SUBSTITUTION PLAN

Legal name of applicant(s):	IDEXX Laboratories Limited
Submitted by:	IDEXX Laboratories Limited
Substance:	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated [covering well-defined substances and UVCB substances, polymers and homologues] 4-Nonylphenol, branched and linear, ethoxylated [substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and/or combinations thereof]
Use title:	Use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated and use of 4-Nonylphenol, branched and linear, ethoxylated in *in vitro* diagnostic veterinary products (SNAP tests and ELISA Plate tests) as an ingredient in the wash solutions, sample diluents, control solutions, conjugate solutions, SNAP wash solutions, tissue soaking buffers and detection solutions
Use number:	Use #1

CONTENTS

TABLES

FIGURES

LIST OF ABBREVIATIONS

4-NPnEO	4-Nonylphenol, branched and linear, ethoxylated
4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated
ADV	Aujeszky's Disease
AI	Avian Influenza
AI-MS	Avian Influenza MultiS-Screen
ALV	Avian Leukosis Virus
ALV-J	Avian leukosis virus subgroup J
AoA	Analysis of Alternatives
APP	Actinobacillus pleuropneumoniae
APV	Avian Pneumovirus
BLV	Bovine Leukemia Virus
BPR	Biocidal Products Regulation
BSE	Bovine Spongiform Encephalopathy
BTV	Bluetongue Virus
BVDV	Bovine Viral Diarrhea Virus
CAEV	Caprine arthritis encephalitis virus
CAG	Companion Animal Group
CARACAL	Competent Authorities for REACH and CLP
CAS	Chemical Abstract Service
CH	Switzerland
CLP	Classification, Labelling and Packaging
CMR	Carcinogenic, mutagenic or toxic to reproduction
COFRAC	French Accreditation Committee
COO	Country of Origin
CSFV	Classical Swine Fever
CSR	Chemical Safety Report
CWD	Chronic Wasting Disease
DE	Germany
DEREA	Food and drug administration export reform and enhancement act of 1996
DU	Downstream User
EC	European Commission
EDTA	Ethylenediamine tetraacetic acid
EFSA	European Food Safety Agency
ELISA	Enzyme-Linked Immunosorbent Assay
EMS-ISO	Environmental Management System-International Organization for Standardization
ES	Spain
EU	European Union
FeLV	Feline Leukemia Virus
FIV	Feline Immunodeficiency Virus
FR	France
FSC	Free Sales Certificate
FTE	Full-time equivalent
IBR	Infectious Bovine Rhinotracheitis
IBV	Infectious Bronchitis virus
IgG	Immunoglobulin G

IgM	Immunoglobulin M
IMS	Integrated Management System
IP	Import Permit
ISO	International Organization for Standardization
IT	Italy
IVD	In Vitro Diagnostics
JMAFF	Japanese Ministry of Agriculture, Forestry, and Fisheries
LAO	Latin America
LC	License
LC-PG	License for Program Diseases
LPD	Livestock, Poultry and Dairy
MAP	Mycobacterium avium subsp. paratuberculosis
MVV	Maedi-Visna Virus
NDV	Virulent Newcastle disease
NL	The Netherlands
NSB	Non-Specific Binding
OIE	Office International des Epizooties/World Organisation for Animal Health
OPS	Operations
PI	Parainfluenza
PRRS	Porcine Reproductive and Respiratory Syndrome
PRV	Pseudorabies Virus
QA	Quality Assurance
R&D	Research and Development
RA	Regulatory Affairs
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REO	Avian Reovirus
RoC	Receiver Operating Characteristic
RSV	Respiratory Syncytial Virus
RT	Real-time
SEA	Socio-Economic Analysis
SVHC	Substance of Very High Concern
TSE	Transmissible spongiform encephalopathies
UK	The United Kingdom
US	The United States of America
USA	The United States of America
USDA	The United States Department of Agriculture
UVCB	Chemical Substances of Unknown or Variable Composition

INTRODUCTION

This application for authorisation covers the downstream use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) and 4-Nonylphenol, branched and linear, ethoxylated (4-NPnEO) in in vitro diagnostic veterinary products (SNAP tests and ELISA Plate tests) as an ingredient in the wash solutions, sample diluents, control solutions, conjugate solutions, SNAP wash solutions, tissue soaking buffers and detection solutions. The downstream use takes place in the UK by the IDEXX's customers, which are veterinary clinics, reference laboratories, universities, governmental laboratories or private livestock and milk laboratories.

The parent company, IDEXX GLOBAL, is a global leader of in vitro diagnostics with the aim of enhancing the health and well-being of pets, people and livestock. With their extensive portfolio, IDEXX serves tens of thousands of customers in more than 175 countries providing them with elegant solutions for monitoring animal health and water and milk quality.

IDEXX's IVD products are used for the detection or quantitative measurement of a wide variety of antigens and antibodies linked with infectious diseases. They contribute to disease prevalence monitoring (including emerging diseases), control of disease outbreaks, animal health movements, food safety and fighting against zoonoses (infectious diseases transmitted by animals to humans). By allowing the early detection of diseases in animals, the spread of diseases can be controlled. The benefits to animal/human health include less infected animals, less euthanised animals, lower risk of animal-to-human transmission of zoonotic diseases and timely treatment of diseases. While some animals are tested individually, several tests and programs use pooled serum and milk samples, as well as tank milk samples, with milk from 100 or more cows. Poultry tests for between 5-10 animals can usually represent epidemiological units of 500 to several thousand chickens.

The diseases tested by IDEXX's IVD products are critical in terms of animal/human health and economic impact. For example:

- Avian Influenza: A highly contagious viral disease affecting food producing birds, pet birds and wild birds. Highly pathogenic strains can be associated with high mortality rates among poultry. Some strains of the avian influenza virus may also be transmitted to humans (e.g. the well-known H5N1 and H7N9). Outbreaks of avian influenza are considered a global public health concern.

- Classical Swine Fever: A contagious viral disease affecting domestic and wild swine. Affected swine may present no symptom thus, testing is required to detect the presence of the virus. In case of infection, no treatment is attempted. Affected swine must be culled.

- Bluetongue: A viral disease affecting domestic and wild ruminants, primarily sheep. Symptoms may include weight loss, disruption in wool growth and death. In endemic areas, the presence of the virus is actively monitored by testing herds.

- Canine Leishmaniasis: A potentially fatal zoonotic disease transmitted by sand flies. One-third of infected dogs will experience swollen lymph nodes, an enlarged spleen, and will progress to kidney failure.

- BVDV: The most costly bovine viral disease. Eradication programs in several countries in Europe ongoing (Ireland, Belgium, Germany) or starting (France) or planned (Spain, The

Netherlands, etc.). The bovine industry loses up to 100 EUR per animal if virus is circulating in the herd. Testing is crucial as persistently infected animals cannot be identified otherwise. IDEXX tests are the most widely used in these programs.

- Paratuberculosis: A non-curable disease in bovines which causes diarrhea, weight loss and much reduced performance and ends usually fatal. Testing ensures to identify animals as early as possible and helps apply cost saving management programs in dairy and beef herds.

IDEXX manufactures two different types of products, the ELISA Plate tests and the SNAP tests. The ELISA plate test kits contain one or several 96-well ELISA plates, which are pre-coated with either inactivated antigen or antibody. These pre-coated antigens and antibodies are immobilised at the bottom of the wells and act as "anchors" for the target antibodies and antigens present in the sample to bind to. In addition to the pre-coated plates, the kits typically also contain a bottle of sample diluent, a bottle of conjugate, a bottle of substrate, several bottles of controls and a bottle of wash concentrate. Some kits contain fewer components as each test is designed for a specific disease. The components of different kits or lots cannot be mixed as each component is carefully manufactured and specifically optimized to work as a unit. For additional information on ELISA assays, please refer to sections 4.2.2 and 4.2.5.1 of the AoA-SEA report.

SNAP tests were developed by IDEXX scientists in the early 1990s. They combine ELISA technology with well-known diagnostic markers to deliver reference-laboratory quality results within minutes. IDEXX SNAP tests are compact plastic devices that encase a sample wash solution, a substrate solution and a matrix pre-coated with a layer of antigen-specific antibodies or antibody-specific antigens. Each test is designed to detect the diagnostic markers for one or multiple diseases or semi-quantitatively measure the level of a specific enzyme. For additional information on SNAP tests and how they work, please refer to sections 4.2.3 and 4.2.5.2 of the AoA-SEA report.

4-tert-OPnEO and 4-NPnEO are used in IDEXX's in vitro diagnostic kits to prevent the non-specific binding of undesired macromolecules, such as conjugates and sample impurities, to the bottom of the wells in ELISA plate tests and to the assay's matrix in SNAP tests. As the colour signal arising from the assays is proportional to the amount of substrates that react with the conjugates, non-specifically binded conjugates leads to falsely high signal. This is unwanted as it can lead to false positive results, which in worst cases can result in a healthy animal being euthanised. For additional information on substance function, please refer to section 4.2.4 of the AoA-SEA report.

In order to find alternatives solutions to 4-tert-OPnEO and 4-NPnEO, IDEXX carried out preliminary tests on Tergitol 15-S-9, Tergitol 15-S-40 and SNAP wash formulations containing 0.1 % of Triton X-100. Based on the initial tests on SNAPs, Tergitol 15-S-9 is considered the most promising alternative candidate of the three. However, as issues with spot colour development were observed during the tests, Tergitol 15-S-9 is not technically feasible at the present time. A significant amount of R&D work remains in order to fully determine its applicability as a replacement for the 4-tert-OPnEO and 4-NPnEO used in the products covered by this application.

In order to substitute 4-tert-OPnEO and 4-NPnEO from their products, IDEXX must reformulate the 60 products covered by this authorisation application. These products are manufactured in three different sites, which are located in Montpellier (FR), Westbrook (USA) and Bern (CH). The practical work for the substitution of 4-tert-OPnEO and 4-NPnEO in the products covered by this

authorisation application is starting at all sites in H2 2021 and is expected to last 18-23 years depending on the site. As the Applicant is aware that a review period of more than 12 years should not be considered for non-threshold substances for which the risks cannot be quantified, IDEXX is requesting for a review period of 12 years. The Applicant will apply for a review of the authorisation in order to finish the reformulation of all products.

As outlined in chapter 6.7 of the AoA-SEA reports, the Applicant fulfils the criteria for a long review period of 12 years. In particular, the reformulation of products in order to substitute 4-tert-OPnEO and 4-NPnEO will require extensive validations and regulatory approvals from all the countries the products are placed in. The reformulation process is described in more detail in this document.

1. FACTORS AFFECTING SUBSTITUTION

1.1 Regulatory and customer requirements

The accuracy of the results given by an in vitro diagnostic test is paramount. It is typically measured by means of sensitivity and specificity. A test with low sensitivity will falsely diagnose an infected animal as healthy, in which case the animal will not receive the treatment it needs, and the disease may spread to other animals. A test with low specificity may diagnose a healthy animal as infectious, in which case the animal may be unnecessarily given a treatment or even euthanized.

