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Methodology of setting limits on antibiotic residues in Milk

with a special focus on the issues, evidence/data/agricultural practice

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Statement of Steve Wearne, Director of Policy and Science Group at the UK Food Standards Agency , on 13th Nov 2017

In July 2017 he was elected as Vice Chairman of the Codex Alimentarius Commission.

- Emergence of AMR has become a global threat. Lord O'Neill, in his authoritative report commissioned by the UK Government, says that without action at the global level, by the middle of this century there would be an extra 10 million deaths each year as a result of AMR and it will overtake cancer as the biggest cause of death.
- Both pathogenic and non-pathogenic resistant bacteria can be transmitted from livestock to humans via food consumption, or via direct contact with animals or their waste in the environment.
- Any mechanism that helps spread bacteria has the potential to transfer resistant bacteria.

- Antibiotic residues are remnants of drugs or their active metabolites that are present in the milk from treated animals.
  - It may lead to potential threat of direct toxicity in human
  - At low levels of antibiotic exposure, this would result in possible development of resistant strains which cause failure of antibiotic therapy in clinical situations.
  - May lead to allergic conditions
- Antimicrobials are necessary evil. However, its prudent use is required. Can enter food chain
  - If animals are treated without proper precautions
  - If biological conditions in animals show major deviations from the norm.
- For this reason, many countries have defined legislation on residue levels

- The antibiotics used in veterinary medicines belong to 6 major groups, viz.
  i. Beta-lactams (eg: penicillin),
  ii. Aminoglycosides (eg: gentamycin),
  iii. Tetracyclines (eg: oxytetracycline),
  iv. Macrolides (eg: erythromycin),
  v. Quinolones (eg: fluroquinolone),
  vi. Sulphonamides (eg: trimithropin).
- Any of the drugs belonging to these groups can appear in milk.

Ramesh Kumar Nirala, Kumari Anjana, K.G. Mandal and Jayachandran, C. 2017. Persistence of Antibiotic Residue in Milk under Region of Bihar, India. Int.J.Curr.Microbiol.App.Sci. 6(3): 2296-2299.

- Study on 250 milk samples from 5 districts in Bihar during Jan – April 2015
- HPLC method used for estimation of residues of tetracyclines, sulfonamides and fluoroquinolones [MRL values 100 µg/l].
- A total of five samples for tetracyclin, two for sulfadimidine and one for sulfamethoxazole were found to contain residues above MRL values but no any sample of enrofloxacin and ciprofloxacin were found to concentration above MRL values i.e., 0.1 µg/ml.
- It was found that out of all the milk samples analyzed, eight samples (3.2 %) were found to contain antibiotics residue. Three samples (1.2 %) exceeded the maximum residue levels (MRL), which on pooling would not have any adverse effect on human beings.

NDRI, Bangalore survey in 2000.

- Common drugs used for treatment in dairy animals in the area were tetracyclines, gentamycin, ampicillin, amoxicillin, cloxacillin and penicillin.
- The major drugs used for the treatment of mastitis in the area are beta-lactams alone or in combination with streptomycin.
- There are only a few published data on the occurrence and levels of antibiotic residues in Indian milk samples.
- This could be due to
  i. No laws on antibiotic residues in milk
  ii. the perception that this is not a major problem in processed milk sold by commercial dairies in our country. Contaminated milk gets diluted in bulk supplies.

- Milk producers, dairy cooperatives, personnel involved in processing, marketing and the veterinarians are directly or indirectly responsible to provide the safe milk for the society. Veterinary drugs are extensively used to promote the animal health, control and treat the infection and to step up the production
- Hazards caused by long term exposure of an individual to residues:
  - Public health aspects include carcinogenicity , teratogenicity, Mutagenicity and reproductive effects.
  - Technological aspects e.g. in Cheese, fermented milks

7 elements for appropriate Regulatory framework

- Government's policy regarding its public health objectives applying appropriate science-based measures.
- Guidance documents should be provided on how to put the regulatory framework in place.
- Have resources for conducting food safety assessments and developing regulatory standards for drug residues
- Risk based residue control programs
- Effective surveillance and compliance programs for pharmacovigilance and enforcement of residue limits
- To facilitate residue control programmes, effective analytical methods are required.
- Finally, adequate data and information systems are critical for the assimilation and dissemination of information regarding national and international standards for residues of veterinary drugs.

