinolones have been available in Europe for nearly **20 years. AVC agrees that** it would be surprising if some degree of resistance did not develop over this time. Norfloxacin resistance was described in human isolates back in the late1980s. However, that fluoroquinolone resistance is not more extensive for more bacteria shows how **slowly** resistance has developed, even given the use of fluoroquinolones in	The text has been slightly modified based on this comment. However, resistance to fluoroquinolones was reported quite soon after the introduction of these substances into food animal use. Levels of resistance vary related to uses in practice. We would also like to make a remark that at least in some countries, fluoroquinolones were first marketed as antimicrobials with no development of resistance.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	animals, e.g. Table 4 of the document, for *A. pleuropneumoniae, P. multocida* and *M. haemolytica*. In many countries still, the level of resistance to *E. coli* is also relatively low. The quoted high resistance levels in cattle are surprising, but AVC would need to be satisfied that this data does not include use in veal calves and results from clinical cases rather than slaughter survey data. Similarly, some of the pig *E. coli* data is also surprisingly high (76% Portugal) and does not correlate with Table 3 of the document. If real, then further investigations into these local or specific high levels might give some pointers to a resistance avoidance implementation strategy. This section is key to supporting continued veterinary use of fluoroquinolones. There are diseases where fluoroquinolones are critical for effective control, such as colisepticaemia in chickens where the organism is resistant to tetracyclines, amoxycillin and trimethoprim/sulphas. Neonatal *E. coli* septicaemia in piglets is another example. We have already referred to post-viral colisepticaemia in turkeys, calf neonatal colisepticaemia and *E. coli* mastitis in cows, where fluoroquinolones are first-choice rather than last-resort.	The occurrence of multiresistance highlights the need for avoidance of unnecessary use of antimicrobials.
IFAH-Europe		
Page 12, second paragraph, Bosch and Hartman report:	55. Note that neither antibiotic used, irrespective of susceptibility properties, was successful in treating the diseased calves.	Noted, but the statement is still valid.
	56. See comment under Table 2 about numbers of isolates	See comments on table 2.
Page 12; Table 4:	57. No history data is provided. IFAH-Europe assumes that the isolates investigated are at least in part from animals recently treated with antimicrobials. Hence, the current figures may present an overestimation of the resistance rates. Indeed, in the national German	Agreed, and the text modified.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	resistance monitoring programme pathogens were isolated from untreated animals, reflecting the practice more appropriately (Wallmann et al. 2003). The rates of resistance of major veterinary pathogens in this study were clearly less than previously assumed.	
	58. Point 1: As point 1 is a derivative of number 4, a slight correction of point 1 seems justified. Proposal: Please add the word "potentially": "…resulting in potentially negative effects…"	Agreed, and changes made accordingly.
AVC		
	59. This statement is too general. The statement 'has selected for resistance' is too broad and is misleading, since resistance to fluoroquinolones remains relatively low, especially in slaughter house surveys, which are the most relevant to the transmission of zoonotic infections via meat. It is to be expected that coupling quinolones and fluoroquinolones has a much greater negative impact, and AVC cannot see a valid scientific rationale for doing this.	Not agreed. The statement is supported by the data available. The text is modified to state "potentially negative effects".
IFAH-Europe		
	60. Potential detrimental effects on public health have been over-emphasised	Not agreed. The statement is supported by the data available.
	61. Point 4: First, regarding *Salmonella*, the impact of infections with nalidixic acid-resistant *Salmonella* (*S. typhimurium)* on public health is conflicting, as discussed above. The second sentence of this point relates to *Campylobacter* and it seems that this sentence is only based on the conflicting single study of Helms et al. (2005). Of the two available extensive studies, the Sentinel study didn't detect a difference in hospitalisation between ciprofloxacin-resistant and susceptible infections whereas Nelson et al. (2004) demonstrated a significantly decreased rate of hospitalisation after infection with ciprofloxacin-resistant campylobacter as compared to susceptible infections! Two further limited-in-size studies did not	Proposal not agreed, but changes on the text have been made to clarify the CVMP/SAGAM position.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	explore hospitalisation (Smith et al. 1999; Engberg et al. (2004). Severity/complications were only studied by Nelson et al. and they didn't find any difference between resistant and susceptible infections. None of these four studies explored macrolide resistance for hospitalisation rates and severity. The Helms findings do not justify the stated conclusion because of the many flaws explained on page 7 of this response. **Proposal**: we wish, therefore, suggest the following wording: "There are concerns that infections in humans with nalidixic acid-resistant *Salmonella* and *Campylobacter* may impact public health. As conflicting evidence exists that nalidixic acid-resistant infections result in adverse effects, it is recommended to investigate this subject in further detail."	
AVC		
	62. Para 4 – Is the statement generally accepted that 'Infections in humans with nalidixic acid resistant *Salmonella* Typhimurium has resulted in increased risk of hospitalisation and mortality'? There has been criticism of both studies used in the document to support this conclusion (Helms *et al*, 2002 and 2004).	See comments above.
	63. Para 6 – 'Currently there is no harmonised approach in the conditions of use of fluoroquinolones in food-producing animals or companion animals through the different Member States of the EU'. AVC believes this could be a critical opportunity to standardise use. AVC suggests adding to the sentence 'Antimicrobial resistance should be addressed internationally as resistant bacteria can spread via imported food' the following: 'and infections can be contracted by foreign travel as highlighted in Danmap 2004; in such foreign-acquired situations, resistance to (fluoro)quinolones is frequently higher'.	Although companion animals might be relevant, these were left out of the scope of this document, which addresses the use in food-producing animals. The text has been revised to include also the spread via travel.
IFAH-Europe		
	64. **Point 7:** In the 7th point, IFAH-Europe suggests replacing	See definition of breakpoints which has been introduced in the chapter on