It is crucial that the substitution of 4-tert-OPnEO and 4-NPnEO does not affect adversely the specificity and the sensitivity of IDEXX IVD tests. In fact, IDEXX has to comply with specificity and sensitivity requirements set by regulatory authorities as well as a plethora of other regulatory, product licensing, national animal health competent authority requirements and commercial tender procedures that may further narrow the product requirements. Please refer to section 4.2.6 of the AoA-report where these requirements are described in detail and Appendix 6 of this document for a table of countries/regions that require licenses or other permits.

1.2 Requirements for alternatives

IDEXX has set requirements that alternative candidates must fulfil in order to be selected for further testing. The alternative candidates should not:

- Be classified as CMR or SVHC.
- Present a greater exposure/safety risk as current substances.
- Represent a higher compliance risk.
- Represent a higher supply chain risk.

In addition, the alternative substance should provide the same technical functionalities to prevent non-specific binding:

- Ensure optimum protein conformation and stability.
- Prevent non-specific binding of samples and controls.
- Be as effective to remove non-target material on the sample spots/wells of the tests.

The effectiveness of alternative substances for each of the functions above may not be easily predicted and is highly dependent on the specific type of purified proteins used in the diagnostic test.

Many ingredients of animal origin used in diagnostics such as sera, foetal bovine serum, milk, albumin etc…, can be considered as UVCB substances and IDEXX's experience with past formulation changes shows that the delicate balance between competing affinity processes in antibody or antigen capture systems is easily upset and that unwanted side effects are frequently observed (e.g., stability issues, precipitation, viscosity problems, colour variations, field issues related to the variety of laboratory equipment and consumables in laboratories, field sample treatments etc…). Further optimization or changes may be necessary to counter the undesirable

effects. For this reason, each IVD kit will need to be tested with the alternative detergent to ensure the product still meets the performance requirements.

The alternative should also offer similar operational benefits:

- Substance stability and robustness under existing standard laboratory conditions and with existing formulations
- No incompatibilities with other reagent formulations which are part of the test kits.
- Same formulation is suitable across a broad variety of tests in technical manufacturing and in sample diluents and controls (generic reagents shared by multiple tests).
- Be effective at low concentration.

In addition to the above requirements defined by IDEXX, the alternative also needs to be demonstrably technically feasible, economically feasible and available for purchase in required quantities and purities.

1.3 Constraints for the substitution work

There are several factors that will affect IDEXX's reformulation work. The first one arise from the fact that IDEXX has a high diversity of methods and reagents used in their products. This means that even a simple change in the products' composition, such as a change of detergent in the sample diluent, can have unintended technical complications and change product performance to no longer meet current specifications. In some situations, more than one kit component or step in the manufacturing process need to be changed. This further complicates the development timing, validation and the registration and licensing of the new kit.

IDEXX has had significant growth over the last two decades, which includes multiple acquisitions of existing companies and product lines. This resulted in a wide variety of protocols and processes used for product manufacture. Evidence of this can be seen in the number of different substances used by IDEXX, currently over 500, and in the lack of consistency in the diluents or reagents used in the product kits. Furthermore, the lack of standardization can be seen in the variety of concentrations of 4-tert-OPnEO and 4-NPnEO in reagents that have the same purpose or usage in different products. Even though IDEXX is making efforts to standardize their processes for new product developments, this complexity and lack of standardization is one component to the length of the timeline for reformulation.

Adding to the overall timeline, is the sheer difficulty in gathering samples that can be used to verify the new processes or reagents. Several of IDEXX's tests are used to detect very rare diseases in animals, some with prevalence rates well below 1 %. If the naturally occurring prevalence rate is low, it can take several years to collect enough samples to create a population that will provide statistically relevant results to base the validation on and to re-licence the products. Many of IDEXX's orginal sample sets were collected though partnerships with Key Opinion Leaders from international locations to support geographical prevalence and unique species of organisms that are unique to specific regions. The importance of prevalence is discussed in further detail in Appendix 6.

In addition to the challenge of sample prevalence, sample volume can also be an issue. Even if samples positive for the target are found, they might not be available in sufficient volumes to

allow testing across multiple lots, verification against current gold standard and replicate testing. In addition, some samples are needed for R&D activities, validation and data collection for licensing submissions. Many of IDEXX products are approved for multiple sample types. For example, many of IDEXX's SNAPs can be used with whole blood, serum, or plasma. In order to maintain the accuracy of the tests, matched serum/plasma pairs need to be collected from animals. These are incredibly challenging to identify and collect. Some percentage of the samples used for validation testing must be fresh sample rather than frozen in order to compare storage conditions. This also creates a challenge in acquiring the appropriate sample set for testing.

Some diseases states can cause symptoms that make it difficult to collect blood from the animal, which adds to the volume concerns. In addition, the volume of samples that can be taken from animals of less than 10 lbs (4.5 kg) is limited. This is specifically true for feline samples, where blood draw can be challenging. When approved or possible, the Applicant will use a pool of samples to represent each detection level of the test in order to compensate for the low volume of specific samples. In these situations, the Applicant's validation plan must be approved by the licensing agency that require strict testing guidelines (naturally occuring infections, unique animal identification and traceability). A final complication, certain samples are needed in higher volumes due to the fact that IDEXX has multiple kits testing the same antigen or antibody.

In some cases, it is not possible to wait for naturally ocurring infections and experimental infections are needed. Experimental infections are highly regulated and require official approval from the relevant regulatory Agency (e.g. USDA), which adds a level of complexity and is time consuming. In addition, they require review and approval of the animal welfare practices in the validation plan, compliance to the laws that suppliers are held to. This creates added risk to the validation plan.

Some diagnostic kits require sample sets from multiple species as well as multiple strains of the virus of interest, which lenghtens the process. In the case of kits used in "panel" testing, such as the NDV, IBV and REO diagnostic kits, the revalidation work is prolonged due to the fact that also the products, which do not include 4-tert-OPnEO and 4-NPnEO but are part of the "panel" test kits, need to be reformulated as well.

As the number of products that needs to be reformulated is significant, it is impossible for IDEXX to work on the reformulation of all the products at the same time. Instead, the reformulation work will need to be staggered to accommodate for the number of staff available for the task and the physical space at hand. For instance, IDEXX cannot run all stability studies, which require specific storage with controlled temperature, for all the products at the same time because their facilities are not designed to handle so many studies concurrently. In addition, IDEXX can only allocate a limited number of staff to the reformulation work as the Applicant also has to carry out other product reformulations as well as develop new products.

Moreover, during process validation of the full-scale production, the production equipment cannot be used to manufacture on-market products. This requires the reformulation of products to be staggered as it allows the Applicant to schedule the validations lots around on-market productions to avoid product available issues. Failing to do so would have a significant negative economic impact on the Applicant's business.

In addition to the arguments mentioned above, each product reformulation for infectious tests kits (i.e. the majority of kits covered by this application) will need to be reviewed and approved by the USDA before any execution occurs. In addition to a lengthy data collection process, each dossier needs to be compiled and reviewed by IDEXX's bio-statisticians and regulatory staff

before it can be submitted to the Agency. Once submitted, it can take up to a year for the product change to be accepted and licensed by the USDA. Furthermore, IDEXX has an internal validation process that each reformulated products need to pass in order to ensure that product changes meet all applicable licensing and other requirements (please refer to the Animal Health Agency requirements in chapter 4.2.6 of the AoA-SEA report for additional information).

As IDEXX market their products worldwide, they are required to seek global regulatory approvals. These prolong the time required for the reformulation of products. In particular, the registration process for Japan is time-consuming as the JMAFF has longer times of approval and may be inconsistent with their requirements. In addition, some products require additional regulatory approval. One example, is the BSE-Scrapie kit, which is referenced in EU directives (Regulation (EC) No 956/2010 amending Annex X to Regulation (EC) No 999/2001) for use in TSE control programs and for which there are strict requirements due to the criticality of the test to protect the food chain.

1.4 Additional constraints for livestock and poultry ELISA plate assays

For some sample populations, like BSE-Scrapie and Chronic Wasting Disease, Avian and Swine Influenza, the original sample sets used to validate the kits would be impossible to reproduce. These sets were collected when the disease prevalence was much higher. In many cases, government agencies or livestock breeders have collaborated with IDEXX, providing samples because they had a need to understand the disease state within their countries or herds. At this point, those suppliers have moved on to other diseases that they are focused on and concerned about and because the prevalence is so low, gathering native samples would be extremely challenging.

2. LIST OF ACTIONS AND TIMETABLE WITH MILESTONES

Although IDEXX has identified several potential alternative candidates, none are currently technically feasible. A considerable amount of work is still required before a suitable alternative can be implemented in all the products covered by this authorisation application.

In order to substitute 4-tert-OPnEO and 4-NPnEO from their products, IDEXX must reformulate 60 products in total: 19 products in Montpellier (5 of which are not covered by this authorisation application, see chapter 2.9.1 for more detail), 33 products in Westbrook and 13 products in Bern. The list of products covered by this authorisation application is given in Appendix 4.

The Applicant has identified 8 steps that they need to go through in order to successfully reformulate one product or one wave of products. These steps along with an indicative timeline to substitute 4-tert-OPnEO or 4-NPnEO from one product or one group of products are presented in **Table 1**. There is a certain amount of uncertainty with the timeline, which arise from the length of time to find a suitable alternative and the time needed to obtain regulatory approval (in certain cases, regulatory agencies may request for additional testing or the processing time can last longer than usual).

Table 1. The steps required to reformulate a product. The duration is calculated for one product or one wave of products

Step	Task Name	Duration (days)	Duration (months)	Resource Names
1	Feasibility testing	360	12	R & D
2	R&D - Validating substitutes still meet technical and regulatory requirements	270	9	R & D
3	Verification testing and prototype lot production (including stability)	180	6	R & D
4	Field sample testing	180	6	R & D
5	Regulatory licensing activities	180	6	RA
6	Determination of process control limits and scale-up	90	3	QA/OPS
7	Process validation and full-scale production	90	3	QA/OPS
8	Implementation (document updates, additional regulatory submissions, inventory phase-out)	540	18	OPS/RA

The steps to reformulate a product are discussed in further detail. The same activities are performed at each of the 3 manufacturing sites however, there may be instances when some steps are done in a different order due to the specifics of the reformulation effort.

2.1 Step 1: Identification of possible alternatives and feasibility testing

Identification and feasibility testing of possible alternatives is considered an early phase activity at IDEXX. This often means that resources are not dedicated to this task, but instead the work is conducted, as time allows, in between other commitments. Dedicated resources on a project occurs once feasibility is confirmed and an official project is chartered. Resources will be fully allocated to this effort once the ongoing reformulation work related to the Biocidal Product Regulation (BPR, Regulation (EU) 528/2012) is complete.

The goal in feasibility for CAG is to identify a single surfactant that will work for all affected SNAP products as it would make the management of stock solutions easier. The wash solution is a

common component in all SNAP devices therefore, finding a single alternative applicable to all product lines would give IDEXX the necessary flexibility in planning and scheduling. In addition, it allows the Applicant to maintain a single safety stock that can be used in the manufacture of all of the SNAP products and simplifies the management of expiration dates of the manufactured batches. On the contrary, maintaining separate SNAP wash solutions for different SNAP products would have a large impact on the Applicant's day to day manufacturing processes. IDEXX would have to manage separate stocks of wash solutions, each needing to be planned and scheduled individually. In addition, the lines on the production equipment would need to be cleared more often to ensure no cross-contamination from one formulation to the next, adding time, labour and costs to each run. There would also be a potential for an increase in wastes due to the complexity of managing the expiration dates of several different stock of wash solution.