Generally, developing countries seek assistance for their regulatory frameworks by looking to Codex to incorporate food safety standards into their regulatory frame work, including national legislation

- FSSAI is the main body for establishing the scientific standards for articles of food including milk and milk products and to regulate their manufacture, storage, distribution, sale and import, to ensure availability of safe and wholesome food for human consumption.
- Section 21(1) of FSSA, 2006 specifies that the "food should not contain any insecticides or pesticides residues, veterinary drugs residues, antibiotic residues, solvent residues, pharmacological active substances and micro-biological contaminants in excess of limits prescribed under the regulation"

- FSSAI has published a Draft Regulation which can be finalized any day
- The MRLs for most of the drugs is given as 10 ppb, which are very stringent. Even EU, CODEX or US norms are relaxed, except for unsafe drugs
- We are not sure if any Risk assessment is done before prescribing the MRLs for India. Per capita availability of milk in India is just 337g/day (2015-16), while consumption of milk and milk products is many times higher in the EU or USA, and the MRLs fixed are at much higher levels.
- So the MRLs prescribed definitely need to be reviewed.

FSSAI proposed MRLs and approved MRLs by CODEX, EU, and USFDA

TABLE 1 – Antibiotics used in human beings and animals

Sr. No.	Name of Drug	FSSAI, mg/kg	FSSAI, ppb	CODEX, ppb	EU,ppb	US FDA, ppb
1	Ampicillin	0.01	10		4	10
2	Cloxacillin	0.01	10		30	10
3	Chloramphenicol	0.01	10	Unsafe	Unsafe	Unsafe
4	Dihydrostreptomycin Sulphate (Dihydrostreptomycin)/ Streptomycin	0.01	10	200	200	125
5	Chlortetracyline Hydrochloride	0.01	10	100	100	300
6	Erythromycin Thiocyanate	0.01	10		40	50
7	Flumequine	0.01	10	NA	50	
8	Furazolidone	0.01	10	Unsafe		Unsafe
9	Lincomycin	0.01	10	150	150	
10	Oxytetracycline	0.01	10	100	100	300
11	Salinomycicin	0.01	10			
12	Spectinomycin Hydrochloride (Spectinomycin)	0.01	10	200	200	
13	Sulphadiazine	0.01	10			
14	Sulphathiazole Sodium	0.01	10		100	10
15	Trimethoprim	0.01	10		50	50
16	Cloxacillin	0.01	10		30	10
17	Dicloxacillin	0.01	10		30	NA
18	Sulfadiazine	0.01	10			
19	Sulfanilamide	0.01	10	25 (Sulfadimidine)	100 (Sulfadimidine)	10 (Sulfadimidine)
20	Sulfaguanidine	0.01	10			
21	Zinc Bacitracin (minimum 60IU/mg dried)	0.01	10		100	

FSSAI proposed MRLs and approved MRLs by CODEX, EU, and USFDA

TABLE 2 – Antibiotics for exclusive use in animals

Sr. No.	Name of Drug	FSSAI, mg/kg	FSSAI, ppb	CODEX, ppb	EU,ppb	US FDA, ppb
1	Amprolium Hydrochloride	0.01	10			
2	Apramycin Sulfate	NA				
3	Carbadox	0.01	10	Unsafe		
4	Ceftiofur Sodium (Ceftiofur)	0.1	100	100	100	50
5	CeftiofurHCl (Ceftiofur)	0.1	100			
6	Cephapirine Benzathine interauterine	0.01	10		10	20
7	Clopidol	0.01	10			NA
8	Cloxacillin Benzathine	0.01	10			
9	Colistin Sulphate	0.15	150	50	50	
10	Danofloxacin	NA		NA	30	NA
11	Enrofloxacin	0.01	10		100	
12	Ethopabate	0.01	10			
13	Flavophospholipol (Flavomycin)	0.01	10			
14	Monensin Sodium (Monensin)	0.002	2	2		10 Canada
15	Moxidectin	NA			40	
16	Sulphaquinoxaline	0.01	10			
17	Sulfadimidine Sodium	0.02	20	25	100	10
18	Tilmicosin	NA			50	
19	Tylosin	NA		100	50	50
20	Tyvalosin Tartrate	0.01	10			
21	Virginiamycin	0.01	10			

FSSAI proposed MRLs and approved MRLs by CODEX, EU, and USFDA

TABLE 3 – Other Veterinary drugs

- As per FSSAI : 77 no.
- CODEX : 7 no.
- EU : 30 no.
- USFDA : 3 no.

