CANADIAN ANIMAL HEALTH INSTITUTE FEEDBACK

FEE PROPOSAL FOR DRUGS - CONSULTATION

Introduction

The Canadian Animal Health Institute (CAHI) appreciates the opportunity to provide feedback on the service fees proposed for veterinary drugs. The Service Fee Act was introduced as part of an Omnibus Budget 2017 bill and in the Institute's opinion did not get the parliamentary scrutiny it needed, particularly as it relates to public/private good and competitiveness. The fact that the fees can now be increased by Ministerial Order outside of the Canada Gazette I and II consultative process is disconcerting for veterinary drug manufacturers which serves a small market but make an important contribution to Canadian public health and animal welfare.

Our analysis of the proposed service fees for veterinary drug review and maintenance bring us to the conclusion that should this proposal come to be implemented, as is, sales for 58% of the current livestock products will not support a new registration, while 52% of companion animal product sales will not support introduction to the Canadian market. If innovation costs of 5% of the total R&D costs are included in the calculation, 79% of the livestock products (74% for companion animal) fall below the financial threshold to support product registration and launch in Canada (Appendix 1).

Consequently, we will lose products currently licensed for the Canadian market and many new products will never seek marketing authorization in this country. The new fees will effectively undermine all current initiatives put in place to ensure responsible or prudent use of veterinary drugs, particularly medically important antimicrobials (MIA), as veterinarians and producers will look to manage animal welfare in the absence of licensed product. It will also undermine research and development into alternatives to antimicrobials, a pillar of the Federal Government's '*Antimicrobial Use and Resistance Framework*' document as well as the Federal Government's *Plant and Animal Health Strategy* targeting animal disease management.

Increased compounding of veterinary drugs, illegal importation and use of unapproved animal medications will require restructuring of Canada's veterinary drug programs. This is due to fewer resources being needed to manage the reduced submissions submitted, while greater compliance and enforcement measures will need to be taken to manage the increased risk of non-compliant veterinary drug use. Furthermore, our veterinarians and food animal producers will not have access to the same health management tools as those in other countries that we compete with, resulting in global competitiveness, market access and trade implications.

CAHI is not opposed to paying service fees but does believe that the fees should be relative to the services provided, the market size and public good provided by veterinary drugs. The following outlines our thoughts in these three areas and the Fee Proposal itself.

Regulatory Performance Standard Competitiveness

Further to the fee proposal presented, it needs to be known that the Veterinary Drugs Directorate (VDD) did not update its fees in 2011 along with the human drugs and medical devices largely because it was in a state of rebuilding its services to meet international regulatory performance standards. Serious management issues consumed the VDD for over a decade to the detriment of the veterinary drug review process and competitiveness of Canadian animal health manufacturers. A regulatory benchmarking survey done by the International Federation for Animal Health (now operating as HealthforAnimals) in 1999 found VDD regulatory performance lagged behind other developed countries including the EU, USA, Australia, New Zealand and Japan. Ultimately the most serious consequence of this situation was that Canadian animal owners did not have timely access to the health management tools their counterparts had in other countries.

Without access to new medicines, veterinarians were also unable to deliver modern veterinary services to their patients. In fact, in the late 1990's it was recognized that licensure of Canadian veterinary drugs lagged by about 7 years from that of the USA. Significant improvements needed to be made and it is only in the last few years that VDD has been able to provide competitive regulatory services for Canadians.

Market Size

The Canadian animal health business is only 2.5% of the global animal health market. The human pharmaceutical industry in Canada which benefits from socialized medicine is a 35 times larger market than the Canadian animal health market. From a transnational corporation perspective, animal health in Canada is considered a lower tier commercial market. Therefore, Canada at 10% of the sales of the USA, has a lower return on investment and is therefore a lower priority for registration. Drug innovation costs are $29 million and $39 million Canadian for companion and livestock drugs, respectively, and the return on investment is not realized for 3 – 7 years. For Health Canada to calculate the service fees based on program, corporate and capital costs without consideration of the market size and benefit to society makes no sense. It becomes a budgeting exercise that will stymie innovation and negatively impact the availability of safe and effective animal health products in the Canadian market. A consequence of this situation will be the introduction of greater risks to Canadians due to use of unlicensed animal drugs. As noted previously, increased pressures on Health Canada compliance and enforcement costs will be a consequence.

With Canada being only a small player in the overall global animal health market, it is estimated that any approved "blockbuster" drugs presently sold in the Canadian veterinary market would represent only 2-4% of the industry's current approved drug portfolio with over 50% of this portfolio falling into sales of

less than $500,000 annually. The proposed fees will make justifying a Canadian registration next to impossible when registration and maintenance fees surpass yearly sales. Niche products are likely to disappear from the market and alternative products not come to the market due to the inability to justify high regulatory costs with the small Canadian market size.