For LPD, a similar goal exists where IDEXX is looking for a single alternative to use in all the ELISA plate products concerned. However, as a result of the complexity of IDEXX's product portfolio, it is unlikely that a single alternative substance would support functionality of the full portfolio. But for operational efficiency, IDEXX will have a goal of minimizing the number of formulations and surfactants used.

After the alternative(s) has been identified, the Applicant needs to ensure they can receive a consistent supply of the substance. This is achieved by selecting multiple suppliers and validating each of them for a particular kit and a specific manufacturing process.

2.2 Step 2: R&D

During this step, new solutions are formulated with the alternative detergent identified in the previous step. An evaluation of the robustness of the new formulations occurs to ensure that the new formulation does not cause precipitation, changes in pH that might affect the target molecules, changes in viscosity that could affect the flow of liquid within IDEXX's tests, and other relevant assessment factors.

The assay is then optimised to meet the required specifications. This is done by testing several titers of conjugates along with varying concentrations of the solid phase components which are attached to the SNAP matrix or coated on the bottom of ELISA plates. Testing with a range of positive and negative panel or samples help to define the optimal ranges for each reagent used in making the test. Several experiments are carried out to ensure the substitute still meets technical and regulatory requirements. Typically, experimental design methods are used to confirm this. In addition, response surface maps are created and the reagents are characterized. The response surface map provides the manufacturing teams with a charted view of the relationship between input variables (like concentration and titer of components) with response variables. Statistical analysis can be used to predict the optimal ranges of concentration or titer of each reagent which allows production to be more predictable.

2.3 Step 3: Verification testing and prototype lot production

Verification testing involves creating R&D scale lots of a product with the new alternative detergent formulation and comparing the product's performance with the performance of products containing 4-tert-OPnEO or 4-NPnEO in their forumulations. Typically, validation is conducted using multiple lots of detergent purchased from each approved supplier in order to replicate the true lot to lot variability occuring during normal production processes.

In addition, the stability of each R&D scale lots will be tested, at a smaller scale than full validation stability studies, in order to get an understanding of stability expections before moving too far forward with the formulation change. A typical stability study include storage of a kit or kit components at the recommended storage conditions for a least one month past the given expiration date. The expiration date in the majority of IDEXX's products is 12 months, while some are dated 18-24 months thus, each kit lot will need 13–25 months of stability data to prove that the new formulation is stable throughout the life of the kit. This entire cycle needs to be replicated for each product being tested. As the storage conditions recommended for the majority of the Applicant's product is 4°C, IDEXX needs environmentally controlled cold room space for the stability studies. This limits the number of kits that can be tested at once.

2.4 Step 4: Field sample testing

Field sample testing requires a set of samples that has been characterized by existing test methods or diagnostic tools that can be used to evaluate performance of the kit with native samples. As outlined in chapter 1, sample collection is a challenging task for multiple reasons. Low disease prevalence is one of the largest challenges, in particular, with programs that have effectively erradicated disease.

2.5 Step 5: Regulatory licencing activities, which include protocols, additional testing, submissions, regulatory review

Regulatory licensing is a time-consuming process, which is often complicated and opaque. Within the regulatory process, approvals need to be obtained for the testing plan for all USDA licensed products prior to any data being collected. The initial approval process can take 6 months. Once steps 6 and 7 are completed, a final data package must be submitted to regulatory agencies. A USDA final data package will include a description of experiments done to show diagnostic accuracy, analytical sensitivity and specificity, determining the cutoff values, ruggedness and interlaboratory comparisons along with all data, statistical analysis and conclusions associated with these experiments.

Other agencies have similar requirements for product information, manufacturing overviews and data packages to be submitted for approval prior to selling product in that country. Timing for approvals varies depending on the agency and the complexity of the change. Submitting multiple products concurrently would delay the approval timeline, which is why staggered submission is the recommended approach. Approval of the final data package is necessary in order to proceed with production and sale of the new version of the product. USDA and country dossiers can take 1-3 years per product.

It is common for regulatory agencies to request additional information or testing that need to be carried out before the approval is granted. Any additional testing consumes materials, samples, resources and lenghtens the approval timeline. In some situations, the additional requests by the agency can delay the approval of the data package and validation plan by 6-12 months.

For both the testing plan and the final data package, 1-2 months should be added to incorporate time for IDEXX's Biostatisticians to validate the strategy of the plan and to evaluate the confidence of the data package. The Biostatistics group at IDEXX has limited resources and would need submissions to be staggered to incorporate the additional work that will come with reformulation of so many products.

2.6 Step 6: Determination of process control limits and scale up

Control limits are established during the development of a new product using statistical analysis of the first several lots of the product. Analytic norms are established and subsequently monitored to ensure product lot to lot consistency and over time consistency. When changes to a product are introduced, the control limits often need to be reset, which requires time and resources from the Applicant's biostatisticians and operational excellence teams.

Scale up of reagent production typically reflects a 3-20 fold increase in size of each reagent made from the R&D scale used in step 3. The increase in size often requires different equipment to be used or sometimes a slight difference in process. Scale up is not always a linear process. The inputs used to make R&D scale product do not always yield similar reagents that perform similarly at a larger scale. Due to these factors, scale up is not always predictable and can lead to further optimization work before moving forward with the validation of the product.

2.7 Step 7: Process validation of full scale production

Process validation involves producing three lots of the product with the new alternative detergent formulation and comparing the testing results to at least two lots of products manufactured with the previous formulation containing 4-tert-OPnEO or 4-NPnEO. Similarly to the procedure for verification testing, several lots of detergent are used in order to replicate lot to lot variability. In addition, each of these lots will need to be set up on another round of stability testing. Overall, the stability testing will last for 13 months for the majority of the kits that are covered by this application and tested at regular intervals such as monthly or quarterly, if no issues or errors occur during the process.

It should be noted that during the process validation of the full scale production, the production equipement cannot be used to manufacture on-market products. As a consequence, the Applicant needs to stagger the reformulation work of all the products covered by this application across multiple years. This way, the validation lots can be scheduled around on-market production efforts to keep IDEXX inventory at appropriate levels and avoid product availability issues. Failing to do so would have a significant negative economic impact on the Applicant's business.

2.8 Step 8: Implementation control plan and other preparations such as inventory management, update of documents, and country-specific licensing.

The implementation control plan will involve several of the Applicant's operations focused teams. The teams will need to divide their resources between on-market products, newly developed products and product reformulations. Due to the reformulation of solutions containing 4-tert-OPnEO or 4-NPnEO, the change control team and technical writers will have to update all manufacturing documents, inventory control documents, SDSs, product inserts, labels and purchasing documents in order to reflect the changes. In addition, all regulatory agency document changes such as outlines of production (USDA) and DEREA (USDA requirement for products exported from US but not sold in the US) are also handled by these teams.

To apply for the ability to sell internationally, including in the UK, Regulatory teams need to prepare country specific application dossiers which may involve obtaining or generating Free Sales Certificates, import permits as well other country-specific documents such as

manufacturing overviews, stability data, performance data against local requirements… for licensure which can take 3 to 24 months for approval. It is often not possible to release for sale a reformulation product version before all regulatory approvals are obtained since IDEXX diagnostics are universal.

In addition to the tasks described above, the Applicant will need to make several other adjustments. For instance, IDEXX's procurement department will need to update and manage safety stock requirements, internal product specifications and bills of materials whereas Operations Systems teams will need to update IDEXX's resource planning system. In addition, planners will need to manage the scrap of the old version of the products and create an effective run out strategy to minimize losses.

2.9 Reformulation timeline

The practical work for the substitution of 4-tert-OPnEO and 4-NPnEO in the products covered by this authorisation application is starting at all sites in H2 2021 as this is the earliest feasible date for IDEXX. It was not possible for IDEXX to start the reformulation work earlier as the product support teams were focused on other product reformulations for biocide removal (triggered by the BPR Regulation[1]) and other product support issues.

2.9.1 Reformulation in Montpellier (FR):

IDEXX Montpellier uses 4-tert-OPnEO in the plate coating of ELISA plates (technical manufacturing) of 10 products. As the 4-tert-OPnEO containing solutions used in plate coating are removed from the ELISA plates during the technical manufacturing, the finished ELISA plates contain <0.1 % of 4-tert-OPnEO thus, their downstream use does not require authorisation. However, 5 out of the 10 products include in their kits sample diluents and standard solutions containing >0.1% of 4-tert-OPnEO and are covered by this authorisation.

Due to the ban of 4-tert-OPnEO in the EU, IDEXX Montpellier needs to reformulate the solutions used in the technical manufacturing to make them free of 4-tert-OPnEO. This also applies to the 5 products not covered by this authorisation and thus, their reformulation needs to be taken into account in the reformulation timeline for the products covered by this application. In addition, there are 9 other products manufactured by IDEXX Montpellier that are covered by this application where the kits include sample diluents and standard solutions that contain >0.1% of 4-tert-OPnEO. The situation is illustrated in **Figure 1**.

[1] Regulation (EU) No 528/2012

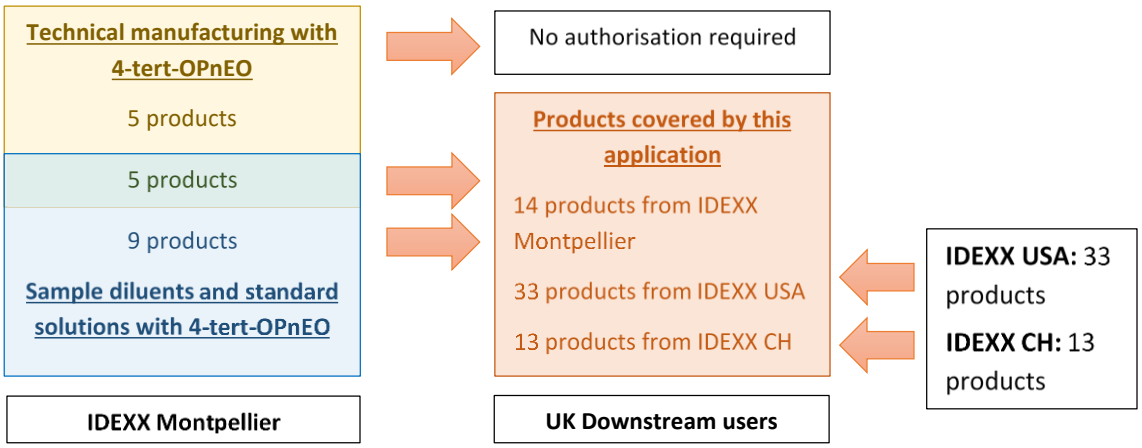


Figure 1. Diagram representing the products covered by this application and the ones affecting the reformulation timeline

As the antigen used in the coating of the ELISA plate is selected based on its ability to bind to a specific antibody, all *in vitro* diagnostics for the same disease will have the same antigen in them. The surfactant-antigen interactions vary from case to case depending on the antigen and surfactant used. Consequently, the Applicant expects the same alternative detergent to be at least applicable to all the products designed to test the same disease, which is why these products have been grouped to the same reformulation wave.

