Review of the draft *Guidelines on compounding of medicines*

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DATE: 30 June 2014

BACKGROUND

The use of compounded veterinary medicines has become a critical and necessary part of modern veterinary practice in all areas other than food animal practice (where compounding has a very limited role, for example, compounding of antidotes for various intoxications encountered in grazing animals). Today it is not possible to provide the standard of care expected by animal owners without the use of compounded veterinary medicines.

Why is this the case?

There are a number of factors that contribute to this important role of compounded medicines.

LARGE NUMBER OF NON-FOOD ANIMAL SPECIES

Across the veterinary profession in Australia there is a need to examine and potentially treat more than 500 species of animal. The diversity of species presented for veterinary examination include domesticated, native, exotic and zoo vertebrate species which comprise mammals, birds, reptiles, amphibians and fish as well as a growing list of invertebrate species.

SMALL MARKET FOR VETERINARY MEDICINE DEVELOPMENT

The breadth of species of veterinary importance necessarily means that the vast majority are minor species and can never expect to enjoy the benefit of medicines developed and approved specifically for them. This is because the absolute number of each species will be small and the likely return on investing in product development will be unattractive to any pharmaceutical company.

LIMITED NUMBER OF PRODUCTS APPROVED BY THE APVMA

The cost of registration of a veterinary medicine can be very high, in the order of tens of millions of dollars for a pioneer product and tens of thousands of dollars for a generic product. Because of the

need to recover the costs of development and registration only the most widely used products are generally developed and submitted to the APVMA for approval.

Currently (30 June 2014) the APVMA database of registered products contains 3,422 products for veterinary use. Of these products, there are 1,013 that are scheduled PRESCRIPTION ANIMAL REMEDY (S4). Amongst the S4 veterinary medicines there are 559 products registered for use in dogs, 311 in cats and 333 in horses.

While this may seem a large number of products, they are all prepared from a total of only 176 active pharmaceutical ingredients (APIs) (see APPENDIX).

There are 148 prescription only (S4) active pharmaceutical ingredients (APIs) contained in products approved by the APVMA for use in dogs. The top twenty most common classes of S4 product approved by APVMA for use in dogs include antibacterials (12 actives, 191 products), NSAIDs (3 actives, 54 products), corticosteroids (3 actives, 41 products), local anaesthetics (1 active, 9 products), ACEIs (1 active, 8 products).

For cats there are 105 prescription only (S4) active pharmaceutical ingredients (APIs) contained in products approved by the APVMA

For horses there are 96 prescription only (S4) active pharmaceutical ingredients (APIs) contained in products approved by the APVMA.

This number of APIs should be considered in the context of how many APIs are considered necessary for the practice of veterinary medicine. The report entitled VETERINARY PHARMACOLOGY CURRICULUM RENEWAL TO IMPROVE GRADUATE OUTCOMES AND PUBLIC SAFETY was published in 2011 by the Australian Government Office for Leaning & Teaching.

Australian Government Office for Leaning & Teaching
http://www.olt.gov.au/resource-library?text=veterinary%20clinical%20pharmacology
http://www.olt.gov.au/system/files/resources/PP9_1340_Mills_Report_2011.pdf
Veterinary pharmacology curriculum renewal to improve graduate outcomes and public safety
Author/s: Paul Mills, Stephen Page, Amanda Craig
Lead Institution: The University of Queensland
Partner Institutions Australian Veterinary Association, Chapter of Veterinary Pharmacology, Charles Sturt University, James Cook University, Massey University (NZ), Murdoch University, The University of Melbourne, The University of Sydney
Published: 2011

The curriculum included a formulary that was compiled from a consolidation of important medicines in veterinary textbooks and veterinary undergraduate teaching at Australian universities. The formulary (which is presented in the project report) identified 1,425 substances, each of which could be included in a variety of formulations. Approximately 1,100 of the substances would be scheduled as Prescription Animal Remedies. Clearly there is a major mismatch between what products are approved by the APVMA for use in veterinary practice and the products that are needed to practice veterinary medicine according to current standards. It is this mismatch, this vast chasm between approved medicines and the unmet need, that presents a significant role for compounded medicines.