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	"resistance" by "decreased susceptibility" and it is important to replace *"low breakpoints"* by "epidemiological cut-off values". It is also valuable to include ciprofloxacin in each resistance monitoring survey of *Salmonella* to potentially detect high-level resistance. IFAH-Europe proposes the following wording: "When monitoring for decreased susceptibility and resistance to fluoroquinolones in *Salmonella*, both nalidixic acid and ciprofloxacin should be used, respectively. Alternatively epidemiological cut-off values for fluoroquinolones could be used."	mechanism of resistance.
AVC		
	65. Para 7 – 'When monitoring for resistance to fluoroquinolones in Salmonella nalidixic acid should be used as a marker for decreased susceptibility.' AVC strongly disagrees with this conclusion: the concern is with fluoroquinolone resistance, not nalidixic acid. Quinolones are hardly used in human medicine and have been largely superseded by fluoroquinolones, so really there is little relevance. Setting sensible breakpoints based on PK/PD data would be far more realistic and valid.	Not agreed. See above comments.
	66. Para 9 – More information on use by species would also be helpful, especially for the fluoroquinolones. More comparative human use data would also be beneficial.	In agreement with the comment, but no more data are available.
IFAH-Europe		
	67. The wording of the paragraphs 4 and 7 in the conclusions on page 14 should be amended (on the basis of major concerns raised in the text).	Not agreed, please see previous comments.
	68. Differentiation between prophylactic use of fluoroquinolones in individual animals and medication of groups of diseased animals.	The recommendation does not exclude the medication of groups of animals according to the Codex definitions but highlights the need for careful consideration. It should be noted that in-feed or in-water medication can be for treatment. They are not synonyms for "prophylactic use". Prophylactic use is not proposed to be prohibited but