Public Good of the Veterinary Drug Program

Registration of animal drugs is a benefit to both animal health companies and to our public. Our pets are important household members providing emotional stability and health benefits to their owners. Animal health products contribute to the welfare of our food and companion animals and to food safety in the case of production animal drugs. Keeping our animals healthy is also critical to keeping people healthy. According to the American Centers for Disease Control and Prevention "*Scientists estimate that more than 6 out of every 10 known infectious diseases in people are spread from animals, and 3 out of every 4 new or emerging infectious diseases in people are spread from animals. Every year, tens of thousands of Americans will get sick from harmful germs spread between animals and people."*[i] How can we not recognize our public and animal patients as beneficiaries of animal medications?

The government of Canada is implementing new measures to ensure responsible or prudent use of medically important antimicrobials used in veterinary medicine. This action is a part of the stewardship pillar of the Federal Government's '*Framework on Antimicrobial Use and Resistance*'. Lack of accessibility to licensed veterinary drugs will undermine this initiative as animal owners and veterinarians seek options to manage animal welfare using compounded and other unlicensed products. Furthermore, the Federal Plant and Animal Health Strategy will be challenged to meet its goals to manage animal diseases without access to the same health management tools as those used in other developed countries that food animal producers compete with.

The take home points from the above comments are:

- Veterinary drug regulatory services need to meet equivalent regulatory performance standards to that of other developed countries;
- Veterinary drug service fees in Canada need to reflect market size if they are indeed to be a benefit to the manufacturer and not a barrier to availability of animal drugs; and
- The veterinary drug service fees need to account for the benefit Canadian food and companion animal owners and our public receive in having access to health management tools that ensure animal welfare and in the case of production animals, food safety.

To meet these three points CAHI agrees that veterinary drug service fees must be revisited and modernized; however, consideration must also be given to ensure Canadian veterinarians and animal owners have access to the same health management tools as their counterparts in other countries. This is particularly true for food animal producers who are competing in global markets. As an example, Appendix 1 identifies issues relating to Post-NOC changes in accessibility and pricing of animal drugs in

Canada relative to other markets. Additionally, the current fees don't take into account the reduced burden when a review is shared with another competent foreign agency which should reduce costs. Canadian veterinarians need access to new medications so they can deliver modern veterinary services to their patients.

Without modernization of the veterinary drug fee structure and without it reflecting market size the following will be impacted:

- There will be little incentive for companies to participate in collaborative evaluations or joint reviews;
- There will be no incentive for companies to submit products for minor use and minor species (MUMS), compatibility, or niche markets;
- Veterinarians will increasingly be required to prescribe drugs Extra-Label since manufacturers will not look to expand label claims due to high regulatory costs;
- There will be increased compounding of veterinary drugs to meet animal welfare needs in the absence of licensed products, which will increase risk, veterinarian liability and further erode the competitiveness of license holders with that of compounding manufacturers (as outlined in Appendix 2);
- Enforcement and compliance resources will subsequently need to be increased as an illicit market grows to meet animal owner needs; and
- There will be increased emergency drug release (EDR) requests resulting in the generic registration path not being available, thus having negative unintended consequences on veterinary drug pricing and availability as well as increasing product costs to the animal owner through having to use the EDR process.

The above impacts will compromise Canada's ability to manage animal welfare and food safety

Health Canada needs to rethink its delivery of the veterinary drug program

What do we propose?

1. **The following are specific CAHI comments and recommendations on the Summary – pages 4 - 5:**

   - **Fee setting ratio** – There is a lack of recognition of public good in establishing veterinary drug service fees. Where is the logic in the animal health industry having its cost setting ratios being the same as that of the human side? The cost of registering a human drug (highest is $600 thousand if a new active, otherwise around $300 thousand) which will be very similar to a new food animal. The human drug industry also does not have to service multiple species/subspecies which subsequently increase registration costs. Human medicine is socialized and is 35 times the market size of animal health and can only lead one to believe the costing process used for setting the proposed veterinary drugs service fees is flawed.

- **Annual Adjustment** – We concur with the proposed CPI adjustment annually.

- **Fee Mitigation** – The one time only for submissions over $10,000 for a small business having a product reviewed the first time is not of great benefit. Costs for review could exceed $237,250 (production animal) and $128,300 (companion animal) so a $10,000 break is meaningless. The current fee reduction request (registration) and fee remission (DEL) should be maintained as it remains a greater incentive in continuing to bring new technologies/products to the marketplace, including niche products.

- **Penalty Provision** – We agree with the proposal for the 25% rebate of fees assessed if the regulatory performance standards are not met. However, there needs to be a clear definition of what type of missing information constitutes a Minor Information Request versus a Notice of Deficiency which stops the clock. It is also important that the principles outlined in the VDD Guidance for Industry: "*Management of Regulatory Submissions (MoRS)*" remain consistent related to MIR responses (15 days).

  A robust appeal process however, must also exist for companies to question performance should a disagreement arise.