To meet the standard of veterinary practice compounded veterinary medicines must be of high quality and for this reason the veterinary profession has a considerable interest in the guidelines on compounding practice and professional practice profile.

There has not been time to prepare a comprehensive response to the two consultations, but a summary of key points is set out below.

RESPONSES TO CONSULTATION QUESTIONS ON THE DRAFT GUIDELINES ON COMPOUNDING OF MEDICINES

Do the draft guidelines clearly differentiate between simple compounding and complex compounding?

YES

Do the draft guidelines clearly outline which requirements apply to pharmacists who undertake either or both types of compounding (simple and/or complex compounding), and which requirements apply only to pharmacists who undertake complex compounding?

YES

Is the content of the draft guidelines helpful?

YES

Is there any content that needs to be changed, added or deleted in the draft guidelines?

YES

Do you have any suggestions for questions to be answered in Frequently Asked Questions developed by the Board to support the guidelines?

YES

Is the purpose of the practice profile clearly explained in the draft guidelines?

YES

Do you have any other comments on the draft guidelines?

<u>Regulatory Status</u>

It is not clearly stated at present in the guidelines that compounded veterinary medicines prepared on instructions from a veterinarian are not subject to the AgVetCode Act as they are not included in the definition of a veterinary chemical product:

Agricultural and Veterinary Chemicals Code Act 1994
Act No. 47 of 1994 as amended
Section 5 Definition of *veterinary chemical product*
Subsection (4) A veterinary chemical product does not include:
(a) a substance or mixture of substances that is:
(i) prepared by a pharmacist in accordance with the instructions of a veterinary surgeon

Therefore compounded veterinary products are not subject to regulation by either the TGA or APVMA.

Veterinary Compounding Guidance

The **Australian pharmaceutical formulary and handbook** is solely focused on human medicines and does not address the special requirements of compounding for non-human species of veterinary interest. It would be invaluable to include in future editions sections specifically on veterinary compounding. The Chapter of Veterinary Pharmacology of the Australia New Zealand College of Veterinary Scientists could assist in this initiative.

Competence to undertake veterinary compounding

Pharmacists need to obtain competence in veterinary compounding from an accredited source relevant to Australian veterinary practice.

Suppliers of training on veterinary compounding and experts and mentors on this subject need also to have met a standard that currently is not described but needs to be co-developed by the pharmacy and veterinary professions.

Unique aspects of formulation in veterinary compounding

Inter- and intra-species differences in pharmacokinetics, pharmacodynamics and toxicology need to be understood by the veterinary prescribed and the compounding pharmacist.

Reputable references

A database of reputable references to support decision making in the appropriateness of compounding needs to be developed.

Counselling of patients

It is unlikely that pharmacists will have the skills or experience to counsel owners of animals to be treated with veterinary medicines. It is preferable in almost all cases that the prescribing veterinarian retains the responsibility for counselling and ensuring that the medicine can be readily administered.

Raw Materials

It is likely that many substances not approved for human use will be included in compounded veterinary medicines.

Quality Standards

The quality standards set out in the Therapeutics Goods Act 1989 may not be applicable to veterinary medicines. Nonetheless, a quality standard is necessary.

Adverse Reactions

For compounded veterinary medicines there is no regulatory agency with an interest to receive and investigate adverse reactions. How this can be best resolved is something that the pharmacy and veterinary professions could discuss.

Reference Texts

A list of recommended reference texts that address the issues of compounded veterinary medicines needs to be developed. Again, the Chapter of Veterinary Pharmacology could assist in developing such a list.

Batch production

The needs of the veterinarian are substantially different from his medical counterpart. In many case veterinarians have patients who may need daily treatment for long periods of time. For example, to treat cardiovascular or endocrine disorders. This may necessitate the provision of sufficient medication for some months, or at least the period of time between reexaminations. This will require the compounding of sufficient medicine for an identified patient, but the medication may be administered over a period of months.

