European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON REFLECTION PAPER ON THE USE OF 3RD AND 4TH GENERATION CEPHALOSPORINS IN FOOD-PRODUCING ANIMALS IN THE EUROPEAN UNION: DEVELOPMENT OF TESISTANCE AND IMPACT ON HUMAN AND ANIMAL HEALTH

EMEA/CVMP/SAGAM/81730/2006-CONSULTATION

Interested party (Organisations or individuals) that commented on the draft Guideline as released for consultation

Stakeholder No.	Name of Organisation or individual
1	AFSSA (Agence Française de Sécurité Sanitaire des Aliments)
2	AVC (Association of Veterinary Consultants)
3	ECDC (European Centre for Disease Prevention and Control)
4	EFSA (European Food Safety Authority)
5	IFAH-Europe (International Federation for Animal Health Europe)
6	The Soil Association
7	Swissmedic (Swiss Agency for Therapeutic Products)

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GENERAL COMMENTS
1- AFSSA 1 – General comments on "recommendations for action": The recommendation of prudent use is very close to those proposed in 2006 for fluoroquinolones[1]. However, there is some feedback that that these measures are not sufficient as there is an increase of exposure, related to increased availability on the market, and consequently a risk for an increase in the rate of resistance. It is likely that more marketing authorisations will exist in the future as the marketing exclusivity will soon expire for most of the innovative products. Both National Competent Authorities and professionals bear heavy responsibilities with regards to this matter. Therefore the position of the AFSSA-ANMV is the following: • First line treatment should be banned through SPC and specific regulatory requirement unless there are specific scientific grounds such as antimicrobial susceptibility testing justifications (in this case, the vet prescription should keep ad hoc recording) This is of utmost importance for any use (under SPC recommendations and off label use). If that was not possible, ban of off label use of 3rd and 4th generation of cephalosporins will have to be considered. • Marketing authorisations should be delivered under certain conditions (see below). • Prescriptions in respect to the indications and national epidemiology of the target disease should be monitored.

[1] See http://www.emea.europa.eu/pdfs/vet/srwp/49682406en.pdf

GENERAL COMMENTS
1- AFSSA (cont.) 2 – On an assessment view: The recommendations for action raised the fact that the 3rd and 4th generation of cephalosporins should be saved for the treatment of clinical inffections, which have not responded or responded poorly to other class of antimicrobials. Thus, they should be limited to second intention treatment. However, the CVMP and SAGAM pointed out the fact that 3rd and 4th generation of cephalosporins are used for systemic therapy of food producing animals, where "equal of better alternatives are available". Currently, when comparative clinical trials are provided, no statistical superiority is requested for the cephalosporins, when compared to other antimicrobials. There are no regulatory grounds for such a requirement either. This should be re-considered in a way that no equivalency can be accepted. Thus, the 3rd and 4th generation of cephalosporins should only be authorised for usual claims if statistical superiority has been shown, when compared to first intention treatment (such as respiratory infections), or when efficacy is demonstrated, when failure has occurred with first line treatment. This would be in line with having the product use only if failure occurred with the first intention treatment. **CVMP comment**: We appreciate your comments and note your proposals for further risk management activities which will be further discussed. Regarding prohibition of first line treatments we would like to point out that specific regulatory requirements other than those that could be presented in SPC texts are outside the CVMP remit. Regarding restrictions of off label use this is a complicated issues as there might be a need for (prudent) off label use in case of minor species and indications where approved alternatives might not be available on all EU markets. This idea to require superiority design for studies is interesting. However, in case of bacteria resistant to first line treatment we cannot require a control group treated with first line antimicrobials for ethical reasons.

GENERAL COMMENTS

2- AVC

The AVC sees this consultation document as an important contribution to the continuing debate about the potential for microbial resistance development to antimicrobials as a result of veterinary use *per se* and the possible effect on human health. In particular, there is an increasing concern about the impact that this might have on the availability of medicines for animals and the continuing effectiveness of antimicrobial therapy.

The more recent emergence of increasing resistance of human pathogens to 3rd and 4th generation cephalosporins highlights the need to examine more closely the use of these compounds in veterinary medicine and follow any possible trends in animal pathogen resistance. This will enable the development of strategies which will ensure their continuing availability to veterinarians and to maintain animal health and welfare standards; also that any possible transfer of either resistance to human pathogens, or resistant organisms pathogenic to humans, is minimised.

AVC is in full agreement with the objective of the reflection paper.

CVMP comment:
The CVMP agrees with the views expressed.

AVC is in general agreement with the reflection paper and the conclusions, especially those aimed at gathering more information.

AVC believes resistance data presented in the paper indicate the immediate need to monitor resistance in poultry. Also AVC considers that the "off label" and prophylactic use of 3rd and 4th generation cephalosporins should be actively discouraged as a precautionary measure.
The reflection paper is comprehensive and rightly refers to the resistance situation in humans. This is a current topic of concern, but the implications in human medicine are not totally clear in some instances. AVC feels that it would be unfortunate if this concern was unjustifiably transferred to the veterinary use of these compounds to the detriment of animal welfare and the EU livestock industry.

AVC thinks that it is important that the reflection paper is more balanced especially in regard to the very low uptake of these compounds for veterinary use in the EU compared to human use in order to avoid this possibility.
In limiting resistance development within both the animal and human populations, approaches contributory to this aim, in addition to the responsible and prudent use of antimicrobials, should be considered such as farm biosecurity and food hygiene.

CVMP comment:
The risk manager, CVMP, has recommended among other things to discourage off-label use and to implement biosecurity (pages 35 and 37 of the draft for consultation)

GENERAL COMMENTS

5-IFAH-Europe:

IFAH-Europe appreciates the opportunity to review and to comment on the valuable Reflection Paper EMEA/CVMP/SAGAM/81730/2006-CONS. We would like to commend SAGAM and CVMP on this extensive and well-balanced report about a highly complicated subject. However, IFAH-Europe has some major comments, which we believe will need consideration. In brief, our concerns are as follows:

- There are a number of incorrect statements throughout the Report and some additional explanations or references would be useful. The terms "frequent" and "often" are regularly found in the document without quantitative precision. Quantitative information, with appropriate citations would be useful for further interpretation of the statements. Indeed in the case of co- and cross-resistance, some different patterns and percentages are encountered depending on whether bacterial species were isolated from hospital, community or even animal species.
- In the paragraph dedicated to use of cephalosporins in the EU, where data is available the amount of cephalosporins could be put in perspective in relation to the European use of beta-lactams. Such data indicate that these compounds are not used as "mass" medication. As examples:
    - In Denmark, where beta-lactams (except cephalosporins) consumption is 32,560 kg, Cephalosporins (pigs+cattle+miscellaneous) with 167 kg only represents 0.5% of the whole beta-lactams consumption (DANMAP 2005).
    - In France (Suivi des ventes de medicaments vétérinaires contenant des antibiotiques en France en 2006) for the parenteral route of administration which is considered in the document, cephalosporins account for 3% of the whole beta-lactams consumption (60.2 vs 1.8 tonnes).

CVMP/SAGAM comment:
CVMP/SAGAM agrees that more exact information on use of antimicrobials in the EU is needed (both more countries and per animal species). However, comparing different antimicrobial groups as suggested would not increase clarity or put in perspective. The potency, dosage, indications and main target species of different beta-lactam antimicrobials differ and total sums of beta-lactams can therefore be misleading. More interesting for the aim of this paper could be information on trends in use, and CVMP/SAGAM notes that in e.g. UK and Denmark the sales of 3rd and 4th generation cephalosporins have increased markedly over the last five years. This information has, however, at this stage of the document not been added.

- Usage of different interpretive criteria in Tables 3 and 4, which makes data incomparable and highly prone to misunderstanding. The Report does not take into account the EUCAST or CLSI clinical breakpoints (e.g. page 23).

CVMP/SAGAM comment:

See response to specific comments

- The limitations of the indications for cephalosporins in animal health do not take the registration process of the drugs into consideration. Indeed registration dossiers have to document safety issues, notably resistance development as recommended in VICH GL27 and EMEA/CVMP/SAGAM/428938/2007. Moreover clinical trials include reference products and statistical analysis for the validation of the relevance of the drug in requested indications.

CVMP/SAGAM comment:
The existing guidance mentioned by IFAH-Europe indeed takes into account AMR however, the SAGAM notes that most products containing cephalosporins, were authorised before or long before the time when VICH GL27 (or previous CVMP guidance) entered into force in EU.

GENERAL COMMENTS
• The recommendation on the use of oral cephalosporins is inappropriate for 3rd and 4th generation cephalosporins and should be omitted. **CVMP/CVMP comment**: Not agreed, see comments later on.
6-The Soil Association 1. The Soil Association very much welcomes the CVMP's Reflection Paper on the Use of 3rd- and 4th-generation cephalosporins in food-producing animals in the European Union. We strongly agree with the CVMP's statement that cephalosporins should not be considered in isolation and that a 'global approach to the problem of antibiotic resistance is needed' (p35, lines 1284-6). We believe that the conditions in which farmed animals are kept greatly contribute to disease problems, which in most situations are currently controlled more by the use of antibiotics and other antimicrobials than by management means. We believe this situation needs to be reversed, but recognize that action will be required at a number of levels, and that this will only become possible once there is a wider understanding of the problems which make this necessary. Below we provide background information about the Soil Association and its interest in this issue, and some additional information on the use of cephalosporins and the development of resistance. We also provide further data on the UK situation, using not just peer-reviewed and published papers, but also information published on UK government websites, which we feel is sufficiently authoritative to be cited. In our view, however, the Reflection Paper has two fundamental weaknesses. We makes some comments and suggestions in relation to these at appropriate points in the text, but since both aspects are largely avoided in the paper, we feel constrained from exploring them as fully within the text as we feel they merit. We therefore outline our concerns here in the next two sections of our 'general comments'. If the CVMP accepts either or both of these points as areas which require further consideration, then it might like to consider producing additional text and putting this out during a brief further consultation period. **CVMP/SAGAM comment**: See comments below

GENERAL COMMENTS

6-The Soil Association (cont)

2.The intramammary use of 3rd- and 4th-generation cephalosporins on the development of antibiotic resistant bacteria

The Reflection Paper dismisses the potential for intramammary use to contribute to resistance problems (p7, lines 141-3). Although the CVMP does not justify its stance on this issue, in the US some commentators have argued that, since milk is pasteurised, the development of resistant strains in milk would pose no threat to human health. However, for reasons outlined below, we believe that the CVMP is underestimating resistance problems associated with intramammary use of cefquinome and cefoparazone, and that the same level of prudence should be applied when selecting intramammary preparations containing 3rd- and 4th-generation cephalosporin antibiotics as with their systemic use. If, after further consideration, the CVMP still holds to its original opinion, we feel that evidence should be provided to support its position and that this should be included in the CVMP's paper.

We base our view on the fact that on many dairy farms calves are fed milk taken from cows being treated with intramammary antibiotics (Langford et al. 2003), both during the treatment periods, when residues in milk will be significant, and during the withdrawal period, during which time they will progressively decline. Given the extent to which 3rd- and 4th-generation cephalosporins are used in some countries within the EU for the treatment of mastitis, and the fact that on some farms there are over 70 cases of clinical mastitis cases per 100 cows per year (Bradley et al. 2007), it is inevitable that on many farms calves will be reared for protracted periods on milk containing low-level residues of 3rd- and 4th-generation cephalosporin antibiotics. On some farms, particularly smaller mixed farms, such milk will also occasionally be fed to other animals, such as pigs and orphan lambs.