The Applicant has distributed all the products that require reformulations into eight waves based on the disease type the product is designed to test. The list of waves including the repartition of products is given in

Table 2**.** During the first wave, IDEXX aims at finding a generic sample diluent based on an alternate detergent that would be suitable to replace 4-tert-OPnEO-based sample diluents in all applicable products. As samples diluents represent only a part of the product, no regulatory licensing activities are required for this step. The reformulated sample diluents will be revalidated together with the rest of the kit during the subsequent waves.

Table 2. The list of products that require reformulation in IDEXX Montpellier

	Product name	Disease
Wave 1	Sample diluents	
Wave 2	IDEXX IBR Individual Ab IDEXX IBR Pool Ab	IBR
Wave 3	IDEXX Leukosis Blocking Ab* IDEXX Leukosis Milk Screening Ab* IDEXX Leukosis Milk Verification Ab* IDEXX Leukosis Serum Screening Ab	Leukosis
Wave 4	IDEXX Brucellosis Ovine/Caprine Serum Ab	Brucellosis
Wave 5	IDEXX MAP Ab IDEXX Paratuberculosis Screening Ab IDEXX Paratuberculosis Verification Ab	Paratuberculosis
Wave 6	IDEXX BVDV P80 Ab IDEXX MVV/CAEV P28 Screening Ab* IDEXX MVV/CAEV P28 Verification Ab*	BVDV MVV/CAEV
Wave 7	IDEXX Fasciolosis Verification IDEXX Bluetongue Competition Ab	BTV Fasciola hepatica
Wave 8	IDEXX PI-3 Ab IDEXX RSV IgG Ab IDEXX RSV IgM Ab IDEXX Trivalent Ab	Respiratory diseases

*Products that are not covered by this application but affect the reformulation timeline

The substitution timeline to reformulate all the products that require reformulation at IDEXX Montpellier is presented in **Appendix 1**. The reformulation work is starting in H2 2021 and is expected to last approximately 19 years in total.

2.9.2 Reformulation in Westbrook (USA):

IDEXX has grouped the 33 US products to reformulate into waves of products based on format of assay and disease type. For Westbrook, ELISA plates and SNAP tests will be considered on separate timelines due to the R&D teams that will conduct the majority of the reformulation work being separate. Shared resources in Quality Assurance, Regulatory Affairs, and Operations will still need to manage the overlap in the staggering of product changes.

The list of waves including the repartition of products is given in the tables below. There are 13 products in the LPD reformulation waves shown in

Table 3 and 18 products in the CAG reformulation waves shown in **Table 4**. The two products that are produced in both Bern and Westbrook (IDEXX PRV/ADV gB and IDEXX PRV/ADV G1 are listed in the Bern reformulation waves in **Table 5** as reformulation efforts will only take place at one site and the new process will be transferred to both sites at the implementation step.

Table 3. The 13 LPD IVD kits produced in Westbrook divided into reformulation waves

	Product name	**Disease**
Wave 1	IDEXX ALV Ab IDEXX ALV-J Ab	ALV / ALV-J
Wave 2	IDEXX SNAP BVDV Ag	SNAP BVDV
Wave 3	IDEXX *M. Bovis* Ab IDEXX *M. Hyo* Ab	M. bovis / M. hyo
Wave 4	IDEXX IBV Ab IDEXX NDV Ab IDEXX REO Ab	IBV / NDV / REO
Wave 5	IDEXX AI MultiS-Screen Ab	AI-MS
Wave 6	IDEXX *Neospora* Ab	Neospora
Wave 7	HerdChek BSE-scrapie Ag IDEXX BSE Non-biohazard pos control material HerdChek CWD Ag	BSE-Scrapie / CWD / Pos. IRM

Table 4. The 18 CAG IVD kits produced in Westbrook divided into reformulation waves

	Product name	**Disease**
Wave 1	SNAP Wash	Applies to all SNAPs
Wave 2	SNAP cPL SNAP fPL	Canine pancreatic lipase / Feline pancreatic lipase
Wave 3	SNAP Feline proBNP	Heart function biomarker
Wave 4	SNAP Foal IgG	IgG
Wave 5	SNAP 4Dx Plus	Dirofilaria immitis, Lyme disease, Erlichia, Anaplasma
Wave 6	SNAP Feline Triple SNAP Feline Heartworm	Feline immunodeficiency virus, Feline leukemia virus, Dirofilaria immitis
Wave 7	SNAP FIV/FeLV Combo SNAP FIV/FeLV Combo Plus SNAP FeLV Antigen	Feline immunodeficiency virus, Feline leukemia virus,
Wave 8	SNAP Giardia	Giardia
Wave 9	SNAP Parvo	Parvovirus
Wave 10	SNAP Heartworm RT	Dirofilaria immitis
Wave 11	SNAP Leishmania	Canine leishmaniasis
Wave 12	SNAP Lepto	Canine leptospira
Wave 13	Canine Cardiopet Plus (ELISA plate) Feline Cardiopet proBNP (ELISA plate)	Heart function biomarker
Wave 14	Lyme Quant C6 Antibody (ELISA plate)	Lyme Disease

The substitution timeline to reformulate all the products containing 4-tert-OPnEO produced in Westbrook is presented in **Appendix 2**. The reformulation work is starting in H2 2021 and is expected to last approximately 17-19 years in total.

2.9.3 Reformulation in Bern (CH):

The reformulation work for the 13 products that are manufactured in Bern follow the steps presented in **Table 1**. Additional time has been added to Wave 8: IDEXX PRV/ADV gB Ab and IDEXX PRV/ADV g1 Ab to incorporate implementation of the new formulation into both Westbrook and Bern production as these 2 products are made in both locations.

IDEXX has grouped the 13 Swiss products to reformulate into 9 waves of products based on disease type. The list of waves including the repartition of products is given in **Table 5**.

Table 5. The 13 IVD kits produced in Bern divided into reformulation waves

	Product name	**Disease**
Wave 1	IDEXX BVDV Ag/Serum Plus IDEXX CSFV Ag Serum	BVDV Ag / CSFV Ag
Wave 2	Bovine pregnancy IDEXX Milk Pregnancy IDEXX Rapid Visual Pregnancy	Pregnancy
Wave 3	IDEXX APP-ApxIV Ab	APP
Wave 4	IDEXX APV Ab	APV
Wave 5	IDEXX BVDV Total Ab	BVDV Ab
Wave 6	IDEXX CSFV Ab	CSFV Ab
Wave 7	IDEXX IBR gE Ab	IBR gE
Wave 8	IDEXX PRV/ADV gB Ab IDEXX PRV/ADV gI Ab	PRV
Wave 9	IDEXX Swine Salmonella Ab	Salmonella

The substitution timeline to reformulate all the 13 products containing 4-tert-OPnEO or 4-NPnEO produced in Bern is presented in **Appendix 3**. The reformulation work is starting in H2 2021 and is expected to last approximately 23 years in total.

2.9.4 Factors affecting the reformulation timelines

The identification of an alternative and feasibility testing (step 1) has greatest unknown component to the timeline. Typically, IDEXX expects this work to take up to five years. Based on historical work, once a viable alternative is found, steps 2-6 can be estimated to take two to three years, when working on one product reformulation. Within this phase, the regulatory approvals discussed in step 5 are the greatest risk to the timeline, in particular for USDA regulated products. Due to the number of products that need to be reformulated, the activities in steps 2-6 must be staggered to allow for resources both at IDEXX and within the regulatory agencies.

An overlap of 24 months is deemed necessary for LPD products due to the limit R&D resources and the need to reserve time for unplanned projects which may receive a higher priortity. A 6 month stagger is used for CAG products due to a greater similarity of usage of 4-tert-OPnEO in most CAG products, plus an additional 1.5 full time equivalent resource. Multiple feasibility phases have been added to reflect the fact that a feasible solution may work for a certain number

of products but then not work in one Wave. Time to conduct a second round of feasibility to account for challenges in any Wave allows for a more realistic estimate.

Due to the limited amount of cold room space available for the stability testing and the number of staff available for the task, the steps 2-6 will have to be staggered for all the products of a particular manufacturing site. IDEXX estimates to have the capacity of starting the verification testing of a new product every six months on each manufacturing site. When steps 2-6 of the reformulation work are completed, the last step will begin and is expected to last for six months for all products and for each site.

3. MONITORING OF THE IMPLEMENTATION OF THE SUBSTITUTION PLAN

IDEXX Laboratories is governed by an Integrated Management System (IMS), which encompasses both requirements for the Quality Management System (ISO 9001:2015) and Environmental Management System (EMS-ISO 14001).

As such, both IDEXX's product development and product support projects are supported and governed by universal processes, such as Management review, Internal Audit programs, Corrective Action and Continual Improvement, Deviation Management, and Document and Record Control. In addition, IDEXX's processes are monitored for internal and external factors and associated risks, as part of their evaluation and determination of decisions. Once opportunities and risks are identified, then actions are planned to address them. IMS records are the objective evidence of activities, results and decisions that reflect the operation of the IMS in practice.

For any changes that need to be made to existing products on the market, IDEXX follows a product support project plan, with resources, schedule and timeline established. There are 4 steps that need to be taken to work through the process.

- **Step 1** is to identify and define the project and the work teams. This includes evaluating customer impact, a financial analysis, creating a manufacturing and supply plan, a risk analysis, establishing design requirements, creating a regulatory plan if needed and establishing a Technical Review team.
    - A change assessment is created during Step 1 to assess unintended impacts to IDEXX globally. This change assessment is reviewed at each Step exit.
- **Step 2** is to design and verify. In this step a draft implementation plan is created, IDEXX revisits the manufacturing and supply plan to ensure all affected aspects are captured, approved suppliers are identified, and the solution is verified.
- **Step 3** is the validation step. The implementation plan is finalized, the solution is validated according to the validation plan, regulatory submissions are made to the appropriate governing bodies and any changes to manufacturing documents or process are completed.
- **Step 4** is implementation, including inventory runout of the existing product, changes to documentation are finalized, regulatory approvals are complete where necessary and the project solution is made in production for the first time.

In between each step, the plans and processes are evaluated by the appropriate internal Product Review teams. There is cross-functional management oversight of each product support process. There is also a Technical Review team (established in Step 1), which is an independent body, authorized to review the technical components of the changes. Functional data evaluated by the Technical Review will lead to decisions for approval by those conducting the Product Review.

For each product support project, the work is defined by a project charter following a structured format to ensure all relevant information is included. For reformulation related to product compliance, the project charter would detail specific requirements for the reformulation, such as ensuring the alternative substances selected do not have other environmental or health hazard concerns for consideration. The charter includes the following:

- Product Description
- Project Objectives
- Project Scope
- Business Rationale
- Customer Impact
- Affected Requirements
- Manufacturing Assessment
- Regulatory Impact Assessment
- Financial Impact

It also describes who the members of the Product Support team are (those who are doing the work defined in the charter); who the members of the Extended team are (those that are impacted by the work and provide inputs to the project but who are not doing the work defined in the charter); and who is on the Technical Review (those that evaluate the work done by the Product Support team). In addition, the Product Review is a standing committee with oversight to any product changes.