Public consultation on the draft *Professional practice profile for pharmacists undertaking complex compounding*

Responses to consultation questions on the draft *Professional practice profile for pharmacists undertaking complex compounding*

Does the draft practice profile clearly explain its purpose, and how it should be used in relation to complex compounding?

YES

Is there any content that needs to be changed, added or deleted in the draft practice profile in relation to complex compounding?

YES

Do you have any suggestions for questions to be answered in Frequently Asked Questions developed by the Board, to assist pharmacists in using the practice profile for complex compounding?

YES

Do you have any other comments on the draft practice profile?

YES

Because of the importance of the compounded veterinary medicines in veterinary practice and the issues identified above, it is recommended that specific guidance on professional practice be directed at:

Standard 1.5 Maintain and extend professional competence

Standard 4.1 Undertake initial prescription assessment

Standard 4.2 Consider appropriateness of prescribed medicines

Standard 4.3 Dispense prescribed medicines

APPENDIX

PRESCRIPTION ANIMAL REMEDY ACTIVE PHARMACEUTICAL INGREDIENTS IN PRODUCTS APPROVED BY THE APVMA*FOR USE IN CATS, HORSES AND DOGS			
105	**96**	**148**	**176 ACTIVE PHARMACEUTICAL INGREGIENTS**
FEL		CAN	4-AMINO PYRIDINE
FEL	EQU	CAN	ACEPROMAZINE MALEATE
FEL	EQU	CAN	ADRENALINE TARTRATE
		CAN	AGLEPRISTONE
FEL		CAN	ALPHAXALONE
	EQU		ALTRENOGEST
	EQU	CAN	AMBROXOL HYDROCHLORIDE
FEL		CAN	AMINOPHYLLINE
FEL	EQU	CAN	AMOXYCILLIN
		CAN	APOMORPHINE HYDROCHLORIDE
FEL		CAN	ATIPAMEZOLE HYDROCHLORIDE
FEL	EQU	CAN	ATROPINE SULFATE
FEL	EQU	CAN	BACITRACIN ZINC
FEL		CAN	BENAZEPRIL HYDROCHLORIDE
FEL	EQU	CAN	BENZATHINE PENICILLIN
FEL		CAN	BETAMETHASONE VALERATE
	EQU		BOLDENONE UNDECYLENATE
FEL	EQU	CAN	BROMHEXINE HYDROCHLORIDE
	EQU		BUSERELIN ACETATE
FEL			CARBIMAZOLE
FEL	EQU	CAN	CARPROFEN
FEL		CAN	CEFOVECIN AS SODIUM SALT
	EQU	CAN	CEFTIOFUR AS CEFTIOFUR SODIUM
FEL		CAN	CEPHALEXIN AS THE SODIUM SALT
		CAN	CEPHALONIUM DIHYDRATE
FEL		CAN	CHLORAMPHENICOL
FEL	EQU	CAN	CHLORPHENIRAMINE MALEATE
FEL		CAN	CHLORTETRACYCLINE HYDROCHLORIDE
FEL	EQU	CAN	CLAVULANIC ACID AS POTASSIUM CLAVULANATE
	EQU		CLENBUTEROL AS CLENBUTEROL HYDROCHLORIDE
FEL		CAN	CLINDAMYCIN AS CLINDAMYCIN HYDROCHLORIDE
FEL		CAN	CLOMIPRAMINE HYDROCHLORIDE
	EQU		CLOPROSTENOL AS SODIUM
		CAN	CLOTRIMAZOLE
FEL	EQU	CAN	CLOXACILLIN AS THE BENZATHINE SALT
	EQU	CAN	COPPER INDOMETHACIN
FEL		CAN	CYCLOSPORIN A
		CAN	DELMADINONE ACETATE
FEL	EQU	CAN	DEOXYCORTONE PIVALATE
		CAN	DERACOXIB
	EQU	CAN	DESLORELIN AS DESLORELIN ACETATE
	EQU		DETOMIDINE HYDROCHLORIDE
FEL	EQU	CAN	DEXAMETHASONE TRIMETHYLACETATE
		CAN	DEXMEDETOMIDINE HYDROCHLORIDE
FEL		CAN	DEXTROMETHORPHAN HYDROBROMIDE
	EQU	CAN	DIAZEPAM
FEL	EQU	CAN	DI-ISOPROPYLAMINE DICHLOROACETATE