Langford et al (2003) found that calves receiving milk from treated cows developed higher levels of antibiotic-resistant bacteria in the lower gut than controls, that the level of resistance is related to the levels of residues in the milk and the duration of exposure to them, and that resistant strains persisted after consumption of milk containing residues ceased. These findings may explain why the highest incidence of ESBL *E. coli* strains in UK cattle has been found in calves on dairy farms. In the UK, many of the seriously ill scouring calves which have been found with ESBL *E. coli* gut colonisation were under two weeks old (HPA 2008), which also suggests that in some cases the colostrum fed to these calves may have contained antibiotic residues from the prophylactic use of long-acting cephalosporins in dry cows. Furthermore, a number of studies have found that the oral administration of therapeutic doses of antibiotics encourages the development of scouring in calves, due to their disruptive effect on the gut micro-flora. This could be of particular significance in relation to cefquinome which is often prescribed for simultaneous systemic and intramammary use, both of which uses can independently leave residues in milk. Although there is a lack of research on the possible effect of low-level oral antibiotics consumed by calves on the development of diarrheoa, it is possible that residues of 3rd- and/or 4th-generation cephalosporin antibiotics in milk may also have contributed to these scouring problems in calves, which itself will encourage the more rapid spread of *E. coli* with ESBL resistance.

More speculatively, we would suggest that on farms where calves with profuse diarrhoea are excreting *E. coli* strains carrying ESBL resistance, that environmental spread may eventually transfer the strains to the orifices on cows' teats. If so, even where the same strains of *E. coli* in the calves do not cause mastitis in cows, the genes carrying ESBL resistance could transfer to strains of *E. coli* or salmonella that do cause mastitis. In such a situation the widespread use of such 3rd- and 4th-generation cephalosporin antibiotics would select for such strains and this could eventually lead to both treatment failures in the cows and the potential transfer of ESBL resistance via milk, especially to farmers and their families who often drink unpasteurised milk.

CVMP/SAGAM comment:

CVMP/SAGAM thanks the Soil association for highlighting a practice that might have an influence on the situation regarding the dynamics of antimicrobial resistance on farms. This matter is broader than just cephalosporins, and more information is needed on, e.g. how common this is in different EU Member States. See further responses to specific comments and Sampimon et al (2008).

GENERAL COMMENTS

6-The Soil Association (cont)

3. Countering entrenched attitudes relating to 3rd- and 4th-generation cephalosporins and the development of resistance

At the end of the reflection paper the CVMP notes that 'Veterinarians should be continuously educated on strategies to minimize antimicrobial resistance' (p36). We agree with this statement, but we feel that it does not go far enough and that if the CVMP is not more specific about what is needed, then adequate action will not be taken, at least in some EU Member States. The CVMP might like to consider the effect that publicity material from manufacturers has had on minimising expectations that resistance to modern cephalosporins would develop. It would be particularly helpful if the CVMP were to point out how the latest science calls into question some of the early industry statements. Another problem in the UK, and perhaps elsewhere, is a reluctance amongst government scientists and regulators to openly acknowledge the possibility that food animals may be a significant source of resistance in bacterial infections affecting humans.

Our experience is limited, but we are aware of recent situations where veterinary surgeons entirely unaware of the issue of ESBL resistance have advised farmers on the basis of early publicity material from manufacturers, that resistance to these drugs will not develop, or is very unlikely to develop. While the statements made by manufacturers (whose job it is to sell the drugs) have changed over time, they still manage to instill confidence that resistance due to the use of modern cephalosporins in food-producing animals will not create resistance problems in human medicine. As such, while we recognise that most vets are aware that the systemic use of modern cephalosporins should be reserved for specific indications, we believe that many of them have no hesitation in prescribing them in preference to older drugs in such situations, because they believe they are the best drugs and will therefore be most effective. It may also be relevant that because enteric strains of *E. coli* are not pathogenic in farm animals, most vets will not have encountered treatment failures with modern cephalosporins, and some may not take the issue very seriously unless updated information is specifically put to them. Education also needs to be extended to farmers, since significant quantities of antibiotics are often prescribed at one time by vets to farmers with large numbers of animals and many farmers and their stockmen are allowed considerable autonomy by their vets in selecting antimicrobials from legally held stocks for use between veterinary visits. We recognise the practical value of such arrangements but feel they are only acceptable if farmers are educated about some of the key issues, not by advertisements in the farming press (as still occurs in the UK), but in a non-commercial and balanced way.

CVMP comment:

The CVMP, as indicated on the reflection paper and quoted by the Soil Association, supports the training of veterinarians and those related to the use of antimicrobials for food producing species and hopes that the Reflection Paper will raise awareness of the implications of the use of 3rd and 4th generation cephalosporins. A recommendation has been included in the paper indicating that advertisement of cephalosporins should not be directed to animal owners.

GENERAL COMMENTS

6-The Soil Association (cont)

4. The Soil Association and the use of antibiotics

The Soil Association is a registered charity based in the United Kingdom. The organisation is principally known for the development of organic-food production standards and for the certification of organic production. We would like to see all food produced and marketed in ways which do not adversely affect the biosphere, the environment, human health or animal health and welfare. We see the development and increasing uptake of organic-farming systems as important for discerning consumers and an important driver in a necessary process of change.

This standard relates to both systemic and intramammary use of these antibiotics. The standard is essentially the same as one already in place for the use of fluoroquinolones. On organic farms certified by the Soil Association the use of both fluoroquinolones and 3rd- and 4th-generation cephalosporins will now usually be considered and discussed during the development and updating of an annual health plan. The plan will indicate that the use of these antibiotics will be limited to the treatment of individual animals, and only where other antibiotics are unlikely to be effective. However, where no dispensation to use 3rd- and 4th-generation cephalosporins has yet been agreed in an annual health plan, in cases where the antibiotics are needed to save life or avoid unnecessary suffering, producers are aware that they may seek permission for their use retrospectively. All such use will be reviewed during the annual inspection and by a certification committee, which scrutinises annual inspection reports anonymously. Our hope is that, in this way, organic producers will be forced to discuss their antibiotic-use policy with both Soil Association inspectors during their annual inspection, and with their veterinary surgeon, which should ensure that they understand why the use of these important drugs should be kept to a minimum, and the type of situation in which their use may be justified in order to avoid animal welfare problems.

We will be publishing guidance in due course, and have found the CVMP's summary of the use of cephalosporins for animals in the EU very informative. However, we feel it would be of further help if the final CVMP paper were to give some indication of the relative priority which should be given to modern cephalosporins in comparison with fluoroquinolones, when considering which drugs should normally be prescribed as a first-line choice for the treatment of serious invasive infections, where either class is likely to be equally effective.

CVMP/SAGAM comment:

CVMP/SAGAM is of the opinion that a general priority cannot be made. We do not have any opinion of the relative priority between fluoroquinolones and cephalosporins but regard both these groups of compounds as second line antimicrobials. For serious life-threatening infections, the choice of antimicrobial must be on a case by case basis and the clinician is guided in his or her choice by clinical examination and prior knowledge of the situation on the farm including results from susceptibility tests in other situations

GENERAL COMMENTS

6-The Soil Association (cont)

5. Emergence of ESBL *E. coli* in humans and farm animals and evidence of gene exchange in the UK

Surveillance carried out by the British Society for Antimicrobial Chemotherapy shows that the first recorded incidence of blood-poisoning in humans caused by ESBL-producing *E. coli* occurred as recently as 2002. However, by 2006, 12% of all *E. coli* blood-poisoning infections were ESBL (Reynolds et al. 2005, Reynolds et al. 2006, Reynolds et al. 2007).

According to an estimate by the UK's Health Protection Agency, there are now approximately 30,000 cases of ESBL infections per year (this estimate includes both urinary-tract and blood-poisoning infections) (HPA 2007). It has been reported that approximately 10-14% of those infected die within 30 days, suggesting around 3,000-4,200 deaths per year (Templeton 2007). Other reports suggest the death rate may be even higher: in 2006, the Government's Chief Medical Officer reported that community-acquired urinary tract infections caused by ESBL *E. coli* have approximately a 30% fatality rate (Donaldson 2006). Furthermore, according to a British study, patients with ESBL *E. coli* blood poisoning are significantly more likely to die (61%) than those with blood poisoning caused by non-ESBL *E. coli* (27%) (Melzer and Petersen 2007).

As mentioned in the CVMP's Reflection Paper (p20), the first cases of a CTX-M ESBL *E. coli* from farm animals in the UK were isolates from diarrhoeic calves from a farm in Wales (Teale et al. 2005). The bacteria produced the CTX-M-14 enzyme. However, there have since been many more cases reported by the UK's Veterinary Laboratories Agency (VLA): by mid-2007, 32 different cattle farms had been found to be positive for ESBL *E. coli*, and there have been regular further isolations since then (VLA 2007). Most of the isolates were from calves under two weeks of age (HPA 2008). Of these, 15 were positive for the CTX-M-15 enzyme and 8 for the CTX-M-14 enzyme (VLA 2007). CTX-M-15 is the most common enzyme in human ESBL *E. coli* in the UK (HPA 2008), and CTX-M-14 is one of the next most common (Xu et al. 2007). According to a recent Health Protection Agency report, other types which have been found in cattle include CTX-M-1, CTX-M-3, CTX-M-20 and CTX-M-32 (HPA 2008).

The *E. coli* strains found in cattle and humans are generally different, however analysis of the plasmids carrying the resistance genes suggests that these have been transferring between human and bovine *E. coli*. A CTX-M-15 plasmid from a bovine isolate was analysed by the VLA using an antimicrobial-resistance-gene microarray and other tests, and was compared with a CTX-M-15 plasmid from a human isolate. Both plasmids were found to be indistinguishable by the tests, and contained various resistance genes, including *aac6'-Ib*, which confers resistance to aminoglycosides and low-level resistance to fluoroquinolones. Because it was considered that it was very unlikely that these plasmids had evolved separately in cattle and humans, VLA scientists concluded that the plasmid had probably originally evolved in human *E. coli* and been transferred to bovine *E. coli* (Teale 2007).

However, if human *E. coli* can transfer ESBL resistance plasmids to bovine *E. coli*, this strongly suggests that transfer may also be occurring in the opposite direction, a point which has not been refuted by the VLA. The spread of these resistance plasmids among bovine *E. coli* may therefore pose a serious threat to human health.

CVMP/SAGAM comment:

CVMP/SAGAM thanks the Soil association for adding very interesting information and notes that indeed, since the first report cephalosporin resistance appears to have increased rapidly among *E. coli* from cattle in the UK, as the figure on cefotaxime /ceftiofur resistance reported for cattle and UK in the EU zoonosis monitoring report for year 2006 was 7.5% (number of isolates = 2260).