- **Non-Payment of Fees** – We concur with this proposal.

- **Annual Fee Updating** – This process needs to be transparent and reflective of the market size and public good as discussed earlier.

- **Veterinary Drug Evaluation Fees** – The fee categories need to be modernized, additional fee categories added and incentives built in for MUMS and Regulatory Cooperation Council (RCC) submission reviews. As well VDD should not be able to charge fees in the absence of updated guidance to facilitate quality submissions. As stated previously, the fee reduction request needs to be maintained.

- **Veterinary Drug DEL fees** – We concur in principle with the proposed streamlining of the base fee but question charging the same amounts for human and veterinary establishments. This is particularly the case when compliance and enforcement of non-compliant veterinary products (including compounded product) is given low priority. As stated previously, the fee remission option should remain for veterinary DEL service fees.

- **Timing of Payment of Fees** – As CAHI understands the process, if a submission is rejected at screening, the company would only be charged 10% of the fees; if accepted for review, then an invoice would be issued for the full amount, regardless of the final decision. We do note,

however, the strain this will put on company budgets when in 2019 they would be paying for not only finishing 50% payments of submissions accepted into the review stream but also be paying full upfront fees for new submissions which would not be approved until 2020.

- **Fee Payers** – We do agree that veterinarians and pharmacists should be assessed DEL fees. However, for the animal health industry, we need to exempt atypical or old drug actives from the DEL fees for API sites as this will result in significant product removal from the Canadian market. We do not believe the proposed service fees are aligned with other jurisdictions without consideration of atypical and old drug actives. Listed atypical API should not be subject to DEL fees if GMP requirements are not the same.

- **Performance Standards** – The only performance standard improving in this proposal is the posting of the Right-to-Sell information to the Drug Product Database. This is irrelevant to a stakeholder and is a Health Canada housekeeping issue. Most important for both the human and veterinary drug industries is for triage/processing changes at the DEL unit to improve on the 250-day performance standard for DEL licence issuance and renewal, and addition of foreign sites. This standard remains unchanged in the proposal. Particularly for foreign sites that may be used by multiple companies, the complete de novo review of the site at each application is not value added. The long timelines and purported lack of resources in this program are due to inefficiencies in the process and will not be "fixed" by fee changes.

- **Performance Reporting** – We concur with what is proposed.

2. Other Comments on the Document:

- **Pg 7 Private Benefit** – The 90% benefit for market access for a new veterinary drug is not realistic in a market that is only 2.5% of the global animal health market. The public benefit of having safe, quality animal drugs available in the Canadian market is critical to human safety, food safety, and animal health and welfare. Trade is also important in the case of production animals who compete globally. Quantification of public and private good for the services provided by Health Canada is challenging however we propose that this topic be integrated into the fees proposal consultation.

- **Pg 7 International Comparison – Australia –** CAHI chose to compare our proposed fees to that of Australia because its tax base of 24.13 million people is more closely aligned to our nation's population of 36.29 million. The USA has a population of 323.1 million which is almost 10 times the size of Canada's. Australia also has yearly sales of animal health products similar to that of Canada. We did not consider the EU to be an appropriate comparator because of their centralized and decentralized veterinary drug programs.

We are also aware that Australia charges a levy on annual sales for approved products; however, considering the difference in regulatory fees between Australia and what is proposed for veterinary products in Canada, the levy would equate to 10-15 years of sales to account for the proposed Canadian filing fees.

- **Pg 8 & 9 Mitigation** – As mentioned earlier we do not believe the proposed one time only fee mitigation for submissions with costs over $10,000 to be meaningful. We believe the submission fee reduction request and the DEL fee remission requests should remain available.

- **Pg 10 Collaborative Evaluations/Joint Reviews –** CAHI concurs with the points made about having flexible performance standards for these types of reviews. Incentives need to be built into the fee structure for these types of reviews if we are going to encourage collaborative and joint reviews.

- **Pg 16 Veterinary Drugs Evaluations (Vet Eval) –** A notification fee for new Veterinary Health Products is expected and should reflect notification services provided. There is no mention of a fee for the safety review of admissible substances that can be used in a notified product nor a performance standard associated. This area needs to be reconsidered.

- **Pg 17 Veterinary Drugs Establishment Licensing** – There are major differences in the structure of Canada's human health system whereby human medicine is socialized and animal medicine is not. Canadian human drugs have a sales volume of around $25 billion: sales of animal pharmaceuticals are estimated at $700 million. These market forces provide a good economic reason for reducing the fees charged to the animal health industry to reflect market size and benefit to the drug establishment holder. Charging the same fees to these regulated establishments is not justified based on this, nor the product risk to human health.

3. Comparison of Proposed Veterinary Drug Service Fees Canada with that of Australia (Appendix 3 and 4)

Attached are analyses we have done of the veterinary drugs review and DEL process for selected submission types. Generally, Canada is proposing to charge significantly more fees than Australia which is of a similar market size to Canada.

