Animal Batch Safety Testing

PROPOSAL: AHI proposes that APHIS amend its regulations in title 9 of the Code of Federal Regulations to eliminate requirements for batch safety testing conducted in animals.

The following sections of Title 9 of the Code of Federal Regulations §113 should be deleted from the Code.

9 CFR § 113.100(b) – *General requirements for inactivated bacterial products- Safety Tests*
9 CFR § 113.33 – *Mouse safety test*
9 CFR § 113.38 – *Guinea pig safety test*
9 CFR § 113.39 – *Cat safety test*
9 CFR § 113.40 – *Dog safety test*
9 CFR § 113.41 – *Calf safety test*
9 CFR § 113.44 – *Pig safety test*
9 CFR § 113.45 – *Sheep safety test*
9 CFR § 113.200(d) – *General requirements for killed virus vaccines - Safety tests*
9 CFR § 113.207(a) – *"Wet chick test"*
9 CFR § 113.300(b) – *General requirements for live virus vaccines- Safety tests*

DISCUSSION: Batch safety testing of veterinary biologics consists of administering a product to a set number of animals (often two per batch) and observing for reactions that may signal the batch of product is unsafe for any number of reasons. This method of safety testing is an outdated, highly-variable, non-specific, and insensitive way of ensuring the safety of veterinary biologics. It is estimated that, in a given five-year period, less than 0.1% of US batches are identified as potentially unsafe via these animal tests, while at the same time involving over 345,000 animals and costing manufacturers over $20 million (see included spreadsheet for annual values).

There is widespread support for elimination of animal batch release safety testing among manufacturers, regulators, animal rights activist, and the international community (see additional information on VICH guidelines). The traditional large-scale Field Safety Tests conducted directly in target species prior to licensure, followed by enhanced monitoring of pharmacovigilance data on marketed serials (Docket Number APHIS-2014-0063 VSTA Records and Reports Specific to International Standards for Pharmacovigilance) is a more practical approach. Additionally, manufactures are required to prepare veterinary biologicals within a series of defined parameters to ensure consistent production.

The international community of vaccine regulatory authorities and manufacturers question the validity of animal batch safety testing (ABST). The Veterinary International Cooperation on Harmonization (VICH) is an international organization working to harmonize technical requirements, and APHIS is on the Steering Committee. Two VICH guidelines focus on target animal batch safety testing (GL #50 & GL #55) and state: "*Over the past two decades, the relevance of batch safety tests has been questioned by representatives of regulatory authorities and vaccine manufacturers*." The VICH GL# 50 covers the criteria to waive the requirements for target animal batch safety testing in inactivated vaccines and has been finalized and approved by all VICH participants, including APHIS. The VICH GL# 55 covers live vaccines and has been

approved by the VICH Steering Committee, including APHIS, for public consultation. However, implementation GL# 50 by APHIS via Veterinary Services Memo 800.115 has been in such a manner as to discourage companies from seeking exemptions to the regulations that require target animal batch safety tests. The European Union no longer requires target animal batch safety tests.

Alignment with International Norms

As presented at the May 2018 OIE World Assembly of Delegates, international guidelines are more focused on non-animal testing as a general rule. The OIE's Terrestrial Animal Health Code is targeted for material changes to its ABST guidance, with waivers for such requirements elevated to "routine" granting in the newly revised language. The two VICH guidelines mentioned earlier go into great detail on reducing animal testing in veterinary biologics as previously described.

US regulatory authorities are widely viewed as pragmatic, data-driven, evidence-based entities on the international stage, and modernizing safety testing requirements to more closely mirror those of the rest of the world would further this status. Eliminating the requirements for routine ABST for every veterinary biological serial release would be a good first step in this direction.

Pooled Data Summary Charts from Veterinary Biologics Manufacturers

Animal Batch Safety Test: Animal Usage Figures												
	Animals Used per Annum (est)											Total
	Mice	Guinea Pigs	Sheep	Goats	Cattle/Calves	Dogs	Cats	Swine	Horses	Ferrets	Chickens	
Number of Animal Used	33,427	5,714	30	30	854	872	239	1,084	12	8	26,835	69,105
Cost	$ 561,527	$ 672,206	$ 6,000	$ 5,400	$ 685,619	$ 903,067	$175,256	$ 927,668	-	$ 20,776	$ 235,375	$4,192,894

	Firm 1	Firm 2	Firm 3	Firm 4
Number of Serials Released Per Annum (avg)	-	-	1300	5500
Number of ABST Performed Total (if known)	2800	3000	6492	3700
Number of Serials Identified as Potentially Unsafe due to Animal Batch Safety Testing (total)	7 in 28 years	3 (time frame unknown)	3	0 in past two years
"Success" rate (percentage of batches with potential safety issues identified due to ABST)	0.0025	0.001	0.0005	0.0000