GENERAL COMMENTS
Soil Association (cont) Despite the emergence of ESBL *E. coli* in British farm animals, little action is being taken: farms affected have been allowed to sell their animals to other farms, spreading the resistance genes more widely, and the consumption of cephalosporins and some other key antibiotics is on the increase. EU Directive (2004/28/EC) requires the advertising of prescription-only antibiotics directly to farmers to be banned. A proposal to implement such a ban was put out to consultation in the UK, but under pressure from the pharmaceutical industry, the Government backed down. The Directive had required a ban on advertising to members of the 'general public', and the Government claimed that the lack of a precise definition of this term in the Directive meant that farmers, as professional keepers of livestock, could be excluded from the ban. As a result, ceftiofur and cefquinome are widely and regularly advertised to pig and cattle producers in the general and specialist farming press in the UK. **CVMP comment** A recommendation has been included in the paper indicating that advertisement of cephalosporins should not be directed to animal owners.
7- Swissmedic The document does not consider some important points, such as the use of cephalosporins (e.g. cefquinome) in intrammamary injectors for mastitis and dry cow therapy, the importance of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community (community acquired MRSA (CA-MRSA)) and nosocomial infections (hospital acquired MRSA (HA-MRSA)) and their impact on human health, the direct transfer of MRSA from animals to humans, the higher prevalence of MRSA in persons working with animals, and the cephalosporin-resistant bacteria in pet animals. **CVMP/SAGAM comment**: Intramammary use is not discussed in detail as we believe the risks related to such use are limited compared to the risks related to systemically acting products. MRSA is dealt with in separate documents CVMP/SAGAM, EFSA and ECDC, as noted in responses to comments below.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[2]. + paragraph no.	**Comment and Rationale**	**Outcome**
L10 Introduction AVC	AVC notes the reference to Livermore *et al* 2007. While AVC applauds the extensive literature search which the CVMP have obviously undertaken in preparing this document, care should be taken to reflect author's opinions in precise terms. The reflection paper draws the conclusion that Livermore *et al "*suggest that animals may act as possible important reservoirs for transferable beta-lactamases". AVC makes this observation only to highlight the need to avoid speculation that veterinary use leads to resistance problems in humans without cogent evidence, as has happened in the past. Suggestion Please correct: Livermore *et al* state that there is *"no proven link between this carriage and human infections"* and mentions that the CTX-M enzyme species encountered in humans is different to those found in animal *E.coli.*	It is noted that *Livermoore et al*. is written on behalf of a European working group within COBRA, an EU funded network, a group that is composed of top experts from many European countries. CVMP/SAGAM therefore takes the view that the hypothesis presented in the quoted paper (also in many other papers) explains to the reader the need to examine the facts in this particular area more thoroughly that was aimed for and in the quoted paper from 2006 (published 2007). In other words, the objective of the exercise (to which AVC agrees) is precisely to examine the evidence, if any. The view that food or environment may be a vehicle for spread of ESBL is further supported in comments in the consultation re. the present opinion by the ECDC. This view is further supported in a recent opinion by EFSA (EFSA 2008) The questioned sentence has been modified here and later in the paper, to indicate that this is one of several hypotheses, and reference to a recent review by Carattoli has been added.
L27 EFSA	Are the *E. coli* referred to all pathogenic (in which case it would be useful to indicate which type,) or are they indicators ?	The sentence in question discusses pathogens and the development of resistance in human medicine where investigations on indicators are rare.
L34-35 EFSA	Suggest modification of sentence to: *animals have the potential to act as possible reservoirs* …… Reason: so far reports are much less common from animal sourced than from human sources. Also diversity of beta-lactamase enzymes reported from animal sources is much lower than from human sources. Nevertheless, animals have the potential to act a great amplifiers if/when an ESBL is introduced.	The sentence has been modified also following comments from IFAH and AVC.

[2] Where available

Line no[2]. + paragraph no.	Comment and Rationale	Outcome
L37 (and 825) IFAH-Europe	The designation "mass medication" is not well defined and prone to misunderstandings. IFAH-Europe prefers using the term "group medication" or "group therapy". We suggest replacing "mass" with "group".	Mass medication has been defined in the text as medication of large groups of animals.
L41-42 EFSA	Would it be instructive to mention the influence of use of 3rd/4th generation cephalosporins in third countries on human exposure through food and introduction into the food chain within the EU of such resistance?	No changes are possible in the objective at this stage. Further, a more thorough examination of human exposure through food (including vegetables) would be more in the competence and the remit of EFSA. However, information from third countries, e.g. US and Canada, has been used throughout the document.
L42 Swissmedic	Objective. The use of cephalosporins in pet animals should also be considered. Pet animals (cats, dogs, horses) represent a reservoir of methicillin-resistant staphylococci. They are present in the skin, nose and ears of such animals. Pets live in close vicinity with humans where direct transfer of bacteria may occur easily. Pet animals have been shown to carry methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus pseudintermedius* (MRSP). These bacteria are important pathogens in human and animal hospitals causing nososcomial infections.	It is agreed that companion animals should also be considered, but that was outside the scope of the present document. CVMP/SAGAM have reviewed MRSA (see below) and will review MRSP, and in those efforts companion animals are also included.

L80 Use of cephalosporins in human medicine AVC	It is generally accepted that the major problem of antimicrobial resistance in humans results from use in humans and not animals. AVC believes that comparative consumption figures for cephalosporins to highlight the marked disparity between human and veterinary use should be introduced. Although such data are sparse, some useful comparative information is published in the VMD report "Overview of Antimicrobial Usage and Bacterial Resistance in Selected Human and Animal Pathogens in the UK: 2004" However, the report does highlight the need to collect more detailed information as there is no differentiation between use in food-producing and companion animals. In this instance it is believed that a significant proportion of the cephalosporins, as 1st generation, were administered to dogs, as also highlighted in Table 1 of the report. Suggestion Please also include: In 2004 in the UK, the total use of all cephalosporins in humans was nearly 40 tonnes, expressed as active substance, whereas veterinary use amounted to only 3 tonnes (7%)! AVC believes that such data would give the paper more perspective. Reference: Overview of Antimicrobial Usage and Bacterial Resistance in Selected Human and Animal Pathogens in The UK 2004 Report Veterinary Medicines Directorate UK	CVMP/SAGAM takes the view that a comparison of one country and year only could be misleading and not clarifying. In addition, CVMP/SAGAM notes that the sales of 3rd and 4th generation cephalosporins for animals appear to have doubled in the UK between year 2001 and 2006 (see comments from Soil association). No change.
Line 89 ECDC	It is important to remind the reader that this only applies to hospitals. The situation is different for outpatients, where use of 3rd- and 4th-generation cephalosporins "… increase in the hospital use of…"	Agreed. Changed.
L90 ECDC	It is important to make it clear that this applies to the 15 countries included in the article since data from other countries were not available to the ESAC dedicated network. "…noted for all 15 countries".	Agreed. Changed
L120-121 Swissmedic	Cephalosporins for food-producing animals. The use of cefquinome (4 GC) in intramammary preparation for preventive (!!) dry cow therapy is not mentioned and should be.	The availability of cefquinome for intramammary use is reflected in Figure 2. See also comments by Soil association. No change needed.

L140-144 EFSA	Provide published evidence that the use of cephalosporins in the prevention/treatment of mastitis by intramammary use is not likely to have a major impact (including human exposure through raw milk and products thereof). This issue has not been addressed in the document but concrete evidence on why this is the case is missing.	The lower likelihood follows standard exposure thinking, reflected in e.g. the principles in VICH GL27. The normal microbiota will be considerably less exposed when treatment is intramammary, compared to systemic use. However, the Soil association has pointed out that milk could be fed to calves during the withdrawal time, and that this might lead to exposure of the intestinal microbiota of the calf. See comments from Soil association and associated changes.
L152 IFAH-Europe	Some clarification is needed Add "However, since the MRL for ceftiofur in poultry was not submitted for renewal by the sponsor, the claim no longer applies in the EU.".	The fact that there is currently no MRL for poultry is mentioned paragraphs earlier, but to clarify this, has been repeated.
L154-160 Swissmedic	Cephalosporins for food-producing animals. Here again the authorization of cefquinome for use in intramammary preparations should be mentioned.	See above. CVMP/SAGAM has chosen to focus on the use that potentially has the major impact, i.e. systemic use and has not, in this document, assessed intramammary use. No change.
L158 IFAH-Europe	Registered indications for cefquinome are missing. Add: (MMA) syndrome in sows, meningitis and arthritis in piglets are also included.	The text mentioned indications "such as" and was not intended to be exhaustive, in particular not for products that are not centrally authorised. However, the suggested addition has been made. MMA has been changed to more modern terminology, i.e. post partum dysgalactia.

L162 Use of cephalosporins for animals in the EU AVC	This section emphasises the paucity of detailed quantitative data available for antibiotic usage in animals. AVC believes that this deficiency should be addressed, as it would allow better conclusions to be drawn concerning resistance development. This would allow strategies to be developed to minimise resistance development, which are not reliant on a macro approach, as evidenced by the use of the "precautionary principle". <u>Suggestion</u> It is essential to collect detailed data on the use of cephalosporins and other penicillins in humans and animals. The very marked difference in cephalosporin sales between some Nordic Member States and France underlines the need for such data to allow a meaningful analysis. It appears from Table 1 that only 15% was used in food producing animals and 16% as topicals in comparison with 69% in pet animals.	CVMP/SAGAM agrees with AVCs opinion on the need to collect data, and this is also expressed in the reflection paper. No change.
L177 and Table 1 EFSA	Information is also available from the Veterinary Medicines Directorate in the UK, and could be included here.	CVMP/SAGAM is aware of the UK statistics, and also of statistics from other countries such as the Netherlands and Germany. However, from the reports from those countries use for that food producing animals, pets and intramammaries cannot be differentiated. The table contains information from some countries where it has been possible to do this break-down, either based on the national report, or on members of SAGAM having access to raw data, making it possible to reinterpret published figures.
L179 IFAH-Europe	Table 1 suggests that based on the figures provided in line 178, the amount of cephalosporins used in pigs in Denmark represent 51% of the total use in food-producing animals. Please check. Please also check and clarify for Sweden intramammary use of 0.1 % in Table 1 because Fig. 2 on page 6 indicates that no cephalosporin products are approved in Sweden for intramammary use. "For ~~both~~ <u>these</u> countries, this represents <u>51 and</u> 89 % of the total use in food-producing animals, <u>respectively</u>."	Correction made. The figures for Sweden are correct. Although there are no products with general marketing authorization, some minor sales of products authorized in other EU countries, and with "special license prescription" (pharmacy-veterinarian specific) in Sweden are recorded.
L186 Swissmedic	**Cephalosporins for food-producing animals**. "Intrammamary" should also be included besides "parenterally".	See above.