As mentioned above we are aware that Australia charges a levy on annual sales for approved products; however, considering the difference in regulatory fees between Australia and what is proposed for veterinary products in Canada, the levy would account for 10 – 15 years of sales to equate to the Canadian filing fee.

Canada is asking for a significant up front regulatory investment on top of the product development

investment companies already make before having a return on investment. This situation will negatively impact both products coming into, and staying on, the Canadian market. We anticipate fewer new products, supplementary new drug submissions, MUMS and RCC submissions based on the proposed fee structure. The high veterinary drug service fees being paid in advance of a return on investment and without accounting for its market size do not make good business sense and will result in reduced investment in veterinary drug products. Similarly, they do not make good business sense for Health Canada and Canadians when resources will need to be directed to a consequential higher risk and illicit market due to illegal importation and compounding of veterinary drugs to meet animal welfare needs.

CONCLUSIONS

Health Canada needs to rethink its delivery of the veterinary drug program

What do we propose?

- Recognition of the veterinary drug regulatory work of other competent agencies. A strong case can be made for accepting the reviews of competent foreign agencies such as the USA Food and Drug Administration (FDA), which we have gained confidence in through the Regulatory Cooperation Council (RCC) work. Canada should exploit the good work of the FDA Center for Veterinary Medicine and accept the reviews it does relative to human safety, companion animal clinical efficacy, manufacturing and, where appropriate, clinical efficacy for production animals. We must be sure that our regulatory services add value. Repeating a review done by another competent agency does not add significant value to Canadians. Elimination of duplicate services to that of other competent agencies would help to facilitate a downward adjustment to fees that would be more in line with the Canadian market.

- The current DEL fees presented are not transparent when reported as an average. We believe the fees are too high for veterinary drugs and lack balance based on risk of activity performed (e.g. *A fee for a non-sterile fabricator is slightly less than for an importer; significantly reduced fee for packager/labeller activity*). We question the rationale of having the same fees for human and animal drugs particularly when compliance and enforcement activities for veterinary products (including compounding) is not given a similar priority and currently issued DEL's are putting the limitation of "veterinary drugs only" when issued.

- Veterinary drug regulatory service fees proposed should not be aiming for 90% cost recovery since it does not recognize the social benefit of these products or market size. The Canadian animal health product regulatory program must be conducive to registration of new products if we are to be able to maintain animal welfare and human safety. The regulatory program in Canada has significantly improved performance standards which has made it a favourable

market; however, the proposed fees will be a barrier and will negatively affect the improvements made.

- Phase-in of increased fees over a two-year period in an industry this small will have a detrimental effect on bringing new products to the Canadian market. The generic pathway will also be compromised leaving concerns with pricing and availability of drugs.

- At this time to ensure a win-win solution for the veterinary drug program, manufacturers, veterinarians, animal owners and the Canadian public we would propose the following:

    - That the veterinary fee schedule be modernized, inclusive of current guidance, to incentivize availability of licensed products in a small market. This is particularly important for supplementary submissions, potential RCC reviews, niche products and MUMS products.

    - An initial compounded increase of 2% be implemented for veterinary drug service fees to reflect the fact that no increases were made in 2011 followed by annual CPI increases thereafter.

Appendix 1: ANALYSIS OF THE CURRENT CANADA DIN PORTFOLIO AND THE POTENTIAL IMPACT TO NEW DRUG REGISTRATION AND LIFE CYCLE MANAGEMENT

Appendix 2: POST NOC QUALITY DOCUMENT- CHANGES HAT CHALLENGE VETERINARY DRUG MARKET ACCESS FOR CANADA

Appendix 3: COMPETITIVENESS OF LICENSED VERSUS COMPOUNDED VETERINARY DRUGS RELATIVE TO THE NEW SERVICE FEE PROPOSAL

Appendix 4: COMPARISON OF SERVICE FEES FOR REGULATORY REVIEW OF VETERINARY DRUGS – CANADA: AUSTRALIA

Appendix 5: COMPARISON OF SERVICE FEES FOR DRUG ESTABLISHMENT LICENSING OF VETERINARY DRUGS CANADA: AUSTRALIA

[i] https://www.cdc.gov/onehealth/basics/zoonotic-diseases.html

APPENDIX 1: ANALYSIS OF THE CURRENT CANADIAN VETERINARY DIN PORTFOLIO AND THE POTENTIAL IMPACT TO NEW DRUG REGISTRATION AND LIFE CYCLE MANAGEMENT

The potential impact to the proposed fee increases was assessed using 2016 full year sales data as recorded by Impact Vet. Analysis of 676 Canadian veterinary DIN products that have 2016 sales of greater than $15k was completed to demonstrate the percentage of products that will support initial registration and regulatory maintenance using the proposed fee structure.