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	EQU	CAN	DIMETHYL SULFOXIDE
	EQU		DINOPROST
	EQU	CAN	DIPYRONE
		CAN	DIRLOTAPIDE
FEL		CAN	DISOPHENOL
	EQU		DOMPERIDONE
FEL	EQU	CAN	DOXAPRAM HYDROCHLORIDE MONOHYDRATE
FEL		CAN	DOXYCYCLINE AS DOXYCYCLINE MONOHYDRATE
	EQU		ELTENAC
		CAN	ENALAPRIL MALEATE
FEL		CAN	ENROFLOXACIN
FEL		CAN	EPHEDRINE HYDROCHLORIDE
FEL	EQU	CAN	ETHYLESTRENOL
		CAN	FIROCOXIB
FEL	EQU	CAN	FLUMETHASONE
	EQU	CAN	FLUNIXIN MEGLUMINE
FEL		CAN	FLUOCINOLONE ACETONIDE
		CAN	FLUOXETINE HYDROCHLORIDE
FEL	EQU	CAN	FRAMYCETIN SULFATE
FEL	EQU	CAN	FRUSEMIDE
FEL		CAN	FUSIDIC ACID
FEL	EQU	CAN	GENTAMICIN SULFATE
FEL	EQU	CAN	GLYCOPYRROLATE
	EQU		GLYCOSAMINOGLYCAN POLYSULFATE
	EQU		GNRF - PROTEIN CONJUGATE
	EQU	CAN	GONADOTROPHIN-CHORIONIC
		CAN	GONADOTROPHIN-SERUM
	EQU		GUAIPHENESIN
FEL	EQU	CAN	HALOTHANE
FEL	EQU	CAN	HYDROCORTISONE AS THE ACETATE
	EQU	CAN	HYDROXY PROGESTERONE HEXANOATE
FEL	EQU	CAN	HYOSCINE-N-BUTYLBROMIDE
FEL		CAN	IBAFLOXACIN
		CAN	IMIDAPRIL HYDROCHLORIDE
FEL		CAN	INSULIN
FEL	EQU	CAN	ISOFLURANE
	EQU		ISOXSUPRINE HYDROCHLORIDE
	EQU	CAN	KETOPROFEN
		CAN	LEVOTHYROXINE SODIUM (AS MULTIHYDRATE)
FEL	EQU	CAN	LIGNOCAINE HYDROCHLORIDE
FEL		CAN	LINCOMYCIN AS LINCOMYCIN HYDROCHLORIDE
FEL		CAN	MARBOFLOXACIN
FEL		CAN	MAROPITANT AS MAROPITANT CITRATE
		CAN	MAVACOXIB
FEL		CAN	MEDETOMIDINE HYDROCHLORIDE
FEL		CAN	MEDROXYPROGESTERONE ACETATE
FEL		CAN	MEGESTROL ACETATE
		CAN	MELARSOMINE DIHYDROCHLORIDE
FEL	EQU	CAN	MELOXICAM
	EQU		MEPIVACAINE HYDROCHLORIDE