L189 IFAH-Europe	This statement is speculative. "Attractive choices" are no basis for determining the extent of use and situations for use. We suggest replacing "attractive" with "*rational*".	Partially agreed. Attractive has been deleted. Rational is not endorsed.
L240 Swissmedic	**Resistance mechanisms and genetics**. It should be included that "MRSA are often resistant to other classes of drugs like fluoroquinolones, aminoglycosides, macrolides, lincosamides and streptogramins B" (see also comment L616).	As noted in lines 519-523, CVMP/SAGAM has chosen to focus this document on Gram-negatives. The reason for this is that CVMP/SAGAM together with EFSA and ECDC, has reviewed MRSA in animals[3] No change.
Table 2 IFAH-Europe	Correction suggested. In the column ***Substrate specificity/Activity pattern***, *"~~extended spectrum group~~"* should be replaced with: "*oxyamino-cephalosporins."* .In the substrate specificity activity pattern for AmpC please write: "*substrate of cephamycins (e.g. cefotetan, cefoxitin) and oxyamino-cephalosporins with the exception of 4th generation cephalosporins (cefepime, cefpirome, cefquinome)."*	The expression "Extended spectrum" is the one used by Jacoby and Munoz-Price (2005). For the reader who is not familiar with all the details of different classes of molecules, this expression is more explanatory. No change A change has been made for AmpC to indicate that 4th generation cephalosporins are normally weak substrates for that group of enzymes.
L309 IFAH-Europe	Note that qnr genes have been demonstrated in *E. coli* and *Salmonella* in several recent studies, but the prevalence of qnr genes in these species is very low in Europe (Cattoir et al., JAC, 2007; Friederichs et al., ECCMID, 2008). In contrast, in some other (pathogenic) species (e.g., *Enterobacter, Citrobacter*) the prevalence can be higher. It has also been shown that qnr determinants do not cause high level (clinical) resistance to fluoroquinolones (Gay et al., 2006; Veldman et al., 2008). Proposal: please mention the low prevalence of plasmid-mediated resistance in *E. coli* and *Salmonella* of animal origin.	The paragraph in question does not deal with prevalence of either CTX-M or fluoroquinolone resistance, but points to a described association "have been shown to carry". The heading of the entire section is "resistance mechanisms and genetics.." and not occurrence and emergence. No change in this section

[3] Reflection paper on MRSA in food producing and companion animals in the European Union: Epidemiology and control options for human and animal health (http://www.emea.europa.eu/pdfs/vet/sagam/6829009en.pdf)

L310-311 IFAH-Europe	These observations emerged from clever experiments with transmissible plasmids responsible for disseminating resistance to ciprofloxacin in Gram-negative bacteria. The observations are intriguing for microbiologists working in basic research, because this previously identified enzyme responsible for resistance to aminoglycosides, a class of antibiotics chemically different from fluoroquinolones. But in respect to risk assessment and clinical impact of infections with cephalosporin-resistant bacteria on human and animal health these observations have no clinical relevance. This should be explained in the text. To the knowledge of IFAH-Europe, the prevalence of AAC (6´)-lb-cr genes in *Salmonella* isolates is extremely rare; this mechanism has only been demonstrated in a few human non-typhi *Salmonella.* Please amend to read: "*…The latter of these genes encodes the enzyme AAC(6´)-lb-cr, a variant of an aminoglycoside acetyltransferase that also modifies some fluoroquinolones such as ciprofloxacin via N-acetylation at the amino nitrogen on its piperazinyl substituent (Robicsek at al., 2006b).* *The only rarely reported mutations that enable this recently evolved enzyme to inhibit the effects of ciprofloxacin are primarily of academic interest and without relevant clinical implications. In addition the enzyme does not inactivate all fluoroquinolones, as newer antibiotics of this class have substitutions at the inactivation site that prevents resistance. None of the (fluoro) quinolones authorized in the EU for food-producing animals (oxolinic acid, flumequine, danofloxacin, difloxacin, enrofloxacin, marbofloxacin, sarafloxacin) are inactivated by this enzyme*."	Agreed that the ".N-acetylation…" addition increases precision, that change has been made. CVMP/SAGAM disputes that AAC(6')-Ib-cr is "extremely rare". For example, in a recent publication from the UK the prevalence of that gene among quinolone-resistant non-ESBL producing *E. coli* from urinary tract infections and bacteriemia was 3 and 9%, respectively (Jones et al, JAC September 2008, doi:.10.1093/jac/dkn406). Further, the enzyme in question appears to be quite common among ceftiofur resistant *E. coli* from animals in China (Zeng et al, 2008 Oct 20 AAC doi:10.1128/AAC.00886-08). However, the questioned sentence makes no statements on the occurrence, be it rare or common, of the enzyme in question. It simply quotes what has been documented in CTX-M carrying bacteria isolated from humans to illustrate the occurrence of co-resistance. The example of ciprofloxacin has been removed. No further changes.
L326 IFAH-Europe	Clarification is needed regarding CLSI breakpoints. Please consider revising the sentence, as recommended Please amend as follows: *"For surveillance purposes, the low epidemiological cut-off values set by EUCAST are ~~more~~ sensitive ~~than the… set by e.g.~~ in detecting organisms that harbour ESBLs. The Clinical and Laboratory Standards Institute (CLSI) also recommends breakpoints that should be used to further test cephalosporins for the phenotypic presence of ESBLs."*	A modification has been made so that the sentence is comparing epidemiological cut-offs with clinical break-points, and not one committee with another.

L330 Swissmedic	**Resistance mechanisms and Genetics**. A paragraph is dedicated to "Laboratory detection of ESBL and AmpC-type beta-lactamase" (L321-L329). A paragraph describing the detection of methicillin-resistant Staphylococcus should also be included (*Laboratory detection of methicillin-resistant staphylococci*). Precise methods based on guidelines (e.g. CLSI guidelines) should be described for the detection of both methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci.	We agree that methods for identification of MRSA are important, but this is dealt with in documents on MRSA by EFSA[4]. See above.
L333-L343 Swissmedic	**Resistance in bacteria from food-producing animals**. Methicillin resistance is also widespread in coagulase-negative staphylococci. Some of these have emerged as nosocomial pathogens (*S. epidermidis*, *S. haemolyticus*) and are present in milk (Walther and Perreten 2007. J. Dairy Sci. 90(12):5351). They may also be present in milk products made with raw milk like raw milk cheese. The problem of food made with raw material of animal origin like raw meat products (e.g. sausage, salami) and raw milk cheese is not considered. These products represent a reservoir of antibiotic resistant staphylococci (Perreten et al. 1998. Syst. Appl. Microbiol. 21:113-120). The use of cephalosporins in farm animals may select for a resistant bacterial population (e. g MRSA and methicillin-resistant coagulase-negative staphylococci (Walther and Perreten 2007. J. Dairy Sci. 90(12):5351) that can contaminate milk during milking and subsequently to be present in raw milk cheese.	Considered when drafting the document on MRSA (see above)
L339 Swissmedic	Transfer of resistant clones from animals to humans. The direct transmission of bacteria between animals and humans and vice versa should be emphasized in a specific paragraph. People working with animals (cattle, pigs, horses) are more likely to be carriers of MRSA (van Loo et al. 2007. Emerg. Inf. Dis. 13(12):1834-9; Anderson et al. 2008. Vet. Microbiol. doi:10.1016/j.vetmic.2007.11.031. in press).	See above
L341-343 IFAH-Europe	The statement is speculative. IFAH-Europe is not aware of any *publications showing that cephalosporins are responsible for the transfer of an SCC mec cassette from coagulase negative staphylococci to MRSA ST 398 occurring in pigs today.* The sentence should be omitted or edited to read as follows: *"The 'pig clone' was previously absent in human infections, which ~~indicates~~ suggests that it ~~has~~ may have emerged in animals."*	Available information clearly indicates that this clone has **emerged** in animals. Whether the original "development" of resistance, i.e. its first acquisition of the mec cassette was in animals or elsewhere is another matter. The last part of the sentence has been deleted as MRSA will be discussed more in detail in coming documents.

[4] Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Assessment of the Public Health significance of meticillin resistant *Staphylococcus aureus* (MRSA) in animals and foods. *The EFSA Journal* (2009) 993, 1-73

L343 IFAH-Europe	The use of cephalosporins as an example is too restrictive. *"…. by, e.g. use of ~~cephalosporins~~ beta-lactams and considering co-resistance to other antibiotic classes such as tetracyclines."*	CVMP/SAGAM agrees that amplification (spread) of MRSA in animals could be favoured by co-selection by non-beta-lactam drugs. As CVMP/SAGAM has reviewed MRSA in a separate document (see above), where this has been addressed more in detail, the last part of the sentence has been deleted.
L340-344 EFSA	Reference to the EU MRSA base-line survey in breeding pigs could be made here. (Commission Decision 2008/55/EC).	As information from this very important study is still to be published CVMP/SAGAM chooses not to add that reference.
L343 EFSA	Please provide some published evidence to the statement that the use of cephalosporins may have contributed to the emergence of MRSA ST398 in animals.	The latter part of that sentence has been deleted following comments from IFAH.
Tables 3 & 4 EFSA	The tables provide data from the EFSA Community Summary Report 2005, however there is also more recent data available in the EFSA Community Summary Report 2006: (http://www.efsa.europa.eu/EFSA/DocumentSet/Zoon_report_2006_en,0.pdf)	At the time when the draft sent for consultation was adopted by CVMP, only the 2005 report was available. The tables have been updated with information from the, currently, most recent report[5]

[5] The tables will have to be updated again as soon as EFSAs report on AMR in 2007 is available (expected in the beginning of 2009) (internal comment to be removed before release)

Tables 3 and 4 Resistance to Enterobacteriaceae AVC	AVC found the Tables (3 & 4) of organisms resistant to 3rd generation cephalosporins of particular interest. With the exception of *Salmonella enterica* in pigs, the apparent lack of resistance development in mammalian pathogens is encouraging. Of all the organisms, some resistant strains of *S.* Typhimurium might be expected to arise, as this organism is well known for its ability to become multi-resistant. Please incorporate: 3rd generation cephalosporin resistance was only evident in Italy and Spain at a level of 5%, whilst *Escherichia coli* resistance from animal isolates was below 1%. Conversely, AVC finds the resistance levels of avian strains of *E. coli* in the Netherlands and Spain of concern. The resistance level of *E. coli* is concerning in the absence of 3rd and 4th generation products authorised for use in poultry and the lack of an MRL. This is probably associated with the in-ovo administration or dayold- chick injection at vaccination. As a result, AVC is drawn towards the conclusion that the resistance development is not likely to be associated with "off label" use, and points to the need for more rigorous monitoring, and increasing awareness amongst veterinarians of the consequences of such practices. This is particularly important in relation to human health as poultry are the main vector for the transfer of animal pathogens to man via food as highlighted in the document under "Exposure to resistant bacteria from animals". It is known, but rarely sufficiently emphasised to the general public, that proper food hygiene practices to prevent the transmission of *Salmonella* spp., *E. coli* and *Campylobacter* spp. would all but eliminate this potential threat. AVC proposes that the last paragraph of this section should be amended to reflect the concern about resistance development specifically in poultry and omit the word "**rapidly**" in relation to resistance development in mammalian species as the data do not support this. A definition of "rapid" resistance development does currently not exist. There is an increase. Please amend last paragraph as proposed. Please omit the word "rapidly", as this does not really reflect the scientifically sound situation.	The table has been updated with information from the most recent zoonosis report. The suggested comment relating to table 3 is therefore no longer in line with the text. Regarding "rapidly" we maintain that the emergence, as observed, is rapid, to the point of being unprecedented. This qualifier is regularly used as exemplified below: 1: Castanheira M, Mendes RE, Rhomberg PR, Jones RN. Rapid emergence of blaCTX-M among Enterobacteriaceae in U.S. Medical Centers: molecular evaluation from the MYSTIC Program (2007). Microb Drug Resist. 2008 Sep;14(3):211-6. 2: Pallecchi L, Bartoloni A, Fiorelli C, Mantella A, Di Maggio T, Gamboa H, Gotuzzo E, Kronvall G, Paradisi F, Rossolini GM. Rapid dissemination and diversity of CTX-M extended-spectrum beta-lactamase genes in commensal Escherichia coli isolates from healthy children from low-resource settings in Latin America. Antimicrob Agents Chemothe. 2007 Aug;51(8):2720-5. Epub 2007 Jun 4. 3: Zaidi MB, Leon V, Canche C, Perez C, Zhao S, Hubert SK, Abbott J, Blickenstaff K, McDermott PF. Rapid and widespread dissemination of multidrug-resistant blaCMY-2 Salmonella Typhimurium in Mexico. J Antimicrob Chemother. 2007 Aug;60(2):398-401. Epub 2007 May 24.