Sales for 58% of the current livestock (production animal) products will not support a new registration, while 52% of companion animal product sales will not support introduction to the Canadian market. If innovation costs of 5% of the total R&D costs are included in the calculation, 79% of the livestock products (74% for companion animal) fall below the financial threshold to support product registration and launch in Canada.

Evaluation of the impact on maintenance and product life-cycle management demonstrates that sales for 40% of the current products in Canada will not support additions of new claims and annual licensing fees.

Species	File Type	Product Description	Third year sales to cover new reg fees	% of products in Canada that are below sales threshold (Impact Vet Data)	Third year sales to cover reg fees and R&D costs	% of products in Canada that are below sales threshold (Impact Vet Data)
Livestock	NDS	Livestock WO MFA Launch	250k	58%	640k	79%
		MFA Launch		21%		31%
Livestock	SNDS & NC	Lifestock WO MFA Maintain	136k	40%	186k	50%
		MFA Maintain		14%		17%
Companion	NDS and NC	Prescription, Parasiticide	199k	52%	589k	74%

Assumptions for the Return on Investment Assessment:

- 676 pharmaceutical products commercialized in Canada were evaluated, with 234 products with sales of less than $15k excluded from the analysis. The products included in the analysis were confirmed to be DIN products listed in the Compendium of Veterinary Products.

- Canadian sales are 5% of the global total so this percentage was applied to expected return on innovation investment.
- The registration fee return on investment was spread over a 3 year period, and based on full third year sales to cover one third of the registration and annual fees.
- Innovation costs were based on the USA Animal Health Institute's industry average.
- Current registered products utilize compendial grade active ingredients.
- Existing products will have two product changes per year and use non-compendial grade active ingredients.
- Product margin for a new product is expected to be above 60% to support a launch. Older products may have lower margins, but the goal is greater than 50%.

Three product registration activities were analyzed: 1 – Livestock product registration; 2 – Livestock product change (new claim or manufacturing site change); and, 3 – Companion Animal Product Launch.

Example 1: Registration of New Livestock Product

Registration Fees: 139 + 174 + 29 = CA$342,000

Annual Maintenance Fee Estimate = CA$36,000

5% of R&D Estimate for Canada = CA$1.95 Million spread over 5 years for ROI = $390,000

Margin 60% (for new product)

Sales needed in year 3 = [$342 + ($36 x3)] / (3 x 60%)] + $390 **= $640k**

If no R&D costs are to be recouped: [$342 + (36x3)] / (3 x 60%) = $250k

Example 2: to Maintain a Livestock Product

Registration Fees for Addition of new Claim = CA$96,000

Annual Maintenance Fees = CA$36,000

5% R&D for Canada, $250,000 for new claim = $50k per year, over 5 years

Margin 50% for an existing product.

Ongoing sales needed (calculated 3 years out for claim) = [$96k + ($36 x 3)] / (3 x50%)] + $50k = **$186k**

Example 3 Launching a Companion Animal Product

Registration Fees: 96 + 174 + 29 = CA$299,000

Annual Maintenance Fee Estimate = CA$20,000

5% of R&D Estimate for Canada = CA$1.95 Million spread over 5 years for ROI = $390,000

Margin 60% (for new product)

Sales needed in year 3 = [$299 + ($20 x3)] / (3 x 60%)] + $390k **= $589k**

If no R&D costs are to be recouped: [$299 + ($20 x3)] / (3 x 60%)] **= $199k**

APPENDIX 2: POST NOC QUALITY DOCUMENT- CHANGES THAT CHALLENGE VETERINARY DRUG MARKET ACCESS FOR CANADA

*NOTE: This document is not an all-inclusive comparison and is being provided with this submission to highlight currently identified major inconsistencies in the Post-NOC Quality guidance that affect market access for veterinary drugs.

Changes to Drug Substance (DS) manufacturing site (Change Nr 2): The need for DS site changes will be driven by the economics of Regulation (GMP, addition to DEL) and inspection (data integrity) and many suppliers will be dropping out of supplying API for finished veterinary drug products. Each DS site addition triggers a DEL fee but also, due to VDD policies, additional charges that would not necessarily apply in other jurisdictions.

Filing revisions for DS is a challenge for products with DS that were registered in the past. As we move to make the file compliant by adding the manufacturing information, or if we want to add a new manufacturing site we run into extensive document requirements. In the past, DS were registered with minimal data since they were listed in Schedule B publications (i.e. USP, BP Vet, EP) DS synthesis is often proprietary manufacturing company property and if a Master File is not available for these sites registered decades ago companies don't have this information for previously registered suppliers. Consequently, registering a new DS supplier is automatically a Supplemental Change and challenges supply.

Changes to Drug Product (DP) manufacturing site (Change Nr 27): Cost recovery registration and DEL fees will increase the rationalization of manufacturing sites with consolidation to fewer sites to keep fees lower.