The work done by the Product Support team uses experimental write ups to record data and analysis of results. Using the data generated in each experiment, next steps are determined and are recorded in the experimental summary and saved to an electronic notebook as permanent, searchable records of the project. More frequent progress of the project is monitored by the Product Support Managers and team discussions typically occur weekly to review the status of each experiment. At each stage exit, the Technical Review occurs to review the data generated by the Product Support team and an output is generated to reflect any decisions made or concerns discussed within the meeting. In addition, project teams can bring unexpected concerns for a Technical Review at any time for review and support.

The Technical Review output includes the following sections:

Section 1: Product Information

Section 2: Description and Summary

Section 3: Readiness Summary for Next Phase/Step

Section 4: Recommendations

Section 5: Risks Identified in Review (to be added to the Risk Assessment for the project)

Once a Technical Review process has determined that the data reflects readiness to move on to the next Step, the Product Review team will meet and evaluate any risks or concerns to determine if the team has approval to move to the next Step. A similar output is generated that outlines Sections 1-5 as described above.

All record outputs, data and meeting notes are stored in a Project file for future reference.

Oversight of products with compliance considerations also occur with Product Compliance Steering Committee to monitor progress of reformulation efforts, related to compliance efforts.

The entire process is a stage-gate process, by which work is broken into defined, sequential stages. Gates consist of management reviews that provide a go, no-go, or redirect decision regarding closing one step and beginning the next.

4. CONCLUSIONS

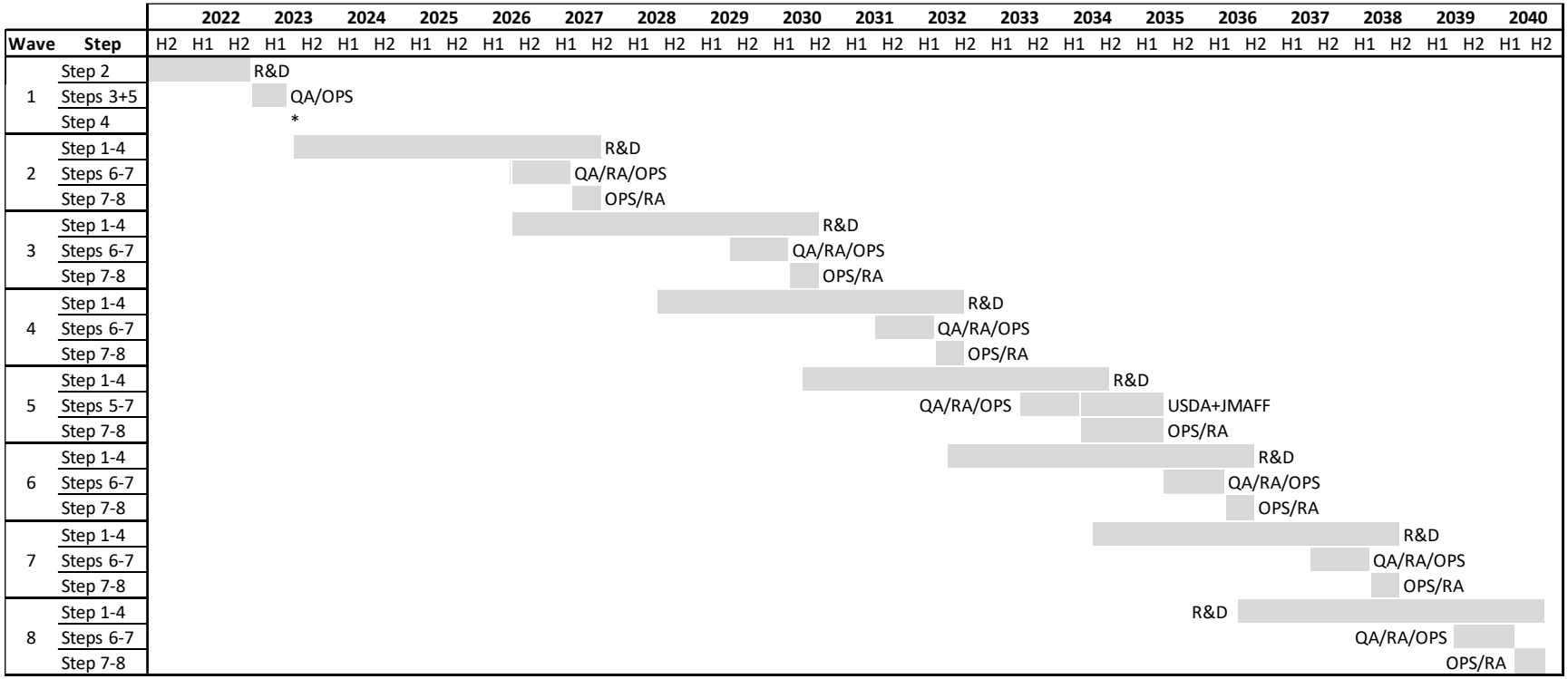
As outlined in this report and in the AoA-SEA report, IDEXX veterinary IVDs must meet a large number of regulatory requirements. As the Applicant's products are sold worldwide, they need to fulfil the regulatory requirements of all the countries where they are placed on the market, not just the ones in the UK. IDEXX must comply with specificity and sensitivity requirements set by regulatory authorities as well as a plethora of other regulatory, product licensing, national animal health competent authority requirements and commercial tender procedures that may further narrow the product requirements.

In addition to the extensive regulatory requirements, the delicate balance between competing affinity processes in antibody or antigen capture systems is easily upset and unwanted side effects are frequently observed when reformulating. Further optimization or changes may be necessary to counter the undesirable effects. Substituting 4-tert-OPnEO or 4-NPnEO from the products will require extensive R&D work where each product will need to be tested and optimised with the alternative.

Overall, a large number of factors affect the substitution of 4-tert-OPnEO and 4-NPnEO. One of these factors is the high number of products that need to be reformulated: 19 in Montpellier, 33 in Westbrook and 13 in Bern. Other factors include sample prevalence, sample volume, the type of product concerned (e.g. "panel" test kits are more complex to reformulate), resource and space constraints.

APPENDICES

Appendix 1. Reformulation timeline for IDEXX Montpellier (FR)



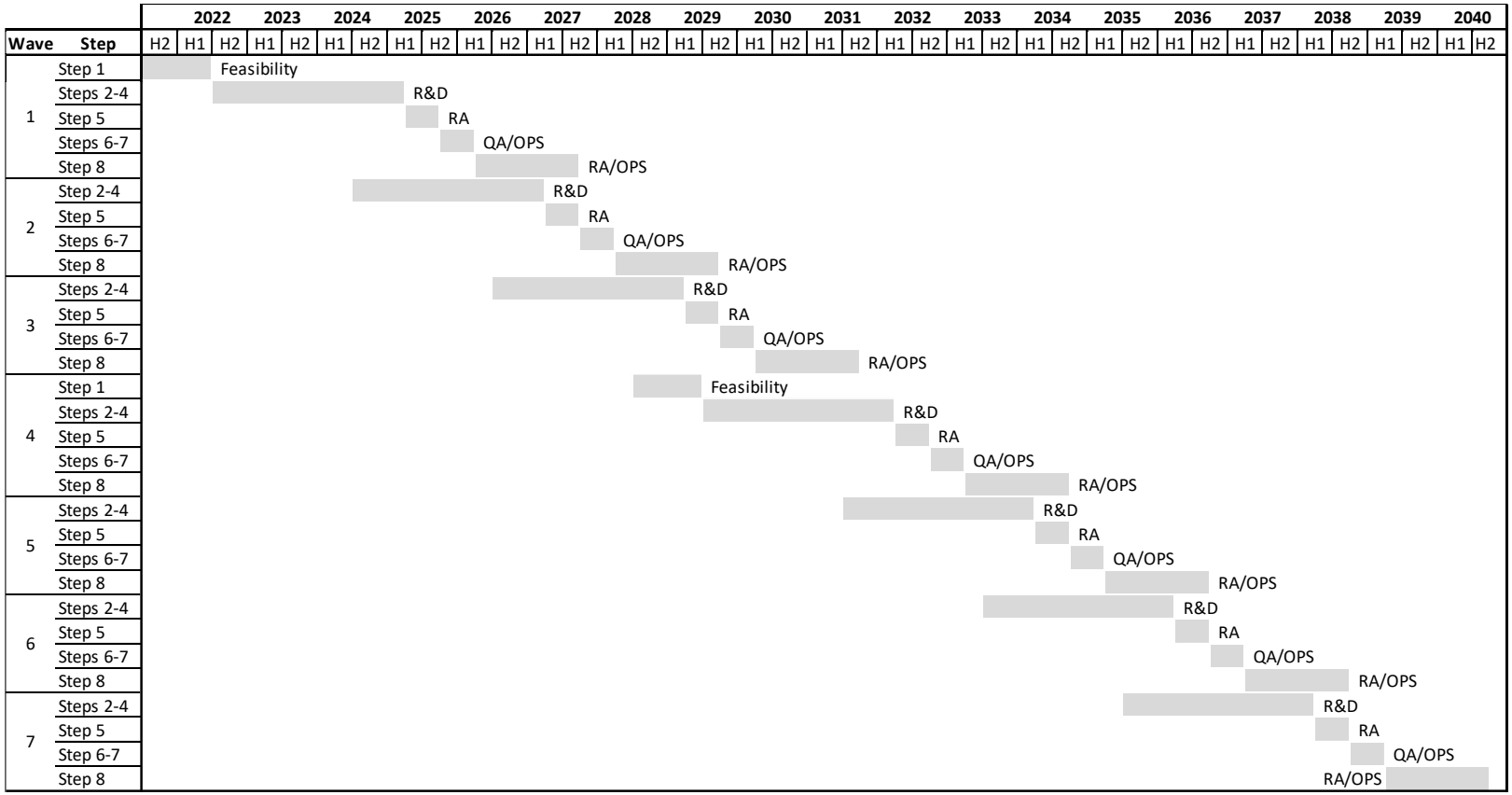
**Wave 1: Shared reagent, no regulatory step is initiated until all kit components are validated in their respective project waves.*

R&D Resources assumptions: 2 at 50% capacity, or 1FTE full time equivalent

Project stacking: an overlap of 24 months is deemed necessary due to the limit R&D resources and the need to reserve time for unplanned projects which may receive a higher priority.