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
		the use needs to be carefully considered. No change proposed.
	69. Comments to point 1: IFAH-Europe agrees that prophylactic use of fluoroquinolones, i.e., to prevent infection in healthy animals, should be carefully considered and preserved for specific circumstances, such as when the exposure to the target pathogen is highly imminent. IFAH-Europe actively supports adherence to this principle. However, IFAH-Europe would like to address the medication of groups of animals with fluoroquinolones separately. Fluoroquinolones are characterised by a high oral bioavailability along with notably high concentrations at the site of infection. Route of administration can, therefore, be either oral or parenteral. Animals are usually treated individually. Where necessary and where individual treatment is impracticable, group medication is a valid therapeutic option owing to the high oral bioavailability. When chickens or turkeys, confined in a poultry house, become ill the infectious agents spread immediately through the flock. Individual treatment of sick birds is rarely possible and indeed even if it was it would favour the exposure of untreated animals to bacteria that had been already exposed to antibiotic. This is likely to result in a cascade of individual treatments and would markedly increase the risk for resistance development. Hence, under such conditions it is inevitable to treat all in-contact birds, i.e. those showing clinical signs as well as those incubating the disease. Fluoroquinolones used for poultry are administered in the drinking water for a short period of time under the close supervision of the prescribing veterinarian. IFAH-Europe is convinced that the prudent use measures (see below) should principally apply equally to individual and group therapy. Proposal: In this respect, footnote 1 of page 22 should be deleted.	Not agreed, see comments above.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
AVC		
	70. Recommendation 1 '… prophylactic therapy (treating early sub-clinically infected in-contacts) should be carefully considered and preserved for specific circumstances and conditions.'	Not agreed.
IFAH-Europe		
	71. IFAH-Europe strongly endorses the proposals to include prudent use wording in the SPCs and to harmonise this in all Member States.	Agreed.
	72. IFAH-Europe offers specific suggestions for cautionary wording which could be included in harmonised SPCs relating to fluorquinolones.	This has been considered and measures taken.
	73. Comments to point 2: IFAH-Europe fully endorses the principles of rational use of fluoroquinolones (and antimicrobials of other classes) to ensure optimal clinical efficacy and concomitantly minimising the selection of resistance. Proposals for sentences for inclusion in the SPCs: • Use of the fluoroquinolone products should, wherever possible, be based on susceptibility testing and take into account official and local antimicrobial policies. • It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials. Inappropriate use of any fluoroquinolone product may increase the prevalence of bacteria resistant to the fluoroquinolone and may decrease the effectiveness of treatment with other quinolones and fluoroquinolones, due to the potential for cross-resistance.	The proposal has been considered and supported by CVMP.
AVC		
	74. AVC does not agree with forced harmonisation of labels (see Suggestions for Action 1. p22), since any over-restriction will lead to	Maybe there is a misunderstanding; harmonising prudent use instructions is not the same than harmonisation of the whole label. The text has been

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	non-compliance and achieve the opposite of the intended effect. AVC suggests that, before making irrevocable decisions in the EU concerning fluoroquinolone use, the EU should commission work that identifies the usage patterns, volumes, origins and nature of active. AVC is ready to assist, as an independent association of veterinary consultants, in such work.	clarified.
	75. Recommendation 2 'This should be an on-going action for the development of new fluoroquinolone-containing products and for products already approved, at renewal.'	In principle could be agreed, but this is not considered for the renewals under current legislation, so it is out of scope.
	76. We would like to add a third recommendation for action: Recommendation 3: Appropriate EU agencies and bodies should collaborate on studies to define more carefully the most appropriate test systems, sampling strategies and breakpoints to use for resistance determination in organisms isolated from livestock and companion animals that may be of public health significance.	The process is currently undertaken by EFSA and the Community Reference Laboratory on Antimicrobial Resistance.

SUMMARY AND RECOMMENDATIONS

GUIDELINE SECTION TITLE		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
The Soil Association		
	77. Soil Association recommends that the prophylactic use of fluoroquinolones in veterinary medicine should be prohibited	The term prophylaxis needs perhaps further defining. In the case that part of animals in a group or flock is showing signs of clinical disease, the rest of the animals have been exposed to the pathogenic organism and may be incubating or carry the infectious agent without showing clinical signs. If antimicrobials are administered to all animals, those who are clinically diseased will receive treatment of the disease (therapeutic treatment)