In support of a manufacturing site change, a validation report for 3 commercial size batches is required for Canada. This is unique to Canada as both the USA and EU can file with 1 executed commercial lot and a protocol and execute validation after approval. Why does VDD place validation as high risk for Canada when the GMP's require industry to meet the 3 lot validation requirement prior to commercialization? It would be ideal and in line with RCC if Canada would accept 1 executed full scale commercial lot at time of filing like the USA. If we must wait for the execution of 3 lots to file, we are put in line with countries that do not have a well-developed regulatory framework. In addition, there is a financial impact to the sponsor to execute 3 lots prior to submission. Three lots of drug product at a commercial scale could have value of over $1 million and may not have shelf-life to support commercialization at time of approval if packaged specifically for Canada.

Changes to Closure System for Sterile Products (Change Nr 40): changes such as these would be occurring downstream of site changes.

All changes for sterile products are shifting to supplements. This is challenging supply of animal drugs to the Canadian market as the USA gains approvals in a much faster timeframe. Also, the USA process does not charge a fee unless a Supplemental Application (ANADA or NADA) is required.

If there are no changes to materials and suitability data are available (e.g., extractable/leachable testing, permeation testing) would VDD consider changing this to an NC. This allows for review but aligns the time more closely to the USA CBE path?

Change or addition of a Test Site (Stability or Release) (Change Nr 27): site rationalization will again result in consolidation of testing sites in order to keep fees lower.

Addition of a test location falls under GMP oversight and we must add each test site to the DEL and have agreements in place. The USA does not require that test sites be registered within a product dossier. The Post NOC Human DS and DP Test site requirement is a Level IV Annual Notification. With all of the DEL revisions, why does VDD mandate a Pre-Approval NC for addition of a test site for both DS (Change 2) and DP (change 27)? Compliance to the DEL and GMP requirements ensure adding a new test site is low risk as aligned with the human path. Now that Vet API will require GMP and DEL listing, the risk aligns with the human DS and DP test site change risk and should be considered for the AN path.

APPENDIX 3: COMPETITIVENESS OF LICENSED VERSUS COMPOUNDED VETERINARY DRUGS RELATIVE TO THE NEW SERVICE FEE PROPOSAL

The proposed fee increases promote the competitive advantage of compounded veterinary drugs over Health Canada licenced innovator and generic veterinary drugs.

The recent veterinary drug updates to the *Food and Drug Regulations* with respect to antimicrobial resistance finally introduced the requirement for veterinarians or pharmacists importing antimicrobials for compounding to hold a Drug Establishment Licence and report quantities of API imported to Canada. While this requirement was a first step to bringing manufacturing under the guise of compounding to an appropriate level of regulatory oversight, the proposed user fees further advantage compounders in the veterinary drug market place.

Please note that we are not discussing compounding in the sense of preparing a small amount of customized drug product for a single patient or a small group of patients. Our concern is compounding as unlicensed manufacturing for food animals, examples we are presently aware of would include:

- Colistin sulfate powder (colistin sulfate has never been licenced for administration to food animals in Canada)
- "Florfenicol" soluble powder (was actually chloramphenicol according to laboratory tests)
- Trimethoprim Sulfadiazine powder ("compounded" in Quebec, sold in Manitoba)
- Lincomycin soluble powder (exact copy of licenced pioneer and generic)
- Tetracycline HCl soluble powder (sold to dairy farmers without instructions for use)

Why does the ability to "compound" provide such a large competitive advantage? An example of a common regulatory maintenance activity required of DIN holders quantifies that advantage:

Change of API Manufacturer

The change of and API manufacturer is one of the most common regulatory activities in veterinary drugs today.

Supplier changes are driven by:

- Regulatory activities: regulatory activities causing supplier changes ranging from GMP non-compliance on inspection by advanced economy regulatory authorities (EU, USA FDA) to environmental permitting issues in the supplier's home country are forcing changes in the supplier base.

- Economics: increasing restrictions on use of some APIs in major markets are causing some suppliers to abandon products as uneconomic.

- Demands for additional characterization of APIs: VDD (and other regulators) demand up to date characterization of APIs and their impurities. The additional testing activities to develop a DMF are causing some suppliers to abandon products as uneconomic.

The need to maintain licensable suppliers will lead to very different expenditures for licenced and unlicensed manufacturers.