Comprehensive Antibiotic Residue Surveillance program

- Includes antibiotic Residue monitoring:
- Ampicillin, Chloramphenicol, Furazolidone, Oxytetracycline, Sulphadiazine and Sulphanilamide. All at 10 ppb level
- Violators shall face legal action under the Food Safety & Standards Act 2006
- Top 4 states for Milk production selected for survey : UP, Gujarat, AP, Maharashtra
- Milk will be tested for
  - Penicillins (Amoxicillin)
  - Fluoroquinolones (Ciprofloxacin)
  - Cephalosporins- 1st, 2nd, third and fourth generations
  - Aminoglycosides (Gentamycin)

- Data will be analyzed and the reports will be used for :
  - Establishing MRL regulations and development of risk communication plan that will be shared with the states.
  - Development of mitigation strategies for reducing the risk and same will be shared with the states
  - Checking the compliance with regulation through State Authorities.
  - Mandating the FSMS (GHP, GAP and HACCP) as a risk management tool for reducing the transmission of food pathogens through food chain.

- Indian Dairy Industry does not have any recorded history of the presence of antibiotics and Veterinary drugs in milk from farmers, but a study two years back in our plant showed high level of positives at tanker levels, as follows:

Period 1st Jan 2015 to 31st Dec 2015				
Type of Antibiotic group	MRL, ppb	No. of tankers tested	Samples found Positive	Positive %
Betalactam	5	19102	3389	18
Aminoglycoside	30	833	239	29
Fluroquinolone	10	480	29	6
Tetracycline	25	1212	11	1
Chloramphenicol	0.3	8048	685	9
Sulfonamide	10	834	346	41

Steps To Prevent Antibiotic Residues

- Establish a valid veterinarian-client-patient relation-ship to ensure proper diagnosis and treatment of disease.
- Implement a preventive animal health program
- Implement an effective mastitis management program
- Implement training and awareness of proper drug use.
- Only use approved over-the-counter antibiotics, according to label instructions, and approved prescription antibiotics which have the proper label.
- Use drug residue screening tests specific for the drug utilized before marketing such milk.
- Legislation is the necessary pill.

Methodology for fixing MRLs:

- The (MRL) is defined as the maximum concentration of a residue, resulting from the registered use of a veterinary chemical that is recommended to be legally permitted or recognized as acceptable in a food.
- The MRL is based on the Acceptable Daily Intake (ADI) for a given compound, which is the amount of a substance that can be ingested daily over a life time without appreciable health risk. An acceptable daily intake (ADI) and a maximum residue limit (MRL) for milk should be established for each antimicrobial agent.
- When setting ADIs and MRLs for antibiotics, the safety evaluation is carried out in accordance with international guidelines and should include
  - effects on the human intestinal flora
  - toxicological effect
  - pharmacological effect
- Lack of good veterinary practice and illegal use of veterinary drugs by farmers will increase this problem

- Acceptable daily intake (ADI): An estimate by the Joint FAO/WHO Expert Committee on Food Additives of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.
- Estimated daily intake (EDI): An estimate of dietary exposure to residues of veterinary drugs for use in the evaluation of chronic toxicity and chronic dietary exposure based on a specific model diet and median residue concentrations, adjusted for marker total. In calculating the median from an array of results including values below the limit of quantification or below the limit of detection, half of the respective limit is used for the calculation of median concentrations of residues.

- MRLs are necessary in order that officially recognized control laboratories can monitor that the antibiotics are being used as approved.
- Withdrawal periods should be established for each antibiotic, which make it possible to produce food in compliance with the MRLs.
- The extra-label use of these antimicrobial treatments, insufficient withdrawal period and lack of records are the most common causes of theses residue in milk, which lead to the increase of these residues in milk above the acceptable maximum residue limits (MRLs).