Tables 3 & 4 IFAH-Europe	None of the tables differentiate between clinical and microbiological resistance; they are therefore highly misleading and as such of very limited value. The figures are not comparable and by putting the data in one table and one column, wrong conclusions are drawn up, which is counterproductive. For instance, IFAH-Europe assumes that 14 and 23 % "resistance" in The Netherlands and Spain is based on epidemiological cut-off values (see MARAN and VAV), which is not the case for other countries. From the MARAN and VAV Report it can be seen that the clinical resistance in both cases amounts to 0% (based on CLSI breakpoint of 64 mg/L for cefotaxime) and hence entirely in line with the other countries. IFAH-Europe considers the publication of only microbiological resistance (i.e., decreased susceptibility) insufficient and provides an incomplete and biased picture. IFAH-Europe requests that for each country both the clinical resistance figures and the decreased susceptibilities are provided. As a minimum, transparency is required as to what breakpoints are used in each case. This can easily be implemented by, for instance, adding two columns (after the first column with the names of the countries): one column includes values in which the interpretive criteria are used, for each country and one with the drug tested.	The tables have been updated and cut-offs used have been added. We note that in defining "clinical resistance" to cefotaxime, IFAH seems to prefer the break-point of CLSI of >32 mg/l and not the clinical break-point used in Europe, (agreed within EUCAST) which is considerably lower: >2 mg/l.
Table 4 IFAH-Europe	Other published data could be cited such as: Bywater et al. European survey of antimicrobial susceptibility among zoonotic and commensal bacteria isolated from food-producing animals. J Antimicrob Chemother. 2004 54:744-54. Add data from Bywater et al: *"Neither decreased susceptibility nor clinical resistance or cefotaxime or cefepime was detected among the salmonella isolates from cecae of chicken at slaughter (n=75 France; n=43 UK) or colons of pigs (n=100 Denmark; n=31 Netherlands; n=15 Spain)"*	The isolates in the quoted reference were from 1999-2001. By that time, the prevalence of resistance to 3rd generation cephalosporins in Salmonellae from European animals was low or very low. Further, such resistance is often associated with certain serovars. The number of isolates from each country is low, and there is no information on serovars of investigated salmonellae. CVMP/SAGAM finds that the suggested reference does not add to the general understanding of the situation as it is today (as opposed to 8 years ago)

L354 IFAH-Europe	We would prefer using a different wording because the use of clinical breakpoints does not underestimate microbiological resistance. It is important to apply both epidemiological cut-offs and clinical breakpoints to characterize the two populations. We suggest changing the sentence slightly: *"…..the clinical breakpoints of the CLSI have been used for interpretation ~~and this may have led to an overestimation of microbiological resistance~~, but these interpretive criteria are not set to detect population of isolates with decreased susceptibility (Queenan et al., 2004; Tenover et al., 2003). The CLSI also recommends breakpoints that should be used to further test cephalosporins for the phenotypic presence of ESBLs."*	The sentence has been changed to indicate that by use of clinical break-points, irrespective of committee responsible for setting these break-points, organisms harbouring ESBLs are not always detected. The reference has been changed to a European and more recent one than those suggested: Kahlmeter 2008.
L380 IFAH-Europe	If this figure remains in the reflection paper, there should be some comment to indicate that this increase occurred after ceftiofur was no longer registered for use in chickens, and there are no oxyimino cephalosporins registered for use in poultry during the time when the increase occurred. Please add: *"… personal communication, 2007). The reason for this rise is unclear as the increase occurred in chickens during years in which oxyaino-cephalosporins were not registered for use in poultry in the Netherlands."*	The section in question describes the occurrence or non-occurrence of resistance, and does not discuss its possible "drivers". The latter is discussed in the section on "influence of use…" There, in lines 630-633, a comment to the same end as that suggested is given. No change in this section.
Figure 3 IFAH-Europe	Need for clarification. Rapid emergence occurs in the absence of cephalosporin use in the species. Lines 631-633 acknowledge that non-beta-lactam drugs could exert selection pressure; this should further be acknowledged in Figure 3. Please add: *"3rd and 4th generation cephalosporins are not registered for use in poultry in the Netherlands or other member States. There is no apparent correlation between cephalosporin use and the increase in resistance recorded in the Netherlands in Figure 3. This is also the case in Belgium where there is a decreased susceptibility to cephalosporins among E. coli isolates from broiler farms, but no cephalosporin use (see Smet et al, Antimicrob. Agents Chemother. 2008, 52:1238-43)."*	See above.

Figure 3 IFAH-Europe	We should avoid misunderstandings by stating that the % in Fig. 3 are based on epidemiological cut-offs and do not refer to clinical resistance. IFAH-Europe is strongly in favour of including such figures which provide significant epidemiological information; on the other hand, we are concerned that clinical resistance (0 %) is not addressed and that only a one-sided presentation is given. Please make clear that the figures do not refer to clinical resistance but to a specific cephalosporin breakpoint using an epidemiological breakpoint to detect organisms that may contain an ESBL or cephalosporinase.	A sentence has been added to indicate that epidemiological cut-offs were used to define resistance.
L396-397 IFAH-Europe	There is essentially no baseline information from which to characterise resistance emergence in many of the member states, therefore it is difficult to characterize resistance trends in Europe generally. Please edit the sentence. *"… indicates that the resistance to 3rd and 4th generation cephalosporins in E. coli and Salmonella isolated from animals in Europe ~~is~~ may be rapidly emerging.*	A change has been made to indicate that resistance is rapidly emerging in some countries, while in others information is still insufficient.
L404 EFSA	TEM-20 and TEM-63 are also ESBLs detected in poultry in The Netherlands (Hasman et al. 2005. Journal of Antimicrobial Chemotherapy 56(1)).	It is acknowledged that Hasman et al reported on one isolate with either of these ESBLs. Please note that the sentence was not intended to be an exhaustive list of all findings by all authors.
L404 IFAH-Europe	Please add a sentence. *"(Arlet et al, 2006).* *However the number of different enzymes found in animals are markedly less diverse than those found in isolates from humans. Furthermore, in the US where diversity of ESBls and AmpC cephalosporinases are high among human isolates, ESBLs are not readily detected, if at all, among E. coli and Salmonella isolates from animals; with the predominant cephalosporinases being restricted to the CMY family (Lynne et al, AAC, 2008, 52:353-356; Arlet et al. 2006)."*	We agree that the difference between humans and different animals in numbers of variant enzymes is relevant. The paragraph where a change is suggested, however, is on salmonella only. A comment has therefore been introduced in the concluding paragraph that discusses both Salmonella and *E coli*.
L409-421 IFAH-Europe	Need for explanation. Add clarifying sentences: *"Many of the ESBLs were found in isolates from poultry or their food products and all isolates were resistant to more than one drug class. 3rd and 4th generation cephalosporins were not registered for use at the time these organisms were isolated. In many cases the authors of the publications cited speculate on non-related drug classes exerting selection pressure for these multi-drug class resistant organisms"*	This section describes the emergence of resistance, and does not discuss selective pressures or other factors that could explain the picture. The latter is discussed under "influence of use…", in question of poultry specifically under co-selection. No change.

Line 439 IFAH-Europe	Need for explanation. *"… trimethoprim. As these isolates are resistant to more than one drug class, there is a potential for co-selection by other antibiotic families."*	Co-selection is discussed elsewhere, and is stressed in the conclusions. See above. No change.
L453 IFAH-Europe	Publications available up to now only report CTX-M in *Salmonella* from poultry. *"... in Europe both in E.coli from food-producing animals and in Salmonella from poultry in recent years."*	CTX-M has been reported in an isolate of S. Typhimurium from a Danish pig. No change.
L503-504 IFAH-Europe	*20-24% of the ceftiofur dose is excreted in faeces http://www.emea.europa.eu/pdfs/vet/mrls/049898en.pdf*	Following exchanges with IFAH-Europe it was clarified that the suggested change (*20-24% of the ceftiofur dose is excreted in faeces)* is not on the public domain. For this reason the text has been modified but not accordingly to the proposal.
L511 IFAH-Europe	Data are needed to support any statement regarding the relative MRSA selection pressures exerted by different groups within the beta-lactam drug classification. Please revise the statement: "*As MRSA are resistant to all beta-lactams, use of any substance in that group ~~can~~ may provide a selection pressure".* Please delete the remaining phrases of the sentence, unless there are specific data to support the phrase regarding relative selection pressure.	The change has been made as these matters have been dealt with more extensively in the MRSA documents of CVMP/SAGAM, EFSA and ECDC.
L511-514 IFAH-Europe	The antibiotic pressures affecting emergence and dissemination in MRSA animals are speculative; an addition is suggested. *"… ~~cephalosporins~~). A recent publication shows that MRSA in pigs occurs in a number of farms wherein different drug use profiles, including non-use of 3rd or 4th generation cephalosporin were operative (Van Duijkeren et al. Vet Microbiol 2008,126: 383-389)".*	Following the changes from above, in the present document, we simply note that "the risk associated with a potential to select for MRSA-colonisation of animals should be further examined" and specifies some aspects that deserve attention. No further change.

L514-515 IFAH-Europe	It is important to mention that the animal MRSA in food-producing animals is clonal and different from the two types of human MRSA (HA-MRSA and CA-MRSA). So far a connection between the newly emerging strain of MRSA in animals and traditional human MRSA has not been established. Up to now, the relevant selection pressure and the role of animal MRSA in human disease is not known. Note the rather outdated references (1996 and 1998); please update. *"...In human medicine, use of cephalosporins or fluoroquinolones is associated with an increased risk of MRSA colonization (Asensio et al., 1996; Hill et al., 1998). This is not the case with MRSA colonization in food-producing animals. The microbiological and epidemiological differences of the recently reported animal MRSA (type ST 398) suggest different selection mechanisms and selection pressure. In contrast to human MRSA the animal MRSA clone is non-typeable by PFGE and demonstrates differing resistant phenotypes. In view of… "*	The references have been updated as suggested. CVMP/SAGAM . No further change.
L540-541 IFAH-Europe	As referenced repeatedly in this reflection paper, isolates that are resistant to 3rd and 4th generation cephalosporins are typically co-resistant or decreased susceptible to other drug classes. Cephalosporin resistance appears to be increasing in isolates from chickens in the EU, where cephalosporins are not registered for use. Hence, the conclusion in lines 538-541 is not correct: it is unlikely that the use of 3rd or 4th generation cephalosporins explains the resistance to cephalosporins in poultry. Thus it is not clear which drug use patterns are likely to favour the evolution of beta-lactamases to exposed populations. Please edit the sentence as follows: *"… populations, and possibly also of other beta-lactams, ~~is likely to~~ may favour the evolution of beta-lactamases in exposed bacterial populations. However, at this stage of our information, the beta-lactamases found in animal populations are not different from those documented in human medicines and are found AFTER they are documented in humans. For example in poultry isolates, the CTX-M enzymes have been documented where cephalosporins are not registered for use. The dissemination routes of these multi-drug resistant organisms may be confounded by epidemic spread of plasmids whose spread may be affected by a number of different selection pressure.*	This section deals with evolution of genes, not with their amplification and spread which is in the following section. The comments and requested changes above relate to the latter. The non use of cephalosporins in poultry etc has been addressed elsewhere. No change

L558	It is questionable if a study including a group receiving both antimicrobials and R-bacteria would add much information based on the negative results from ceftiofur treatment of poultry. Are the R-bacteria selected relevant? If more shedding occurs, how much and how long would be relevant? Furthermore, the intestinal balance of bacteria in this neonatal model is not representative of the flora in poults. It is difficult to extrapolate the meaning of the model to field conditions.	The information added with a group that is also receiving antimicrobials would be on transfer frequencies, and on number of bacteria/g faeces shed. Studies on other antimicrobial-resistance gene-bacterial combinations have shown that exposure of antimicrobials can increase the transfer frequencies. Likewise, shedding of resistant bacteria has been documented to increase for other combinations and also for cephalosporins. Both these factors are important as they would affect the probability of a) transfer to other bacteria and b) spread to other animals.
L562-563 EFSA	What use was reported ?	The authors studied occurrence of resistance in selected herds, and linked the results on cow and herd level to information on use of cephalosporins on cow and herd level in the same selected herds (i.e. the study herds). It has been clarified in the text that use was studied in the same herds..
L575-580 IFAH-Europe	Need for inclusion of other aspects of the study. *"The study did not examine other drug use practices in the farms.* This was acknowledged by the authors.	Change added.
L582-589 IFAH-Europe	Need inclusion of an important aspect of the study. "*It is acknowledged that ceftiofur-resistant organisms were present before the treatment began. An important aspect of the study was that treated animals were co-mingled animals. The co-mingled animals did not have any increase in cephalosporin-resistant organisms*."	The information on co-mingled animals has been added, noting that non-selective techniques were used for culture (colonies picked at random). CVMP/SAGAM is of the opinion that this is important information, as it decreases the sensitivity of the analysis.