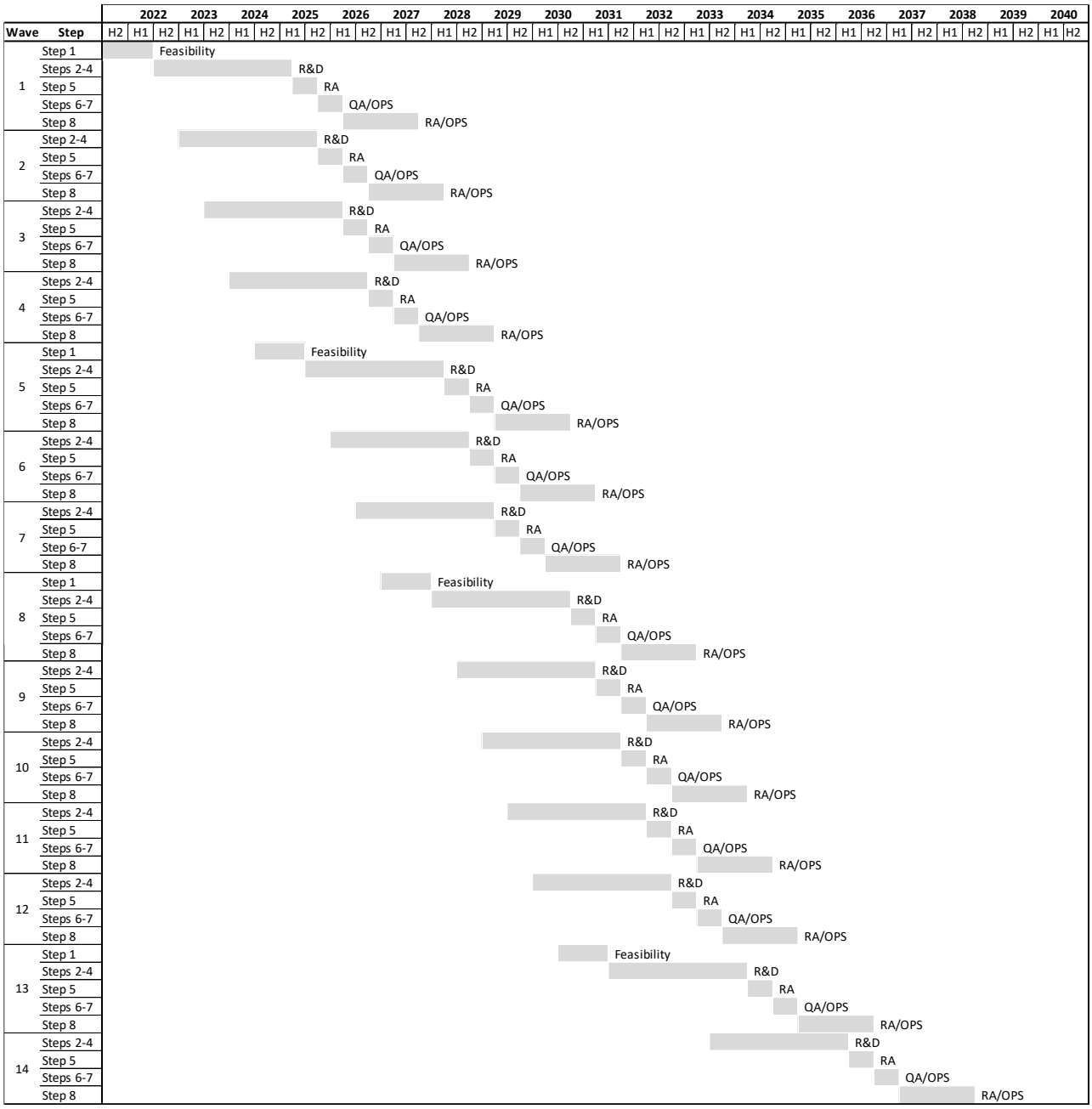
Appendix 2. Reformulation timeline for IDEXX Westbrook (USA)

Timeline for the reformulation of the 13 LPD products:



R&D resources assumptions: 2 at 50% capacity, or 1FTE full time equivalent
Project stacking: an overlap of 24 months is deemed necessary due to the limit R&D resources and the need to reserve time for unplanned projects which may receive a higher priority.
Additional time for feasibility is built in at various stages in the event that a wave has challenges with the existing solution and needs to reassess alternatives.

Timeline for the reformulation of the 18 CAG products:

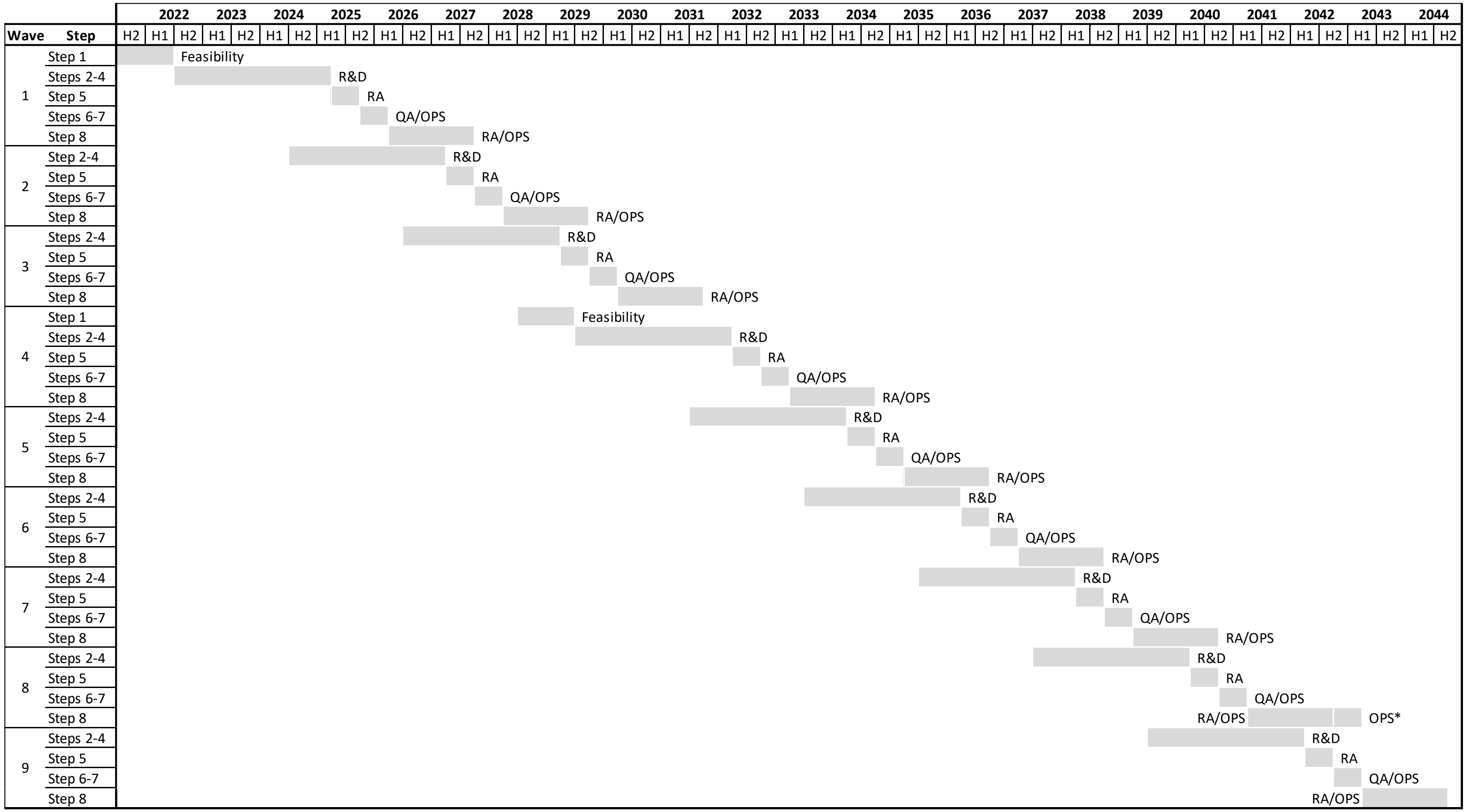


R&D resources assumptions: 2 FTE @ 100% + 1 FTE @ 50% capacity

Project stacking: an overlap of 6 months is deemed necessary for SNAP and 24 months for ELISA plate due to the limited R&D resources and the need to reserve time for unplanned projects which may receive a higher priority.

Additional time for feasibility is built in at various stages in the event that a wave has challenges with the existing solution and needs to reassess alternatives.

Appendix 3. Reformulation timeline for IDEXX Bern (CH)



R&D Resources assumptions: 2 at 50% capacity, or 1FTE full time equivalent
Project stacking: an overlap of 24 months is deemed necessary due to the limit R&D resources and the need to reserve time for unplanned projects which may receive a higher priority.
Additional time for feasibility is built in at various stages in the event that a wave has challenges with the existing solution and needs to reassess alternatives.
*Additional time added in for OPS in Wave 8 to account for having to implement the new formulations into Westbrook as the products in Wave 8 are manufactured in both Westbrook and Bern

Appendix 4. List of products covered by the authorisation application

Table 6. 4-tert-OPnEO or 4-NPnEO is contained in (a) sample diluents, (b) controls, (c) conjugate solutions, (d) SNAP wash solutions, I wash solution, (f) tissue soaking buffer or (g) detection solution

Trade name	Intended use	CAS No.	Detergent Conc. (%)	COO
IDEXX ALV Ab	Indirect ELISA plate assay used to detect antibodies specific to the ALV subgroups A and B in chicken serum.	9036-19-5	0.10[(a)(b)]	USA
IDEXX ALV-J Ab	Indirect ELISA plate assay used to detect antibodies specific to the ALV subgroup J in chicken serum.	9036-19-5	1.00[(a)(b)]	USA
Bovine pregnancy	Capture ELISA plate assay used to detect pregnancy-associated glycoproteins in serum and EDTA plasma of cattle, serum of sheep and goat, EDTA plasma of water buffalo and bison as a marker for pregnancy.	9002-93-1	1.00[(a)(b)]	CH
Canine Cardiopet Plus	Direct ELISA plate assay for the quantitative measurement of NTproBNP from canine EDTA plasma and serum as a marker substance for heart failure.	9036-19-5	1.00[I]	USA
Feline Cardiopet proBNP	Direct ELISA plate assay for the quantitative measurement of NTproBNP from feline EDTA plasma and serum as a marker substance for heart failure.	9036-19-5	1.00[I]	USA
HerdChek BSE-scrapie Ag	Indirect ELISA plate assay used to detect the abnormal conformer of the prion protein (PrPSc) in bovine, caprine and ovine post-mortem tissues (obex, spleen and lymph node samples).	9036-19-5	5.00[(a)(b)(c)]	USA
HerdChek CWD Ag	Indirect ELISA plate assay used to detect the abnormal conformer of the prion protein (PrPSc) in post-mortem white-tailed and mule deer retropharyngeal lymph node tissue.	9036-19-5	5.00[(a)(b)] 1.00 [I]	USA
IDEXX IBV Ab	Indirect ELISA plate assay used to detect antibodies specific to the infectious bronchitis virus from chicken serum samples.	9036-19-5	0.10[(a)(b)]	USA
IDEXX AI MultiS-Screen Ab	Competitive ELISA plate assay used to detect antibodies specific to avian influenza in serum samples from multiple species (chicken, turkey, duck, goose and others).	9036-19-5	1.00[(a)(b)]	USA
IDEXX APP-ApxIV Ab	ELISA plate assay used to detect antibodies specific to Actinobacillus pleuropneumoniae, which is the causative pathogen for swine pleuropneumonia, in serum and plasma of swine.	9036-19-5	0.22[(a)(b)]	CH
IDEXX APV Ab	Indirect ELISA plate assay to detect antibodies specific to the avian pneumovirus in chicken and turkey serum.	9036-19-5	0.11[(a)(b)]	CH
IDEXX BVDV Ag/Serum Plus	ELISA plate assay used to detect the antigens specific to the bovine viral diarrhea virus in bovine serum, plasma, whole blood and ear-notch tissue samples.	9036-19-5, 9016-45-9	1.00[(a)(b)] 0.52[(g)]	CH
IDEXX BVDV Total Ab	Indirect ELISA plate assay used to detect antibodies specific to the bovine viral diarrhea virus in bovine serum, plasma and milk samples.	9036-19-5	0.11[(a)(b)]	CH