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FEL	EQU	CAN	METHANDRIOL DIPROPIONATE
FEL		CAN	METHOCARBAMOL
FEL	EQU	CAN	METHYLPREDNISOLONE ACETATE
FEL		CAN	METOCLOPRAMIDE HYDROCHLORIDE
FEL	EQU	CAN	METRONIDAZOLE
FEL	EQU	CAN	MICONAZOLE PRESENT AS MICONAZOLE NITRATE
		CAN	MOMETASONE FUROATE MONOHYDRATE
		CAN	MOXIDECTIN MICROSPHERES
FEL	EQU	CAN	NANDROLONE LAURATE
FEL	EQU	CAN	NEOMYCIN SULFATE
FEL	EQU	CAN	NITROFURAZONE
FEL		CAN	NORETHANDROLONE
FEL		CAN	NYSTATIN
	EQU	CAN	OESTRADIOL DIPROPIONATE
		CAN	OESTRIOL
	EQU		OMEPRAZOLE
FEL		CAN	ORBIFLOXACIN
FEL	EQU	CAN	OXYTETRACYCLINE HYDROCHLORIDE
FEL	EQU	CAN	OXYTOCIN
	EQU		PENETHAMATE HYDRIODIDE
FEL	EQU	CAN	PENTOBARBITONE SODIUM
	EQU	CAN	PENTOSAN POLYSULFATE SODIUM
	EQU		PERGOLIDE MESYLATE
		CAN	PHENOBARBITONE
	EQU	CAN	PHENYLBUTAZONE
		CAN	PHENYLPROPANOLAMINE HYDROCHLORIDE
FEL		CAN	PHTHALYLSULFATHIAZOLE
		CAN	PIMOBENDAN
FEL	EQU	CAN	POLYMYXIN B SULFATE
		CAN	POTASSIUM BROMIDE
FEL	EQU	CAN	PREDNISOLONE SODIUM SUCCINATE
FEL	EQU	CAN	PRILOCAINE HYDROCHLORIDE
FEL	EQU	CAN	PROCAINE HYDROCHLORIDE
FEL	EQU	CAN	PROCAINE PENICILLIN
FEL	EQU	CAN	PROGESTERONE
FEL		CAN	PROLIGESTONE
	EQU		PROPANTHELINE BROMIDE
		CAN	PROPENTOFYLLINE
FEL		CAN	PROPOFOL
	EQU		RAMIFENAZONE
FEL		CAN	RAMIPRIL
	EQU		RANITIDINE HYDROCHLORIDE
FEL		CAN	RECOMBINANT OMEGA INTERFERON OF FELINE ORIGIN
	EQU		RESERPINE
FEL		CAN	ROBENACOXIB
FEL	EQU	CAN	ROMIFIDINE HYDROCHLORIDE
		CAN	SEVOFLURANE 100%
		CAN	SILVER SULFADIAZINE
	EQU		SODIUM HYALURONATE
	EQU	CAN	SODIUM SALICYLATE

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FEL		CAN	SPECTINOMYCIN AS SPECTINOMYCIN SULFATE
FEL		CAN	SPIRAMYCIN
FEL	EQU	CAN	STANOZOLOL
		CAN	STILBOESTROL
FEL	EQU	CAN	STREPTOMYCIN AS STREPTOMYCIN SULFATE
FEL	EQU	CAN	SULFACETAMIDE SODIUM
FEL	EQU	CAN	SULFADIAZINE
FEL	EQU	CAN	SULFADIMIDINE AS SODIUM ETHANE SULPHONATE SALT
FEL	EQU	CAN	SULFADOXINE
		CAN	TEPOXALIN
FEL	EQU	CAN	TESTOSTERONE PROPIONATE
	F		THIAMAZOLE
FEL			THIAMAZOLE
FEL	EQU	CAN	THIOPENTONE SODIUM
FEL		CAN	THIOSTREPTON
FEL		CAN	THYROXINE SODIUM
FEL		CAN	TILETAMINE HYDROCHLORIDE
	EQU		TILUDRONIC ACID AS DISODIUM TILUDRONATE
		CAN	TOCERANIB
	EQU		TOLAZOLINE AS TOLAZOLINE HYDROCHLORIDE
FEL		CAN	TOLFENAMIC ACID
	EQU		TRANEXAMIC ACID
FEL	EQU	CAN	TRIAMCINOLONE ACETONIDE
		CAN	TRILOSTANE
FEL	EQU	CAN	TRIMETHOPRIM
FEL	EQU	CAN	TRIPELENNAMINE HYDROCHLORIDE
FEL	EQU	CAN	XYLAZINE AS THE HYDROCHLORIDE
FEL		CAN	YOHIMBINE HYDROCHLORIDE
FEL		CAN	ZOLAZEPAM HYDROCHLORIDE
* Approvals obtained from Pubcris 30 June 2014			