APPENDIX 3: COMPETITIVENESS OF LICENSED VERSUS COMPOUNDED VETERINARY DRUGS RELATIVE TO THE NEW SERVICE FEE PROPOSAL

i. Change in Compendial API Supplier (non-sterile) as of April 01, 2019

Fees to Make the Change	**Compounder**	**Manufacturer**
Add new supplier to DEL (foreign site)	$900.00	$900.00
Chemistry & manufacturing for 1 dosage form	$0.00	$24,200.00
Continuing Fees to Market Licenced Product	**Compounder**	**Manufacturer**
Drug Right to Sell	$0.00	$4,587.00
Total Fees to Maintain Product in Compliance with HC	**Compounder**	**Manufacturer**
	$900.00	***$29,687.00***
Internal Costs to Make the Change	**Compounder**	**Manufacturer**
API cost – 3 lots + testing	Not required	$15,000.00
Process Validation – 3 lots manufacturing and testing	Not required	$30,000.00
Stability Study – 2 VICH conditions – 3 lots for 24 months	Not required	$15,000.00
Low temperature (freezing) stability	Not required	$2000*
Submission Preparation & report costs	Not required	$5000.00
Total Internal Costs	**Compounder**	**Manufacturer**
	$0	***$67,000.00***
Total Cost to keep product on the market	**Compounder**	**Manufacturer**
	$900	***$96,687.00***

* VDD frequently asks for "Do Not Freeze", even on labels of solid dosage forms if data not submitted.

ii. Change in Non-Compendial API Supplier (non-sterile) as of April 01, 2019

Fees to Make the Change	**Compounder**	**Manufacturer**
Add new supplier to DEL (foreign site	$900	$900
Chemistry & manufacturing for change in source of non-compendial medicinal ingredient or its manufacturing process.	$0	$24,200
Chemistry & manufacturing for 1 dosage form		$24,200
Continuing Fees to Market Licenced Product	**Compounder**	**Manufacturer**
Drug Right to Sell		$4,587
Total Fees to Maintain Product in Compliance with HC	**Compounder**	**Manufacturer**
	$900	***$53,887***
Internal Costs to Make the Change	**Compounder**	**Manufacturer**
API cost – 3 lots + testing	Not required	$15,000.00
Process Validation – 3 lots manufacturing and testing	Not required	$30,000.00
Stability Study – 2 VICH conditions – 3 lots for 24 months	Not required	$15,000.00
Low temperature (freezing) stability	Not required	$2000*
Submission Preparation & report costs	Not required	$5000.00
Total Internal Costs	**Compounder**	**Manufacturer**
	$0	***$67,000.00***
Total Cost to keep product on the market	**Compounder**	**Manufacturer**
	$900	***$120,887.00***

APPENDIX 4: COMPARISON OF SERVICE FEES FOR REGULATORY REVIEW OF VETERINARY DRUGS – CANADA: AUSTRALIA

	Canadian Category Description	VDD Current	VDD - Year 1	APVMA (40% CR)	Comments
1	Novel non-compendial API (never approved); 1 claim; 1 dosage form; 1 species (companion animal)	**$25,660** (MCED: 4840+4840; CED: 15980)	**$128,300** (MCED: 24200 + 24200; CED: 79900)	**AU$39,950** (Item 2 application with modules 1, 2.1, 3.2, 4, 6.2, 7.3, 8.1, 11.2, 12)	
2	As #1 but for food-producing animal (using lowest HSD category)	**$47,450** (MCED: 4840+4840; CED: 15980; HSD 21790)	**$237,250** (MCED: 24200 + 24200; CED: 79900; HSD 108950)	**AU$94,915** (Item 2 application with modules 1, 2.1, 3.1, 4, 5.1, 6.2, 7.1, 8.1, 11.1, 12)	
3	Well-known compendial API; 1 claim; 1 dosage form; 1 species (companion animal)	**$20,820** (MCED: 4840; CED: 15980)	**$104,100** (MCED: 24200; CED: 79900)	**AU$8,425** Item 10 application with modules 1, 2.3, 8.2, 11.2, 12 + Item 17 application (API approval)	

APPENDIX 4: COMPARISON OF SERVICE FEES FOR REGULATORY REVIEW OF VETERINARY DRUGS – CANADA: AUSTRALIA

	Canadian Category Description	VDD Current	VDD - Year 1	APVMA (40% CR)	Comments
4	As #3 but for food-producing animal (using lowest HSD category)	**$42,610** (MCED: 4840; CED: 15980; HSD 21790)	**$213,050** (MCED: 24200; CED: 79900; HSD 108950)	**AU$19,795** Item 10 application with modules 1, 2.3, 5.4, 8.2, 11.1, 12 + Item 17 application (API approval)	
5	Generic: compendial active; 1 claim; 1 dosage form; 1 species (companion animal) - with bioequivalence waiver	**$4,840** (MCED: 4840)	**$24,200** (MCED: 24200)	**AU$7,445** Item 6 application + Item 17 application (API approval)	
6	As #5 but with no bioequivalence waiver	**$7,740** (MCED: 4840; CED 2900)	**$38,700** (MCED: 24200; CED: 14500)	**AU$8,030** Item 10 application with modules 1, 2.3, 8.3, 11.2, 12+ Item 17 application (API approval)	