[3] Where applicable

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
		while the non-diseased animals will receive prophylactic (preventive) treatment. This type of prophylactic treatment could in specified circumstances be allowed. (Fluoro)quinolones should *not* be used when there is no exposure of animals to the pathogen.
	78. Soil Association recommends that the oral use of fluoroquinolones in veterinary medicines should be prohibited	It is recognised that the oral route of administration should only be used for (fluoro)quinolones when no alternatives are available. However, treatment of flocks of birds or other groups on animals is often unpractical using other than oral route.
	79. Soil Association recommends that the use of fluoroquinolones in poultry production should be prohibited	See previous comment
	80. Soil Association recommends that the use of fluoroquinolones in fish farming should be prohibited, where this is not already the case	The text of the reflection paper has been revised. Use in aquaculture is outside of the scope of the paper.
	81. Soil Association recommends that member states should undertake regular surveillance of fluoroquinolone resistance in campylobacter, salmonella and e-coli in all animals species in which fluoroquinolone use remains licensed	This responsibility of Member States regarding surveillance of resistance in zoonotic pathogens and indicator bacteria is covered by requirements in the zoonosis directive and concur with the proposal
	82. Soil Association recommends that withdrawal periods for fluoroquinolones should be doubled as an interim precautionary measure until studies can be undertaken to allow them to be reset for individual species, based on the known rate of bacterial resistance decline, as well as on the rate of depletion of residues	Withdrawal periods for fluoroquinolones, as those of other antimicrobials, have been set according to the current legal requirements of the EU. The rate of depletion of residues is taken into account. To include decline of resistance would require legislative changes, and should preferably be based on international agreements (VICH procedures). Before decline in resistance could be considered as a marker, science and methodology must evolve further.
	83. Soil Association recommends that consideration should be given to the feasibility of requiring that animals that have been treated with fluoroquinolones are tested for the presence of indicator bacterial species before slaughter, for example, campylobacter and salmonella in pigs and e-coli in cattle	It is assumed that at least for the case of indicator bacteria, the proposal refers to resistant bacteria The proposal is interesting, but it is not considered feasible at this point in time. In practice this would also mean huge extra costs for testing and destruction of animals which would be deemed non-acceptable for slaughter.
	84. Soil Association recommends that all advertising of fluoroquinolones to the veterinary profession should make clear that fluoroquinolones should not be used as first choice drugs, unless there is clear evidence that alternative drugs would not be effective	This has been addressed to a large extent by the texts suggested for SPCs as they stress in different ways that use of fluoroquinolones requires special caution.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	85. Soil Association recommends that where fluoroquinolones are prescribed for farm animals, veterinary surgeons should be required by law to record their reasons	This could be a risk management option for Member States to consider.
	86. Data on the use of fluoroquinolones in EU Member States should be based on the quantities used by individual veterinary practices and prescriptions made up by associated dispensaries, in addition to sales data provided by pharmaceutical companies	It is agreed that better data on the use of fluoroquinolones should be made available. This is also reflected in the body of the reflection paper. It is noted that such systems exist in Denmark, and that for other countries not all who present statistics on overall use base their reports on data from the pharmaceutical industry but on other independent sources.
	87. Use of fluoroquinolones by individual practices should be monitored and advice given where this is significantly higher than average	See comment above
	Veterinary colleges and professional veterinary bodies providing training or refresher courses for qualified veterinary surgeons on pharmacology should include sessions on fluoroquinolone resistance and strategies for avoiding the use of fluoroquinolones wherever possible.	This is addressed in the recommendations of the reflection paper
	89. Soil Association recommends that given that farmers are legally permitted to hold fluoroquinolone antibiotics prescribed by veterinary surgeons for use under their guidance, and given also the significant (though unquantified) use of illegally imported fluoroquinolones in some member states, consideration should be given to educating farmers about the need for extreme caution before they are used. Where animal health planning is practised, the acceptable and non-acceptable use of fluoroquinolones should be included and the use on each farm should be reviewed annually	This is addressed in the recommendations of the reflection paper. It is agreed that education of farmers as well as other animal owners and veterinarians is extremely important.
	90. Consideration should be given at an EU level to providing greater encouragement for less intensive systems of livestock production, where the requirement for antibiotic use is generally lower	This is outside the scope of this document.
	91. Companies importing food from non-EU countries should be required to ensure that their suppliers prohibit or restrict the use of	This is an interesting proposal, but unfortunately outside the scope of this document.

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
	fluoroquinolones in exactly the same way as producers in EU member states	
	92. Soil Association recommends that routine surveillance for fluoroquinolone-resistant bacteria in imported livestock products should be introduced and consideration should given to restricting imports from countries where levels of resistance are found to be significantly higher than those in the EU	Routine surveillance of animal products from EU countries is required by the zoonosis monitoring directive and is gradually implemented. Harmonised guidelines for this monitoring of resistance are being developed by EFSA. It is not clear yet if this monitoring is going to be limited to products from the EU or imported products will also be included.
	93. EU Member State governments should be encouraged to notify all those travelling to South-East Asia about the potential dangers of highly drug-resistant infections and advise them on basic precautions they could take to reduce their risk of contracting them	This is outside the scope of this document that deals with food animal production in the EU.