Portions of 9 CFR referenced in Safety Testing Sections

9 CFR Section	Title		Safety Test Section Reference	Title	Date of most recent update
113.66 c 1	*Anthrax Spore Vaccine (Non-encapsulated)*	↔	113.45	*Sheep safety test*	1983
113.67 c 1	*Erysipelothrix Rhusiopathae Vaccine*	↔	113.33 , 113.44	*Mouse safety tests, swine safety test*	2007, 1983
113.68 c 1	*Pasteurella Haemolytica Vaccine, Bovine*	↔	113.41	*Calf safety test*	1974
113.69 c 1	*Pasteurella Multocida Vaccine, Bovine*	↔	113.41	*Calf safety test*	1974
113.100 b	*General requirements for inactivated bacterial products*	↔	113.33 , 113.38	*Mouse safety tests, guinea pig safety tests*	2007, 1974
113.101 b	*Leptospira Pomona Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.102 b	*Leptospira Icterohaemorrhagiae Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.103 b	*Leptospira Canicola Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.104 b	*Leptospira Grippotyphosa Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.105 b	*Leptospira Hardjo Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.106 b	*Clostridium Chavoei Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.107 b	*Clostridium Haemolyticum Bactern*	↔	113.38	*Guinea pig safety tests*	1974
113.108 b	*Clostridium Novyi Bacterin-Toxoid*	↔	113.38	*Guinea pig safety tests*	1974
113.109 b	*Clostridium Sordellii Bacterin-Toxoid*	↔	113.38	*Guinea pig safety tests*	1974
113.110 b	*Clostridium Botulinum Type C Bacterin-Toxoid*	↔	113.33	*Mouse safety tests*	2007
113.111 b	*Clostridium Perfringens Type C Toxoid and Bacterin-Toxoid*	↔	113.33	*Mouse safety tests*	2007
113.112 b	*Clostridium Perfringens Type D Toxoid and Bacterin-Toxoid*	↔	113.33	*Mouse safety tests*	2007
113.113 c 2 ii	*Autogenous biologics*	↔	113.33 , 113.38	*Mouse safety tests, guinea pig safety tests*	2007, 1974
113.114 b	*Tetanus Toxoid*	↔	113.33	*Mouse safety tests*	2007
113.115 b	*Staphylococcus Aureus Bacterin-Toxoid*	↔	113.33	*Mouse safety tests*	2007
113.119 b	*Erysipelothrix Rhusiopathae Bacterin*	↔	113.38	*Guinea pig safety tests*	1974
113.120 b	*Salmonella Typhimurium Bacterin*	↔	113.33	*Mouse safety tests*	2007
113.121 b	*Pateurella Multocida Bacterin*	↔	113.33	*Mouse safety tests*	2007
113.122 b	*Salmonella Choleraesuis Bacterin*	↔	113.33	*Mouse safety tests*	2007
113.123 b	*Salmonella Dublin Bacterin*	↔	113.33	*Mouse safety tests*	2007
113.200 d	*General requirements for killed virus vaccines*	↔	113.33 , 113.38	*Mouse safety tests, guinea pig safety tests*	2007, 1974
113.206 b	*Wart Vaccine, Killed Virus*	↔	113.33 , 113.38	*Mouse safety tests, guinea pig safety tests*	2007, 1975
113.207 a	*Encephalomyelitis Vaccine, Eastern, Western, and Venezuelan, Killed Virus*	↔	"Wet Chick Test" (no CFR reference section)	-	1996
113.209 d 2	*Rabies Vaccine, Killed Virus*	↔	"Intracerebral/intramuscular mice & rabbits test" (no CFR reference section)	-	2010

Portions of 9 CFR referenced in Safety Testing Sections (cont.)

113.300 b	*General requirements for live virus vaccines*	↔	113.33 , 113.39 , 113.40 , 113.41 , 113.44 , 113.45	*Mouse, cat, dog, calf, swine, sheep safety tests*	2007, 1991, 1995, 1974, 1983, 1983
113.301 a	*Ovine Ecthyma Vaccine*	↔	113.38	*Guinea pig safety tests*	1974
113.303 d 1	*Bluetongue Vaccine*	↔	113.33 , 113.45	*Mouse safety tests, sheep safety test*	2007, 1983
113.304 d 1	*Feline Panleukopenia Vaccine*	↔	113.33 , 113.39	*Mouse safety tests, cat safety tests*	2007, 1991
113.308 c 1	*Encephalomyelitis Vaccine, Venezuelan*	↔	113.33	*Mouse safety tests, cat safety tests*	2007, 1991
113.309 d 2	*Bovine Parainfluenza $_3$ Vaccine*	↔	113.33 , 113.41	*Mouse safety tests, calf safety test*	2007, 1974
113.310 d 2	*Bovine Rhinotracheitis Vaccine*	↔	113.33 , 113.41	*Mouse safety tests, calf safety test*	2007, 1975
113.311 d 2	*Bovine Virus Diarrhea Vaccine*	↔	113.33 , 113.41	*Mouse safety tests, calf safety test*	2007, 1976
113.313 d 1	*Measles Vaccine*	↔	113.33 , 113.40	*Mouse safety tests, dog safety tests*	2007, 1995
113.314 d 1	*Feline Calicivirus Vaccine*	↔	113.33 , 113.39	*Mouse safety tests, cat safety tests*	2007, 1991
113.315 d 1	*Feline Rhinotracheitis Vaccine*	↔	113.33 , 113.39	*Mouse safety tests, cat safety tests*	2007, 1991
113.409 b	*Tuberculin- PPD Bovis, Intradermic*	↔	113.38	*Guinea pig safety tests*	1974
113.450 i	*General requirements for antibody products*	↔	113.33	*Mouse safety tests*	2007