L609 IFAH-Europe	Reports of cephalosporin resistance when cephalosporins are not used in animals. Two examples are provided. Australia: Report of a veterinary hospital in which several cephalosporin-resistant, multi-drug resistant *E. coli* were isolated from dogs. None of the dogs had been treated with any cephalosporins, although they had been treated with a number of other drugs. The authors concluded that the spread of these organisms was probably due to nosocomial transmission within the hospital and lack of appropriate infection control measures. Warren A, Townsend K, King T, *et al*. Aust Vet J. 2001; 79:621-3. Belgium: Report of cephalosporin resistant *E. coli* in cloacal samples from healthy chickens in 5 different farms in Belgium. Cephalosporins are not allowed for use in Belgium. Although ceftiofur was approved in April 1990, the product was not registered for use after January 2000. The authors speculate the cephalosporin-resistance is co-selected by use of non-β lactam drugs. Smet A, Martel A, Persoons D, *et al*. ,AAC; 52:1238-43, 2008.	Warren et al is interesting but all references on companion animals have been excluded from this document. Information from the Smet at al (2008) study has been added here and elsewhere in the document. Another highly relevant study (Cavaco et al, 2008) has also been added.
L616 Swissmedic	Co-selection of resistance. The co-selection of MRSA by the use of other antibiotics should also be mentioned. MRSA are often resistant to other classes of drugs. Additional resistance genes e.g *ermB* (macrolides, lincosamides and stretogramins B) and/or *aadD* (aminoglycosides)) are present within the SCC*mec* of some MRSA (Chongtrakool et al. 2006. Antimicrob Agents Chemother. 50: 1001–1012).	See above.
L622 IFAH-Europe	Term "frequent" is not self-explaining. Since CTX-M is representing almost 3% of the clinical isolates, the association is even more rarely encountered and then "frequent" is not really applicable. Note that in Europe strains carrying plasmid-mediated quinolones resistance genes are usually not associated with ESBLs and qnr determinants in *Salmonellae* are rare. Please replace "frequent" by "possible" or "potential".	Frequent has been replaced by "described".
L630 IFAH-Europe	An addition is suggested. *"… bacterial strains (co-selection). However CMY do not confer resistance to 4th generation cephalosporins ."*	The chapter refers to co-selection, i.e. selection by antimicrobials other than 3rd or 4th generation cephalosporins. No change.
L661 & L700 EFSA	Reference to the EFSA Opinion on "Food-borne antimicrobial resistance as a biological hazard" July 2008.	This reference has been added as suggested.

L637 Exposure to resistant bacteria from animals AVC	While AVC agrees with content of this section, it believes that the incidence of food borne transmission, as evidenced by the incidence of clinical disease should be stated, as it is low. Please include, that the incidence of food born transmission is low.	It is unclear if this comment refers to Salmonella, or to the section as a whole. CVMP/SAGAM takes the view that there is presently insufficient evidence to conclude about the extent (low, very low or moderate) of transfer of, e.g. ESBL plasmids via the food chain. On line 700, in summarizing the whole exposure section, we note that "the present extent of exposure via food is difficult to determine". No change.
L655 IFAH-Europe	This sentence is misleading in several ways: generalization based on single case and the genetic traits were circumstantial evidence only. Suggested re-write: "*Fey et al documented zoonotic transmission of a cephalosporin-resistant Salmonella Newport from cattle to a person.*"	A change in the spirit of the comment has been made.

L665-666 IFAH-Europe	This sentence is referring to an old reference which only suggests a possibility. The comment in the document referred to data showing that people eating sterilized foods showed reduced prevalence in resistant E. coli in their faeces. A literature update would be needed using more accurate methods (PFGE, sequencing). While citing Corpet from 1988, suggesting that most resistant Enterobacteria in faeces come from contaminated food no more recent reference is provided to support that suggestion. In 2008, Carattoli specified that up to now there is no direct evidence of the transmission of ESBL-positive zoonotic pathogens through the food chain (CMI, 14, suppl 1, 117-123, 2008). When looking at specific analyses, i.e. plasmid analysis it was shown that in E.coli plasmids harbouring CTX-M-14 were not from the same incompatibility groups in human and in cattle (Hopkins *et al*., AAC, 50: 3203-3206, 2006).	The quotation of Corpet has been reworded to indicate what the study actually showed. This paragraph (line 665-673) is on general human exposure to resistant bacteria, an the potential for transfer of resistance genes. The comment is more pertinent to the two following paras (lines 675-696) where transfer of AmpC or ESBLs is addressed specifically. The section is *not* on spread of zoonotic pathogens, i.e. Salmonella which was dealt with in the previous section. It is true that one of two cattle CTX-M carrying *E. coli* isolates in Hopkins et al was from a different incompatibility group compared to one human isolate of Salmonella Stanley (epidemiologically unrelated, origin of infection was Thailand) the second included cattle isolate of that type was negative in replicon typing. However, both included cattle *E. coli* carrying CMY2 were of inc groups also found in salmonella-isolates of human origin. The similarity of plasmids carrying CMY2 has been further substantiated by Mulvey et al (Vet Microbiol, 2008 doi:10.1016/j.vetmic.2008.08.018) and that reference has been added. No further change.
Line 700 IFAH-Europe	Need for additional information. *"…exposure via food is difficult to determine. Moreover at that stage human contamination through food processing might also play a role in contamination."*	Added but earlier in the same paragraph.
L702 IFAH-Europe	Need for additional information. *"… on human exposure. However the direct pressure exerted in human medicine is to be considered since the number and the type of enzymes found in human does not always match with those found in animals."*	CVMP/SAGAM does not disagree in principle that the selective pressure in human medicine is very important, but this section, as indeed the whole document (see title) is on the fraction that might or might not be attributable to animal origin. No change

L706 Human health AVC	AVC notes that Livermore *et al* are cited again in support of the existence of an animal reservoir of CTX-M betalactamases producing strains of *E. coli*, when the evidence would suggest that this is unlikely due to the difference in CTX-M species between animal and human strains. Appropriate modification of this paragraph should be considered. Correct the citing of *Livermore et al*. to the appropriate conclusion of the authors (see above).	See above and comment from IFAH. A clarifying change and additional references has been introduced in the text.
L706-755 Swissmedic	Impact of infections with cephalosporin-resistant bacteria on human and animal health. The important problem of nosocomial infections with MRSA is not mentioned in this chapter. The chapter only focuses on *Enterobacteriaceae*. It should be clearly mentioned that MRSA are important pathogens in hospitals. Additionally, community acquired MRSA (CA-MRSA) have emerged in the populations and cases with CA-MRSA have increasingly been reported the last decade.	See above.
L725 IFAH-Europe	Please include references to documented frequencies. *"The frequent (which percentage?) occurrence of community acquired infections and the frequent (which percentage?) occurrence in E.coli…."*.	Good quality prevalence data on this are scarce. However, a recent review summarised some of the information available and the text has been modified and some examples of precise data is given. The modification also serves to illustrate that the development is indeed "rapid".
L729-731 EFSA	Couldn't this statement be stronger ?	See response to comments from IFAH and AVC.
L730 IFAH-Europe	Livermore et al. do speculate, but do not conclude that CTX-M may be transferred via the animals, and they also speculate that any number of pathways of transfer may be occurring simultaneously. Add to the sentence: "…*however the authors did not have data to identify the risk attribution due to animals."*	A change has been made indicating that the authors hypothesized (not suggested), which clearly indicates that there was not direct evidence. Also, the phrasing now indicates that animals was hypothezised to be one of several potential reservoirs.
L739 Animal Health AVC	Some strains of *Actinobacillus pleuropneumoniae* in pigs are resistant to penicillins, and ceftiofur could be considered a very viable alternative. This should be stated in this paragraph to emphasise the need for 3rd and 4th generation cephalosporins in some circumstances to avoid animal suffering. Please add: for the treatment of *Actinobacillus pleuropneumoniae* 3rd and 4th generation cephalosporins may be in some circumstances a very useful and efficacious treatment to avoid suffering of animals.	This section deals with situations where cephalosporins would be not only a "viable" alternative but the only available alternative.

L740-743 IFAH-Europe	Efficacy is more than in vitro activity and PK should also be considered. Penicillin products are not documented according to the latest regulatory requirements as 3rd and 4th generation cephalosporins. Moreover a higher volume of injection is required for penicillins (consequence on local tolerance, animal welfare). *For ~~almost all of the~~ some indications for which ceftiofur or cefquinome are authorized for systemic therapy of food producing animals, ~~equal or better~~ alternatives are available. In particular, this is true for streptococcal infections where cephalosporins have no advantage above benzylpenicillin in terms of antimicrobial activity ~~efficacy and safety~~."*	It is true that penicillin G is an old drug. However there is published scientific evidence on its clinical efficacy in many indications. Local tolerance is no issue here, as tissue irritation caused by penicillin products is close to saline, on the contrary to most other antimicrobial products (see e.g. Pyörälä et al. 1994). We also refer to Prudent use guidance in the OIE Terrestrial Code: spectrum of treatment should be kept as narrow as possible.
L740-48 and L843-4 The Soil Assoc.	We agree that 3rd- and 4th-generation cephalosporins are extremely important agents in human medicine. We also agree that alternatives are usually available in veterinary medicine. However, some vets claim to select them because experience has taught them that the likely causal organism will be resistant to alternative antibiotics. We do not have adequate information to challenge this.	No comments.
L743 Swissmedic	Alternatives are available: The use of cefquinom for preventive (!) dry cow therapy should be mentioned here.	See above. We have chosen to focus on the use that potentially has the major impact, i.e. systemic use. However, some text on intramammary use has been added.
L743-745 IFAH-Europe	Please note that only cefquinome is registered for these indications (see lines 113-160, bovine mastitis caused by *E.coli* septicaemia caused by *E.coli* in calves): Also referring to 3rd generation cephalosporins for these indications is contradictory with the recommendation of the present paper (line 1275: *Off-label use should be discouraged*). *"In cattle, the only indications in which 3rd or 4th generation cephalosporins could be the sole alternative is severe clinical mastitis with life-threatening sepsis and calf septicaemia caused by Enterobactericaeae such as E.coli or Klebsiella. However, these indications have not been approved yet for 3rd generation cephalosporins in Europe."*	The sentence actually refers to evidence on efficacy available in the literature, and did not limit that to authorized EU indications. Cefquinome is not authorised in all Member States, and ceftiofur can in serious life threatening infections be used in accordance with the cascade principle. No change.