APPENDIX 4: COMPARISON OF SERVICE FEES FOR REGULATORY REVIEW OF VETERINARY DRUGS – CANADA: AUSTRALIA

	Canadian Category Description	VDD Current	VDD - Year 1	APVMA (40% CR)	Comments
7	As #6 but for food producing animal (assumes abbreviated residue trial)	**$10,640** (MCED: 4840; CED 2900; HSD 2900)	**$53,200** (MCED: 24200; CED 14500; HSD 14500)	**AU$18,005** Item 10 application with modules 1, 2.3, 5.4, 8.3, 11.3, 12+ Item 17 application (API approval)	
8	Supplemental to add additional claim to a product for food-producing animal species (same species/dosage)	**$12,590** (CED 12590)	**$62,950** (CED 62950)	**AU$3,690** Item 14 application with modules 1, 8.2, 11.2, 12	
9	Notifiable Change (example: site change for fabrication of finished dosage form - nonsterile)	**$1,300**	**$6,500**	If AU site: **AU$175** (Item 13A); If non-AU site **AU$4,295** (Item 14 application with modules 1,2.3,11.2,12)	

APPENDIX 4: COMPARISON OF SERVICE FEES FOR REGULATORY REVIEW OF VETERINARY DRUGS – CANADA: AUSTRALIA

	Canadian Category Description	VDD Current	VDD - Year 1	APVMA (40% CR)	Comments
10	Not new drug DIN application	**$720**	**$3,600**	**AU$1,170** Item 12	Comparative based on label update to product grandfathered from State registration system (1996)
11	Investigational New Drug - unapproved product; non-compendial active; request for investigational efficacy protocol approval in food-producing animal (using lowest HSD category)	**$24,200** (4840+4840+14520)	**$121,000** (24200+24200+72600)	***AU$35,867.50** Tier 3 application with meeting; followed by Item 23 application with modules 1, 2.2, 3.2, 5.3, 7.3, 8.3, 11.1	Comparative based on protocol reviewed under pre-application assistance with a meeting followed by a research permit request
12	Experimental Studies Certificate - approved product in companion animal; request for study to support indication in food-producing species	**$2,900**	**same**	***AU$15,265** Item 23 application with modules 1, 3.2, 5.3, 7.3, 8.3, 11.1	Comparative based on closest type of similar submission

	Canadian Category Description	VDD Current	VDD - Year 1	APVMA (40% CR)	Comments
13	Emergency Drug Request (food producing animal)	**$100**	**same**	**AU$0** Item 22 application (modular fee based on type of study being requested)	
Misc	Fee reduction provision	Remission granted if fee is >10% gross revenue from the product(s) in first 3 years	$10,000 first submission only	none	
	Minor Use/Minor Species (MUMS)	As per fee reduction provision	none available	**AU$350** if minor use permit for minor species use (no MUMS system)	
	Annual DIN renewal	**$250** (or $50 with fee reduction provision)	**$627** (no fee reduction provision)	**AU$430**	

APPENDIX 4: COMPARISON OF SERVICE FEES FOR REGULATORY REVIEW OF VETERINARY DRUGS – CANADA: AUSTRALIA

Canadian Category Description	VDD Current	VDD - Year 1	APVMA (40% CR)	Comments
Annual levy on sales	---	---	0.63% 5000-1 million; 0.35% 1-5 million; 0.25% >5 million	
Time of payment	10% at screening; 40% after screening; 50% after review 1	100% when submitted	**AU$710** at filing; balance after administrative check (approx. 30 days)	

APPENDIX 5: COMPARISON OF SERVICE FEES FOR DRUG ESTABLISHMENT LICENSING OF VETERINARY DRUGS - CANADA: AUSTRALIA

	Canadian Category Description	HC Current	HC - Year 1	APVMA	Comment
1	Small import business: importer activity, 2 dosage forms, 2 foreign sites	**$4,950** (2500+1250+1200)	**$33,545** (31,745+1800)	**AU$1,000** each foreign site imported from (regardless of # of products from that site)	If multiple sites involved (i.e. fabrication, testing, alternative mfg site) you are charged $1000 for each site
2	Sterile fabricator; 2 dosage forms	**$12,000** (6000+3000+3000)	**$41,114**	**AU$7,500** (and AU$900 application fee)	Same GMP licence held by packagers / labellers and analytical labs as well
3	Non-sterile fabricator; 2 dosage forms	**$9000** ($6000+3000)	**$30,481**	**AU$5,000** (and AU$900 application fee)	Same GMP licence held by packagers / labellers and analytical labs as well
4	Packager / labeller; 2 dosage forms	**$6,000** (4000+2000)	**$5,942**	**AU$7,500** sterile **AU$5,000** non-sterile (and AU$900 application fee)	

	Canadian Category Description	HC Current	HC - Year 1	APVMA	Comment
5	Distribution / wholesaling	**$1,500**	**$9,851**	none	
6	Testing	**$1,000**	**$27,109**	**AU$7,500** sterile **AU$5,000** non-sterile (and AU$900 application fee)	
7	Fee reduction provision	remission granted if fee is >1.5% gross revenue from the product(s)	none	50% reduction if wholesale value in previous year <AU$50,000	