			0.50[I]	
IDEXX CSFV Ab	Competitive ELISA plate assay used to detect the antibodies specific to the classical swine fever virus in swine serum and plasma samples.	9036-19-5, 9016-45-9	2.00[(a)(b)]	CH
IDEXX CSFV Ag Serum	Indirect ELISA plate assay used to detect the Erns proteins of the classical swine fever virus in swine serum and plasma samples.	9036-19-5, 9016-45-9	2.08[(f)]	CH
IDEXX IBR gE Ab	Competitive ELISA plate assay that can detect antibodies specific to the infectious bovine rhinotracheitis in bovine serum, plasma and milk sample. It is used to differentiate between naturally infected cattle from vaccinated cattle.	9036-19-5, 9016-45-9	1.00[(a)(b)]	CH
IDEXX *M. Bovis* Ab	Indirect ELISA plate assay that can detect *Mycobacterium bovis* antibodies in cattle serum and plasma samples.	9036-19-5	1.00[(a)(b)]	USA
IDEXX *M. Hyo* Ab	Indirect ELISA plate assay used to detect antibodies specific mycoplasma hyopneumoniae in swine serum and plasma samples.	9036-19-5	0.20[(a)(b)]	USA
IDEXX Milk Pregnancy	ELISA plate assay to detect pregnancy-associated glycoproteins in cow and goat milk samples.	9002-93-1	1.00[(a)(b)]	CH
IDEXX PRV/ADV gB Ab	Competitive ELISA plate assay used to detect antibodies specific to the gB antigen of the pseudorabies virus in swine serum and plasma samples.	9002-93-1, 9036-19-5	1.07[(a)(b)]	CH, USA
IDEXX PRV/ADV gI Ab	ELISA plate assay used to detect antibodies specific to the gI antigen of the pseudorabies virus in swine serum samples. The test differentiates infected from vaccinated animals.	9002-93-1, 9036-19-5	1.07[(a)(b)]	CH, USA
IDEXX Rapid Visual Pregnancy	Indirect ELISA plate assay used to detect early pregnancy-associated glycoproteins in whole blood (EDTA), plasma (EDTA) and serum of cattle, serum of goats, whole blood (EDTA) and serum of sheep and whole blood (EDTA) of water buffalo.	9036-19-5	1.00[(a)(b)]	CH
IDEXX SNAP BVDV Ag	SNAP test used to detect antigens specific to the bovine viral diarrhea virus from serum and ear-notch tissue samples.	9036-19-5	1.00[(d)]	USA
IDEXX Swine *Salmonella* Ab	ELISA plate assay used to detect antibodies specific to several *salmonella* serogroups (B, C1 and D) in serum, plasma and meat juice samples.	9036-19-5	0.20[(a)(b)]	CH
Lyme Quant C6 Antibody Kit	ELISA plate assay for the quantitative measurement of C6 antibodies specific to *Borrelia burgdorferi* in canine serum.	9036-19-5	0.10[(a)(b)]	USA
IDEXX NDV Ab	Indirect ELISA plate assay used to detect antibodies specific to the Newcastle disease virus in chicken serum.	9036-19-5	0.10[(a)(b)]	USA
IDEXX *Neospora* Ab	ELISA plate assay used to detect antibodies specifc to *Neospora caninum* in serum and plasma samples of bovine, caprine and ovine.	9036-19-5	0.25[(a)(b)]	USA
IDEXX BSE Non-biohazard pos control material	BSE positive calibration sample that is sold separately from the IDEXX HerdChek BSE-Scrapie kit.	9036-19-5	0.15[(a)(b)]	USA

IDEXX REO Ab	Indirect ELISA plate assay used to detect antibodies specific to the avian reovirus in chicken serum.	9036-19-5	0.10[(a)(b)]	USA
SNAP 4Dx Plus Test	SNAP test used to detect *Dirofilaria immitis* antigens, antibodies to *Anaplasma phagocytophilum*, antibodies to *Anaplasma platys*, antibodies to *Borrelia burgdorferi*, antibodies to *Ehrlichia canis* and antibodies to *Ehrlichia ewingii* in canine serum, plasma and whole blood samples.	9036-19-5	1.00[(d)]	USA
SNAP cPL Test	SNAP test for the determination of pancreas-specific lipase levels in canine serum.	9036-19-5	1.00[(d)]	USA
SNAP Feline Heartworm Test	SNAP test for the semi-quantitative detection of Dirofilaria immitis antigen in feline whole blood.	9036-19-5	1.00[(d)]	USA
SNAP Feline proBNP Test	SNAP test for the measurement of circulating NTproBNP in feline serum and EDTA plasma.	9036-19-5	1.00[(d)]	USA
SNAP Feline Triple Test	SNAP test for the detection of *Dirofilaria immitis* antigens, antigens to feline leukemia virus and antibodies to feline immunodeficiency virus in feline serum, plasma and whole blood.	9036-19-5	1.00[(d)]	USA
SNAP FeLV Antigen Test	SNAP test for the detection of feline leukemia virus antigens in feline serum, plasma and whole blood.	9036-19-5	1.00[(d)]	USA
SNAP FIV/FeLV Combo Plus Test	SNAP test for the detection of feline leukemia virus antigens and antibodies to feline immunodeficiency virus in feline serum, plasma and whole blood.	9036-19-5	1.00[(d)]	USA
SNAP FIV/FeLV Combo Test	SNAP test for the detection of feline leukemia virus antigens and antibodies to feline immunodeficiency virus in feline serum, plasma and whole blood.	9036-19-5	1.00[(d)]	USA
SNAP Foal IgG Test	SNAP test for the semi-quantitative detection of immunoglobulin G in equine serum, plasma and whole blood.	9036-19-5	1.00[(d)]	USA
SNAP fPL Test	SNAP test for the determination of pancreas-specific lipase levels in feline serum.	9036-19-5	1.00[(d)]	USA
SNAP Giardia Test	SNAP test for the detection of *Giardia* antigens in canine and feline feces.	9036-19-5	1.00[(d)]	USA
SNAP Heartworm RT Test	SNAP test for the semi-quantitative detection of *Dirofilaria immitis* antigens in canine and feline whole blood, serum and plasma.	9036-19-5	1.00[(d)]	USA
SNAP Leishmania Test	SNAP test for the detection of Canine leishmaniasis in canine whole blood samples.	9036-19-5	1.00[(d)]	USA
SNAP Lepto Test	SNAP test for the detection of anti-*Leptospira* antibodies to the serovars Grippotyphosa, Canicola, Pomona, and Icterohaemorrhagiae in canine serum.	9036-19-5	1.00[(d)]	USA
SNAP Parvo Test	SNAP test for the detection of canine parvovirus antigens in canine feces.	9036-19-5	1.00[(d)]	USA
IDEXX Bluetongue Competition Ab	Competitive ELISA plate assay used to detect antibodies specific to the bluetongue virus in sheep, goat and cattle serum.	9036-19-5	2.00[(a)(b)]	FR
IDEXX Brucellosis Ovine/Caprine Serum Ab	ELISA plate assay used to detect antibodies specific to the bacteria Brucella abortus (found in cattle) and Brucella melitensis (found in sheep and goats) from animal serum.	9036-19-5	2.00[(a)(b)]	FR

IDEXX BVDV P80 Ab	Blocking ELISA plate assay used to detect antibodies specific to bovine viral diarrhea virus from bovine serum and plasma as well as bovine milk samples. It can also be used to detect specific antibodies directed to the border disease virus from ovine serum.	9036-19-5	2.00[(a)(b)]	FR
IDEXX Fasciolosis Verification	ELISA plate assay used to detect the level of *Fasciola hepatica* antibodies in bovine and ovine serum samples as well as bovine milk samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX IBR Individual Ab	ELISA plate assay used to detect antibodies specific to the Bovine Herpesvirus-1 from individual bovine serum samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX IBR Pool Ab	ELISA plate assay used to detect antibodies specific to the Bovine Herpesvirus-1 from pool bovine serum samples and tank milk samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX Leukosis Serum Screening Ab	ELISA plate assay used to detect antibodies specific to the Bovine Leukemia virus from individual and pool bovine serum samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX MAP Ab	Indirect ELISA plate assay used to detect *Mycobacterium avium* subsp. *Paratuberculosis* antibodies from bovine milk, serum and plasma samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX Paratuberculosis Screening Ab	Indirect ELISA plate assay used to detect *Mycobacterium avium* subsp. *Paratuberculosis* antibodies from bovine milk, serum and plasma samples as well as serum and plasma of sheep and goats.	9036-19-5	2.00[(a)(b)]	FR
IDEXX Paratuberculosis Verification Ab	ELISA plate assay used to detect *Mycobacterium avium* subsp. *Paratuberculosis* antibodies from bovine milk, serum and plasma samples as well as serum and plasma of sheep and goats.	9036-19-5	2.00[(a)(b)]	FR
IDEXX PI-3 Ab	ELISA plate assay used to detect antibodies specific to the parainfluenza type 3 virus from individual bovine serum samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX RSV IgG Ab	ELISA plate assay used to detect immunoglobulin G antibodies specific to the bovine respiratory syncytial virus from individual bovine serum samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX RSV IgM Ab	ELISA plate assay used to detect immunoglobulin M antibodies specific to the bovine respiratory syncytial virus in individual bovine serum samples.	9036-19-5	2.00[(a)(b)]	FR
IDEXX Trivalent Ab	ELISA plate assay used to detect antibodies specific to the bovine respiratory syncytial virus, parainfluenza virus type 3 and adenovirus from individual bovine serum samples.	9036-19-5	2.00[(a)(b)]	FR

Appendix 5. License and other permit requirements by countries

Legend:

- LC = license
- LC-PG = License for Program Diseases
- MR = Mutual Recognition with (country/disease)
- IP = Import Permit
- FSC = Free Sales Certificate
- n/a = Not applicable