L745-746 IFAH-Europe	The sentence only takes into account data on normal milk but not on milk from mastitis which shows different characteristics. The sentence: "*Cephalosporins are poorly distributed to the milk …"* should be deleted.	Cephalosporins as strongly ionised substances in blood, with limited Vd, do not distribute well into milk. This is reflected in the withdrawal times for milk. Mastitis indeed can affect concentrations slightly (Erskine et al. 1995), but even in such cases the distribution can be considered as poor. For this reason, systemic therapy of mastitis with ceftiofur has not been succesful. No change.
L748-751 IFAH-Europe	Only cefquinome is registered for treatment of foal septicaemia (see lines 113-160). *"In the treatment of this condition, caused by E.coli, cefquinome is a better alternative for benzylpenicillin…"*	It is not our view that cefquinome is a better alternative than standard treatments, unless there is resistance. Text has been slightly revised. Cefquinome is not authorised in all Member States, and ceftiofur can in serious life threatening infections be used in accordance with the cascade principle.
L757-758 EFSA	Include evidence to support this important statement.	This paragraph concludes on the previous paragraph, and there the reasoning behind this conclusion is found in the preceding paragraph. No change.
L757-761 EFSA	A clearer conclusion to this section would be useful.	Agreed, but as treatment failures are rarely documented in veterinary medicine, a more precise conclusion cannot be made at this stage.

L758 IFAH-Europe	Need for clarity. The document repeatedly alludes to the fact that cephalosporin resistant organisms are co- and cross-resistant to a number of structurally unrelated drug classes. Suggested edit to existing sentence: *"However, emergence of resistance among Salmonella and E. coli is mediated by genes encoding ESBLs or AmpC is frequently linked to multiple ~~other~~ antimicrobial agents".* Suggested inclusion of the sentence. *"Cephalosporin resistant E. coli and Salmonella are co-resistant to a variety of beta-lactams and cross-resistant to a number of structurally unrelated drug classes, and thus these organisms may be selected by any number of drug use selection pressures."* This aspect should not be ignored in the conclusion.	Agreed, changed. The terms co-resistant and cross-resistance appear to have been swapped in the suggestion above. This section is not on relation between use and occurrence of resistance, but on potential effects on animal health of emergence of resistance to cephalosporins. Co-selection has not been ignored in concluding remarks, see lines 792-798 (of the consultation document) and in particular lines 818-830.
L761 IFAH-Europe	Please add a sentence: *"…for treatment. Although most of the target pathogens of 3rd and 4th generation cephalosporins are not influenced by ESBLs or AmpC resistance (BRD, mastitis).*	In view of the text above this concluding paragraph, we consider that there is no need to specify this. No change.
L764 Resistance to 3rd generation cephalosporins in e.g. K. pneumoniae and E. coli in human infections is increasing in Europe. AVC	This section once again raises the issue of CTX-M animal reservoirs and possible spread to the human population, when, in reality, the data are equivocal. While AVC agrees that this possibility should be investigated, the text as it stands, and the frequent appearance of this "**possibility**" in the reflection paper gives it undue prominence. This may give rise to unwarranted concern at this time, especially as human cephalosporin, and not animal use would appear to be the driver. First profound data should be generated/present before such conclusions are drawn. Please use appropriate wording to represent current scientific knowledge without bias rather than pose risks that have not been proven.	See comments above. No change.

L769-771 ECDC	"Many of these problems in human medicine are related to use of cephalosporins and other antimicrobials in humans…" There are several reasons for this proposed change. Firstly, a study by Valverde et al. showed that, between two non-outbreak periods in 1991 and 2002 in Madrid, Spain, fecal carriage of ESBL-producing *Enterobacteriaceae* (mostly E. coli) increased from 0.3% to 11.8% in hospitalized patients and from 0.7% to 5.5% in ambulatory patients.[1] Additionally, the study showed a fecal carriage rate of 3.7% in healthy volunteers without recent hospitalization and/or recent exposure to antibiotics within the previous 3 months.[1] This fecal carriage rate in healthy volunteers, comparable to that of ambulatory patients, therefore must have another explanation. Secondly, we performed an analysis of data from the European Antimicrobial Resistance Surveillance System (EARSS) and the European Surveillance of Antimicrobial Consumption (ESAC) network, looking for the presence or absence of concomitant trends (Spearman's rank test, considered significant if $p<0.05$) in the percentage of *Escherichia coli* isolates from blood cultures resistant to 3rd-generation cephalosporins (most of these are ESBL producers) and in the consumptions of 3rd-generation cephalosporins (ATC group J01DD) and of quinolones (ATC J01M) (ESBL-producing isolates often are co-resistant to quinolones), in outpatients and in hospitals. Out of 24 EU and EEA/EFTA countries that reported at least 5 years of consecutive data on *E. coli* (EARSS) and on community antibiotic use (ESAC, incl. hospitals for Bulgaria, Greece and Iceland) during the period 1999-2006: - 13 (54%) showed a significant increasing trend in the percentage of *Escherichia coli* isolates from blood cultures resistant to 3rd-generation cephalosporins. However, none of these countries showed a concomitant significant increasing trend in 3rd-generation cephalosporins and only five (38%) showed a concomitant significant increasing trend in quinolone use in outpatients. Similarly, out of the five EU and EEA/EFTA countries that reported at least 5 years of consecutive data on *E. coli* (EARSS) as well as hospital antibiotic use during the period 1999-2006 and showed a significant increasing trend in the percentage of	Agreed. Changed.

	Escherichia coli isolates from blood cultures resistant to 3rd-generation cephalosporins, two showed a concomitant significant increasing trend in 3rd-generation cephalosporins and one showed a concomitant significant increasing trend in quinolone use in hospitals. These data confirm the increase in the percentage of 3rd-generation cephalosporin-resistant isolates in *E. coli* from blood cultures observed in many European countries. However, it looks like often this increase in resistance is not associated with an increase in 3rd-generation cephalosporin or quinolone use, in outpatients or in hospitals. More data as well as specific research studies are obviously needed to better understand the risk factors for human carriage and infection by 3rd-generation cephalosporin resistant *E. coli* and the reasons for the increase recently observed in many countries. However these preliminary results, together with that of the study by Valverde et al., suggest that other factors than human antibiotic use contribute to the increase in 3rd-generation cephalosporin resistance in *E. coli* in many European countries. References 1. Valverde A, Coque TM, Sánchez-Moreno MP, Rollán A, Baquero F, Cantón R. Dramatic increase in prevalence of fecal carriage of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* during nonoutbreak situations in Spain. J Clin Microbiol. 2004 Oct;42(10):4769-75.	
L777 Available data indicate that resistance to 3rd generation cephalosporins is increasing in E. coli and Salmonella from animals in Europe. AVC	The above paragraph heading should be modified to include poultry. The data indicate that the resistance situation in mammals is of a low order. The only "more pronounced" increase in resistance is in poultry. Please add "poultry" into title, as this statement does appear not to be true for the other animal species. AVC considers that the text be amended to reflect this. Nevertheless, AVC agrees with the need for monitoring along the lines proposed. Use "more pronounced" instead of "rapidly".	Not agreed. Resistance to 3rd generation cephalosporins in *E. coli* is reported also in pigs and cattle, indeed UK reports comparatively high figures for 2006 (7.5%, E. coli from healthy cattle, Zoonosis monitoring report). See also information in comments from Soil association above. Rapidly has been changed to pronounced ("more" is out of place, as the comparison is with countries still reporting zero prevalence)

L785-790 IFAH-Europe	It is serious that in this paragraph the existence of clinical breakpoints is systematically ignored. Neither CLSI nor EUCAST have been included. This will cause much confusion and can not be considered acceptable. Based on cut-offs, the percentages of decreased susceptibilities indicate the acquisition of resistance in an intrinsically susceptible bacteria population but they cannot be translated into therapeutic failure, when antibiotics would be used to treat. This is the information the vet or the physician ultimately needs, but isn't addressed in this bullet point. It is against the principles of organisations such as EUCAST, CLSI or EMEA. IFAH-Europe strongly requests that both interpretive criteria are addressed and included. We would also like to point out that frequently the EFSA Report is quoted in the Reflection Paper, but IFAH-Europe did not have the possibility to be involved; there was no consultation period to the best of our knowledge. IFAH-Europe proposes the following wording is added: *"Work aiming to harmonise methodology and interpretive criteria is currently undertaken by EFSA*. *In addition to the interpretation criteria suggested by EFSA, interpretation criteria for clinical resistance as defined by CLSI or EUCAST must be used in the future. It is significant to characterize precisely both the clinically-resistant population and the population with decreased susceptibility. Both interpretive criteria should be mandatory for European antimicrobial surveillance schemes."*	The criteria suggested by EFSA are based on EUCAST, the European committee on antimicrobial susceptibility. CVMP/SAGAM shares the view of EUCAST and EFSA that in programmes aimed at monitoring zoonotic resistance, epidemiological cut-off values are to be preferred. An addition specifying that this conclusion is valid for monitoring of potentially zoonotic resistance has been entered. No further change.
L792 The genes encoding resistance to 3rd and 4th generation cephalosporins are transferable and often linked to other resistance genes AVC	Biosecurity on farms is becoming a more important aspect of livestock farming today. Consideration should be given to the role of biosecurity in limiting between farm spread of plasmids where the farms are "closed" units. This could emphasise the need to develop more holistic strategies in controlling the emergence of resistance. Please add a sentence to stipulate, that biosecurity measures on farms may also have an effect.	We agree on the paramount importance of biosecurity as a risk management tool to contain spread of infections, including antimicrobial resistance. Biosecurity is among the recommendations of CVMP (see p 36 of draft for consultation, first bullet point) No change.
L800-806 EFSA	Consider adding a comment on the high usage in domestic pets (re: table 1) and subsequent direct exposure of the animal handler when treating the animal.	There are many other sections in this document where information relevant for pets is available but this document is limited to use in food-producing animals, as apparent from the title and objectives. No change.

L140-4 and line 808 The Soil Assoc.	We agree that systemic use of cephalosporins can select for resistance and that mass medication of groups or flocks of animals with cephalosporins or other antibiotics is particularly likely to select for resistance. However, as detailed in section 2 of our 'general comments',we disagree with the SAGAM/CVMP's decision not to address intramammaries in the document. We also believe that, if SAGAM and the CVMP are claiming that intramammaries do not have the potential to select for resistance in bacteria in milk, then some supporting evidence should be provided in the Reflection Paper to justify this claim. Replace sentence beginning 'Potential effects of intramammary use…' on line 141, with: 'The use of intramammaries also has the potential to contribute to resistance, particularly when waste milk, taken from cephalosporin-treated cows during treatment, or before the withdrawal period has elapsed, is fed to calves or other livestock.'.	We agree in principle. The point on possible feeding of waste milk containing cephalosporin residues has been taken into account. Text has been added to address this earlier in the document but not in the concluding remarks (see previous comments).
L818 Co-selection by other antimicrobials is likely to influence prevalence of resistance to 3rd and 4th cephalosporins. AVC	The possibility that the use of other antimicrobials may be driving cephalosporin resistance development in poultry cannot be ignored and should be investigated. Nevertheless the possibility of the off label use of 3rd and 4th generation cephalosporins being implicated is another possibility, especially as poultry use occurs in countries outside the EU. As there is no luoroquin use in the EU, consideration should be given to actively discourage "off label" use, in view of the existing resistance pattern. Please add all alternative influences to the proposed list.	CVMP/SAGAM agrees that co-selection by non cephalosporin antimicrobials is likely to be important (lines 824-825), and moreover, takes the view that this matter should be further documented (lines 828-830 of draft for consultation). No change is therefore needed. CVMP has, in its recommendations in the draft for consultation also addressed off-label use and indeed, as suggested by AVC in its comments, recommends to discourage such use (page 35, 5th bullet point)
L818-9 The Soil Assoc.	We agree. Fluoroquinolones are one antibiotic class which can co-select, and this provides an additional reason for also aiming to reduce luoroquinolones consumption in EU farming.	No need for change.