The process involves six key steps:

- Studies of veterinary drugs on metabolism in cows are reviewed
- Similarly metabolism studies conducted in laboratory test animals are also reviewed to ensure that similar patterns of metabolism exist in these animals.
- Toxicity of the substance is determined by toxicity/carcinogenicity (cancer) testing. This information allows VDD scientists to determine the safe quantity of substances that humans can consume each day for a lifetime, without any threat to their health. This quantity is called the Acceptable Daily Intake (ADI).
- Safe concentration for Total Residue Levels (TRLs) are established by ensuring that consumption of milk does not exceed the ADI. A substance that could be used for the purpose of drug analysis, called marker residue, is identified, and a relationship between the marker residue and the TRLs in tissues or food products is established. An MRL is then set for the concentration of the marker residue that will ensure that humans are not exposed to residues above the safe concentrations for the total residues.
- The analytical methodology developed for the marker residue in food is evaluated.
- A withdrawal period is then established based on the residue depletion data for the marker residue by withholding time for milk.

In the U.S.

- The FDA Center for Veterinary Medicine (CVM) is a consumer protection organization is responsible for ensuring that all animal drugs and medicated feeds are safe and effective for their intended uses.

- The CVM Office of New Animal Drug Evaluation (ONADE) has major responsibility to review information submitted by drug sponsors who desire to obtain approval to manufacture and market animal drugs.

- Before a new animal drug receives FDA approval, it must be clinically tested for effectiveness and safety in the target animal. It must also be tested for safety to human consumers, and the edible animal products must be free of unsafe drug residues.

- It is the responsibility of the drug sponsor (the individual or firm seeking FDA approval of the drug product) to conduct all the necessary tests. The product sponsor also must develop analytical methods to detect and measure drug residues in edible animal products.

RISK ASSESSMENT FOR MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS -- CODEX

- Joint FAO/WHO Expert Committee on Food Additives (JECFA) is the Risk accessor who provides expert scientific advice to codex committee
- The scientific advice developed by JECFA aims to provide maximum residue levels for individual animal products, based on the results of scientific studies, so that these levels can be used by the relevant Codex committee to develop the draft MRLs, which may be adopted by the CAC.
- MRLs are set by the CAC, acting as the risk manager.
- The FSSAI draft regulation appears differently

Challenges in controlling AB in India

- Small production holdings
- Shortage of Vety practitioners
- Milk being regular source of income, so reluctant to follow withdrawal period
- Lack of education
- At the farmer level, contamination would be low, but this low number contaminates the whole lot of milk, and thus positives could be high at tanker level.
- Due to scattered and unorganized dairy farming in India, checking at farmer level is very difficult.
- Need for more legislative efforts to regulate use of drugs in the animals.
- Banned drugs should be removed from the market
- Veterinary care and vaccination by Govt. agencies to be implemented rigorously

Possible strategies for prevention of antibacterial residues in Indian scenario

- Well planned drug use program
- Withholding periods after treatment of cows with veterinary drugs should be respected
- Prevent spread of disease by Good hygiene/management practices
- Evaluation and use of alternative treatment
- Pharmacovigilance program for veterinary pharmaceuticals
- Maintaining treatment records of cows in order to determine appropriate withholding periods.
- Follow drug manufacturer's recommendations regarding dosage, route of administration, treatment intervals and storage condition of antimicrobials
- Development and validation of rapid screening tests for detection of AB.

Alternate therapies

- Studies done by NDDB:
  - 22% of total disorders relate to udder ailments
  - Subclinical mastitis treated with oral regimen of TSC resulted in reduction of SCM from 55 to 18%
  - For clinical mastitis, alternative treatment viz local application of herbal paste of Aloe vera, turmeric powder and lime resulted in a recovery of 88% cases
  - NDDB is implementing a mastitis control program in eight states covering about 1500 dairy coops societies.
  - Such good schemes should be available to private sector also
- Use of Bacterins to prevent mastitis, along with good herd management practices, is being done in the USA.

Conclusion

- Establishing regulatory standards and good management practices that reduce the risk of antibiotic residues in milk supply are essential components of human food safety.
- The issue of antibiotic residues in food chain warrants further policies and guidelines to address the possible risk to public health and environment.

Thank You

Schreiber

Dynamix