Country	Region	Infectious		Non-infectious	
		LPD	CAG	LPD	CAG
Belgium	European Union	LC-PG	n/a	n/a	n/a
Bulgaria	European Union	LC-PG	n/a	n/a	n/a
Croatia	European Union	TSE only	n/a	n/a	n/a
Czech Republic	European Union	LC	LC	LC	LC
France	European Union	LC-PG	n/a	n/a	n/a
Germany	European Union	LC-PG	n/a	n/a	n/a
Ireland	European Union	MR-DE (BVDV)	n/a	n/a	n/a
Italy	European Union	LC-PG	n/a	n/a	n/a
Netherlands	European Union	LC-PG	n/a	n/a	n/a
Poland	European Union	LC	n/a	LC	n/a
Portugal	European Union	LC (Rapid tests only)	n/a	n/a	n/a
Romania	European Union	LC-PG	n/a	n/a	n/a
Russia	Europe	IP	IP	IP	IP
Serbia	Europe	LC	LC	LC	LC
Slovakia	European Union	LC	LC	LC	n/a
Spain	European Union	LC	LC	LC	LC
Switzerland	Europe	LC-PG	n/a	n/a	n/a
Ukraine	Europe	LC/IP	LC/IP	n/a	n/a
Cyprus	European Union	n/a	n/a	n/a	n/a
Morocco	Africa	IP	IP	IP	IP

South Africa	Africa	IP	IP	IP	IP
Egypt	Africa	IP	IP	IP	IP
China	Asia	LC	n/a	LC	n/a
Indonesia	Asia	LC	n/a	LC	n/a
Japan	Asia	LC	n/a	LC	n/a
Malaysia	Asia	LC	n/a	FSC	n/a
Philippines	Asia	LC	n/a	FSC	n/a
South Korea	Asia	LC	n/a	LC	n/a
Thailand	Asia	FSC	FSC	FSC	FSC
Cambodia	Asia	IP	n/a	IP	n/a
India	Asia	IP	IP	IP	n/a
Kazakhstan	Middle East	LC-PG	n/a	n/a	n/a
Turkey	Middle East	LC	n/a	LC	n/a
Canada	North America	LC/IP	n/a	n/a	n/a
United States	North America	LC	n/a	n/a	n/a
Australia	Oceania	IP	IP	IP	IP
New Zealand	Oceania	IP	IP	IP	IP
Argentina	LAO	LC	n/a	n/a	n/a
Brazil	LAO	LC	n/a	n/a	n/a
Bolivia	LAO	LC	n/a	LC	n/a
Colombia	LAO	LC	n/a	n/a	n/a
Costa Rica	LAO	LC	n/a	LC	n/a
Ecuador	LAO	LC	n/a	n/a	n/a
El Salvador	LAO	LC	n/a	n/a	n/a
Guatemala	LAO	LC	n/a	n/a	LC
Panama	LAO	LC	n/a	n/a	LC
Paraguay	LAO	LC	n/a	n/a	LC

Peru	LAO	LC	n/a	LC	n/a
Venezuela	LAO	LC	n/a	n/a	LC
Honduras	LAO	LC	n/a	LC	n/a
Mexico	LAO	LC	n/a	n/a	n/a
Puerto Rico	LAO	MR-USA	n/a	n/a	n/a

Appendix 6. Disease prevalence and how it affects reformulation

ELISA tests are important in low and high infectious disease prevalence situations.

Low prevalence:

Due to successful control or eradication programs using ELISA tests, the livestock industry benefits from healthier herds and flocks. However, programs need to be continued as surveillance programs using ELISA tests to keep prevalence low and obtain early information about possible reinfections. Additionally, with nearly eradicated diseases, obtaining enough field samples for further product development work would be challenging and could take many years.

Additionally, some companion animal health assays, even if low prevalence, can have considerable health implications to the individual animal. As an example, Heartworm prevalence is considered low; however, if not tested early and treated can result in death of a pet. Another example is FeLV, which is highly contagious to populations of cats (e.g. shelters) and without appropriate testing, outbreaks can occur.

High prevalence:

Diseases with high prevalence require high attention especially if they are notifiable[2] or sufficiently infectious to have a negative impact on herd and flock health and productivity. These situations can be very costly for the livestock industry and entire economies can suffer significantly from negative impacts due to trade restrictions (Avian influenza, Bluetongue[3]). If logistically possible and affordable, diseases with high prevalence are fought by control and eradication programs using ELISA tests. Therefore, a review of not less than 12 years is necessary due to the lengthy reformulation work required to bring ELISA tests free of 4-tert-oPnEO or 4-NPnEO to the market to meet the demand for ELISA tests to avoid spreading of infectious diseases.

Additionally, some of the diseases tested for by IDEXX SNAP tests are zoonotic (spreadable from animals to human). These diseases are Lyme, Anaplasmosis, Ehrlichiosis, Leishmaniasis, and Leptospirosis. Testing for these diseases using IDEXX SNAP tests plays a vital role in understanding potential human exposure to these diseases.

Transmission of leptospirosis can occur through direct contact or indirectly through environmental exposure. Leptospires enter the body through mucous membranes in the mouth, eyes, or nose, or through abraded or water-softened skin and can then be shed back into the environment to be transmitted to other dogs, other animals or people.

Canine parvovirus is a highly contagious and life-threatening disease. Early and definitive identification allows for timely management and treatment. The SNAP Parvo Test has been shown not to cross-react with modified live vaccines. Parvo has a high mortality rate if not caught early and difficult to contain if an outbreak occurs (e.g. impact to shelters).

[2] https://www.oie.int/animal-health-in-the-world/oie-listed-diseases-2020/

[3] https://www.gov.uk/guidance/imports-and-exports-of-animals-and-animal-products-topical-issues#bluetongue-virus-in-europe

Table 7. List of IDEXX ELISA plate and SNAP tests and disease prevalence in Europe

Material	Disease	Zoonosis[4]	Notifiable[2]	Prevalence	References
IDEXX ALV-Ab IDEXX ALV-J	Avian Leukosis Virus	N	N	low	
HERDCHEK BSE-SCRAPIE ANTIGEN HERDCHEK CWD	BSE	Y	Y	low	http://www.cfsph.iastate.edu/FastFacts/pdfs/bse_F.pdf
IDEXX IBV AB	Infectious Bronchitis	N	Y	endemic	http://www.infectious-bronchitis.com/variants-europe.aspx
IDEXX AI MULTIS-SCREEN AB	Avian Influenza	Y	Y	Low pathogenic strain outbreak	https://www.ecdc.europa.eu/en/publications-data/surveillance-report-avian-influenza-overview-august-november-2019
IDEXX APP-APX IV AB	*Actinobacillus pleuropneumoniae*	N	N	high	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2327245/
IDEXX APV AB	Avian Pneumovirus	N	N	present	http://www.avian-pneumovirus.com/avian-metapneumovirus-disease.asp
IDEXX BLUETONGUE COMPETITION AB	Bluetongue antibody	N	Y	Frequent outbreaks	
IDEXX BRUCELLOSIS OVINE/CAPRINE SERUM AB	Brucellosis ovine/caprine	Y	Y	Low or absent (eradicated)	
IDEXX BRUCELLOSIS OVINE/CAPRINE SERUM AB	*Brucella abortus*	Y	Y	Low or absent (eradicated)	
IDEXX BVDV AG/SERUM PLUS	BVDV Ag	N	Y	High in non-eradicated areas (PI 1-2%)	
IDEXX BVDV P80 AB IDEXX BVDV TOTAL AB	BVDV Ab	N	Y	High in non-eradicated areas (Ab >50%)	
IDEXX CSFV AB	CSFV Ab	N	Y	absent, monitoring programs	
IDEXX CSFV AG SERUM	CSFV Ag	N	Y	absent	
IDEXX FASCIOLOSIS VERIFICATION	Fasciolosis Ab	N	N	endemic	
IDEXX IBR GE AB IDEXX IBR INDIVIDUAL AB IDEXX IBR POOL AB	IBR Ab	N	Y	low or absent (eradication programs)	
IDEXX LEUKOSIS BLOCKING AB IDEXX LEUKOSIS MILK SCREENING AB IDEXX LEUKOSIS MILK VERIFICATION AB IDEXX LEUKOSIS SERUM SCREENING AB	Bovine Leukosis Ab	N	Y	absent, monitoring programs	IDEXX LPD
IDEXX M. BOVIS AB	M. bovis (bovine tuberculosis) Ab	Y	Y	Low, outbreaks	https://www.visavet.es/bovinetuberculosis/bovine-tb/eradication.php
IDEXX M. HYO AB	M. hyopneumoniae Ab	N	N	various	
IDEXX MVV/CAEV P28 SCREENING AB	CEAV MVV Ab	N	Y	Low or absent	

[4] Zoonosis means a disease which can be transmitted to humans from animals

IDEXX MVV/CAEV P28 VERIFICATION AB					
IDEXX PARATUBERCULOSIS SCREENING AB IDEXX PARATUBERCULOSIS VERIFICATION AB	Paratuberculosis Ab	N	Y	various	
IDEXX PI-3 AB	Parainfluenza-3	N	N	low	
IDEXX PRV/ADV GB AB IDEXX PRV/ADV GI AB	Pseudorabies Ab	N	N	absent (eradicated)	
IDEXX RSV IGG AB IDEXX RSV IGM AB	BRSV Ab	N	N	low	
IDEXX SWINE SALMONELLA AB	Swine Salmonella Ab	Y	N	low	
IDEXX TRIVALENT AB	Trivalent Ab (Bovine respiratory disease (BRD) complex; Parainfluenza-3 virus (PI-3), Adenovirus (ADV) and Bovine Respiratory Syncytial Virus (BRSV)	N	N	Low – higher in cold weather	
IDEXX NDV AB	Newcastle Disease Virus Ab	Y	Y	Low, outbreaks	https://www.oie.int/en/animal-health-in-the-world/animal-diseases/Newcastle-disease/
IDEXX NEOSPORA AB	*Neospora caninum* Ab	N	N	endemic	
IDEXX REO AB	Reovirus Ab	N	N	Can be high	https://www.cabdirect.org/cabdirect/abstract/20143314278
SNAP 4Dx Plus Test	Anaplasma (AP) Ehrlichia (EC) Canine Heartworm (HW) Lyme	Y (AP & Lime) N (EC & HW)	N	Positive rates: AP = 6.8%; EC = 4.3%; Lyme = 3.0%; HW = 2.3%	
SNAP cPL Test	cPL	N	N	36.6% abnormal rate	
SNAP Feline Heartworm Test	Dirofilaria immitis Ag	N	N	2.5% positive rate	
SNAP Feline proBNP Test	NTproBNP	N	N	38.5% abnormal rate	
SNAP Feline Triple Test	FeLV, FIV and feline heartworm	N	N	Positive rates: FeLV = 6.5%; FIV = 10.7%; Feline Heartworm (HW) = 2.5%	
SNAP FeLV Antigen Test	FeLV	N	N	6.5% positive rate	
SNAP FIV/FeLV Combo Plus Test	FeLV and FIV	N	N	Positive rates: FeLV = 6.5%; FIV = 10.7%	
SNAP FIV/FeLV Combo Test	FeLV and FIV	N	N	Positive rates: FeLV = 6.5%; FIV = 10.7%	
SNAP fPL Test	fPL	N	N	37.2% abnormal rate	
SNAP Giardia Test	Guardia Ag	Y	Y	23.4% positive rate	

SNAP Heartworm RT Test	*Dirofilaria immitis* Ag	N	N	2.3% positive rate	
SNAP Leishmania Test	*Leishmaniasis*	Y	N	12.8% positive rate	
SNAP Lepto Test	anti-*Leptospira* Ag	Y	Y	20.4% positive rate	
SNAP Parvo Test	Parvovirus Ag	N	N	34.9% positive rate	