L825-827 EFSA	This could be further emphasised	We agree in principle but as this document is focussed on cephalosporins and not on the array of other antimicrobials that could co-select. Thus, the evidence that would lead to a stronger statement on potential effects of mass medication in general has not been included and discussed in this particular document, and hence the matter cannot be more strongly concluded in this particular document.
L841 EFSA	Could give more examples, e.g. food hygiene, food consumption patterns ……	Food hygiene is related to contamination of food (aims to avoid that), but consumption patterns has been added though not discussed in the body of the text.
L847 IFAH-Europe	Additional argumentation. *"… treatment alternatives are e.g. carbapenems, fluoroquinolones or aminoglycosides. In the case of ESBL association of beta-lactams with enzyme inhibitors, e.g. clavulanic acid represents also an alternative."*	The alternatives given in the text are examples. It is true that the literature gives clavulanic acid combinations as alternatives in certain cases (given that the enzyme is not inhibitor resistant) but, CVMP/SAGAM is reluctant to go too far into the field of human medicine in this matter. No change.

RECOMMENDATIONS FOR ACTION

The below part addresses recommendations on cephalosporins and have been dealt by the CVMP

Line no[6]. + paragraph no.	Comment and Rationale	Outcome
L1254-62 The Soil Assoc.	We strongly agree with the CVMP that it would be wise to take action on the veterinary side to reduce the risk of veterinary use of cephalosporins contributing further than it may already have done to the emergence of resistance in human pathogens. However, even though manufacturers now recommend that sensitivity testing should be undertaken, our experience is that this rarely occurs when treating cattle, in the UK at least	Comment noted. No change in text.
L1254 EFSA	Add reference to WHO and OIE.	Agreed. The reference is added.
L1256-1257 ECDC	"Although it could be assumed that a large part of the increase in resistance levels recorded in human medicine is due to increasing use in humans,…" Same reasons as mentioned above.	Agreed. The text is amended as proposed.
L1264 EFSA	Clarify that the recommendations are limited to use in food-animals	This should be clear from the title of the document. However, a text is added for clarity.
• Systemic broad spectrum cephalosporins should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to more narrow spectrum antimicrobials.		
L1265-1267 EFSA	Would this risk being too late in the clinical case?	In our opinion no. All flexibility needed is included in the expression "are expected to respond poorly". At farm level there should be knowledge e.g. from previous sensitivity testings.

[6] Where available

L1265-7 The Soil Assoc.	We agree. Especially on large farms, vets sometimes prescribe larger quantities of antibiotics than are required to treat individual cases, and farmers then have a free hand to use them for other conditions as well. Add this further recommendations Prescriptions for, or the dispensing of quantities of 3rd- or 4th-generation cephalosporins additional to those needed to finish a course of treatment in an individual animal seen by a veterinary surgeon, should be supported by sensitivity testing.	We do not support this proposal. Precriptions/dispensing of antimicrobials should always be limited to a certain (diagnosed) situation. We would not support that large quantities of any antimicrobial are given to farmers that have a free hand to use them as they please. By adding the text proposed by Soil Association we feel that we might give the impression that this behaviour would be acceptable in case of other antimicrobials but cephalosporins.
L1265-1275 EFSA	Stronger recommendations along the lines of the following could be considered: Withdraw or restrict access to cephalosporins and limit to designated practices/veterinarians with mandatory request for records of use, subject to audit.	Outside scope CVMP.
• The need of prophylactic use should always be preserved for specific circumstances and carefully considered in the conditions for authorisation and reflected in the SPCs.		
L1268-1269 EFSA	Consider recommending that they are never used as prophylactics.	As prophylactic use includes "metaphylaxis" i.e. strategic use to limit the spread of a disease in a flock/herd it could be that banning all prophylactic use would be contra productive increasing the total need for antimicrobials. However, it is agreed that the boundary between general prophylaxis and strategic use is difficult to establish.
L1268-9 The Soil Assoc.	We feel that the prophylactic use of systemic cephalosporins should be reserved only for use only after accidents. Remove 'specific' and between 'circumstances' and 'and carefully considered' add: 'where an accident has occurred'	We are not ready to restrict prophylactic use as proposed by the soil association. There are other situations where prophylactic use is important for animal health although we do agree that mass medication should be discouraged. Se the third bullet point ("Use of systemic cephalosporins for groups or flocks of animals such as use of oral cephalosporins in feed or drinking water should be strongly discouraged") In addition we would not be ready to recommend cephalosporins as first choice antimicrobial in post traumatic treatment.
L1270-1270 and 1275 EFSA	Could be stronger eg. "withdrawn/prohibited" in place of "discouraged".	The expression was use to indicate that this is outside CVMP remit as it relates to nationally approved products only. To be discussed internally between the agencies.

L1270-1 The Soil Assoc.	We agree, but would prefer to see this prohibited, rather than just discouraged since the CVMP has not shown that there are any circumstances where such use would be prudent. Replace 'discouraged by 'prohibited'.	The expression is use to indicate that this is outside CVMP remit as it relates to nationally approved products only.
L1270 IFAH-Europe	The recommendation to "discourage" flock or group treatment is not based on a scientific risk assessment but more of political nature. Therefore such a recommendation is not appropriate for a scientific advisory committee and is also not in line with the actual Codex initiatives, which clearly ask for a risk assessment before risk management measures are taken. Furthermore, and as noted in the FAO #87 (Food and Nutrition Paper #87, FAO, 2006) and the Kiel Report (Joint FAO/WHO expert meeting: "The use of Microbiological Risk Assessment outputs to develop practical Risk Management Strategies", Kiel 2006), the use of the precautionary principle for immediate action should be limited to imminent human health threats. As there are no products of that kind (see lines 115-121, p.5), i.e. cephalosporins of 3rd or 4th generation for group or flock treatment on the market in the EU, it is impossible to identify an imminent hazard or threat, which would justify such a formulated recommendation. Delete this recommendation completely.	We cannot agree that we have to wait until there are products on the market before we give recommendations rather the contrary. By indicating that we are concerned about (possible future) group and flock medication of broad spectrum cephalosporins we give a signal to companies not to invest money in such products as this would be a uncertain investment. We believe this kind of information at an early stage would be valuable for companies. This is also in line with the ongoing discussions at Codex TFAMR where it is said that measures may be taking following risk profiles in cases where full risk assessments are not feasible or cannot be waited for.
• Off label use should be discouraged.		
L1275 The Soil Assoc.	We agree that the off-label use of 3rd- and 4th-generation cephalosporins should be discouraged in all farm animals except poultry, where is should be specifically prohibited. Replace sentence by: 'Off label use of 3rd and 4th-generation cephalosporins should be discouraged, and the off-label use in poultry should not be permitted.'	The text is amended for clarity. However, we do not agree that absolute prohibition of a certain use is an appropriate measure in absence of a risk assessment specifically covering risks related to cephalosporin resistant bacteria or resistance determinants in poultry meat.
L1284-6 The Soil Assoc.	We strongly agree. This should read 'should not be considered in isolation, but a global..'	Agreed. The text is amended.
L1291 EFSA	Fourth bullet point: Could be stronger e.g. withdraw or restrict use.	Se above.

• Other recommendations		
Table p36, suggested action 2 The Soil Assoc.	We agree. However, farmers also need to be educated. See also our points in the general comments section. After 'Veterinarians' add 'and farmers'.	Agreed. The text is amended.
Table p36, suggested action 3 The Soil Assoc.	We agree. In particular, surveillance for ESBLs and other cephalosporin resistance in salmonella and E. coli from poultry, pigs and cattle in both live animals at abattoirs and retail outlets should be introduced. Add: 'In particular, surveillance for ESBLs and other cephalosporin resistance in salmonella and E. coli from poultry, pigs and cattle in both live animals at abattoirs and retail outlets should be introduced.'	We agree in principal. However, we prefer not to be that detailed in this text especially as surveillance for resistance determinants is technically difficult. The comment will be forwarded to EFSA for consideration.
Table p36 suggested action 4 The Soil Assoc.	We agree. We also feel that published data on the use of cephalosporins and other antibiotics in EU Member States should be based on the quantities prescribed by individual veterinary practices, in addition to sales data Add: 'Data on the use of cephalosporins and other antibiotics 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'. There should also be full independent scrutiny of sales data provided by pharmaceutical companies. We are concerned by the extent to which pharmaceutical companies supplying the UK market have voluntarily notified regulators of very large historical changes in sales data for numerous drugs, many years after the original data was published. This indicates that any scrutiny currently taking place is entirely inadequate.	We agree in principle although we are aware of that this is not feasible in most EU member states. For the future we would like to see a harmonised system for monitoring of use of antimicrobials in EU.
Table p36 suggested action 5 The Soil Assoc.	This should read, 'codes of practice'	Agreed. The text is amended.
Table p37 suggested action 6 The Soil Assoc.	We agree and feel this is very important.	Agreed.
Further recommendation to be added The Soil Assoc.	In the UK, despite EU Directive 2004/28/EC, the advertising of modern cephalosporins and other antibiotics to farmers is still permitted. See our points in the general comments section and chapter 9 of our report, 'MRSA in farm animals and meat', which we have sent to you in the post. The European Commission should take steps to ensure that all member states prohibit	The comment will be forwarded to the Commission for consideration.

	advertising of prescription-only antibiotics directly to farmers. 'The European Commission should take steps to ensure that, in line with Directive 2004/28/EC, all member states ban the advertising to farmers of prescription-only antibiotics.'	
Further recommendation to be added The Soil Assoc	'The practice of feeding calves or other livestock with milk taken from cows treated with any antibiotics should be discouraged, and with 3rd- and 4th-generation cephalosporins should be prohibited, until the withdrawal period has elapsed.'	We find this recommendation too specific to be included.
Further recommendation to be added The Soil Assoc	A very recent paper has shown that ceftiofur (3rd-generation cephalosporin), cefquinome (4th-generation cephalosporin) and amoxicillin all select for CTX-M ESBL E. coli in pigs, but the effect was greater for the cephalosporins and persisted beyond the recommended withdrawal times (Cavaco et al. 2008). This finding suggests that the withdrawal times for these drugs, which do not currently take persistence of antibiotic resistance into account, should be reviewed. 'The withdrawal periods for meat animals, in particular those with low- or zero-withdrawal periods such as ceftiofur, should be reviewed in order to ensure that resistant bacteria, as well as antibiotic residues, decline before animals are used for meat or milk.'	The "residues" of resistant bacteria/ resistance determinants is highly unpredictable and we do not believe that this could be addressed with longer withdrawal periods.
Further recommendation to be added The Soil Assoc	'The importation of poultry into the European Union from third countries which permit the use of modern cephalosporins in poultry production should be prohibited.'	The comment will be forwarded to the Commission for consideration.
Further recommendation to be added The Soil Assoc	'Routine surveillance for cephalosporin-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.'	The comment will be forwarded to the Commission for consideration.