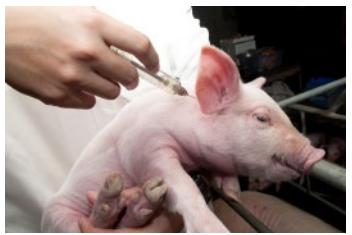









Insight Report – Thailand :
ASEAN Animal Health Regulatory Benchmarking Survey

Prepared for: Asia Animal Health Association

Date: 6. September.2018

Report content

Background & Study Objectives

The 1st ASEAN Animal Health Regulatory Benchmarking Survey…

Background

AAHA (Asia Animal Health Association) is conducting a study to review, track and benchmark the veterinary products' regulation framework and practices across 7 ASEAN countries, namely Thailand, Myanmar, Malaysia, Indonesia, Philippines, Cambodia and Vietnam.

Scope of work

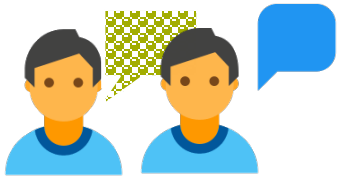
This is the **1st and 2nd phase of a 4-phase project**. In this phase, opinions are derived from business and regulatory managers in animal health (AH) companies. The discussion topics are:

- Assess the impact of regulatory framework that impacted AH industry
- Evaluate the adoption of technology/innovation within the AH regulatory framework
- Gauge the extent of technical harmonization within each country, and across the region
- Evaluate the readiness of the AH regulatory framework for the 21st century

Who do we talk to? How are interviews done? Where we conduct the study?

Total interviews: N=10

Respondent profile	Sample, n=10
MNC Business Managers	5
Local Business Managers	1
MNC Regulatory Managers	4
Local Regulatory Managers	-



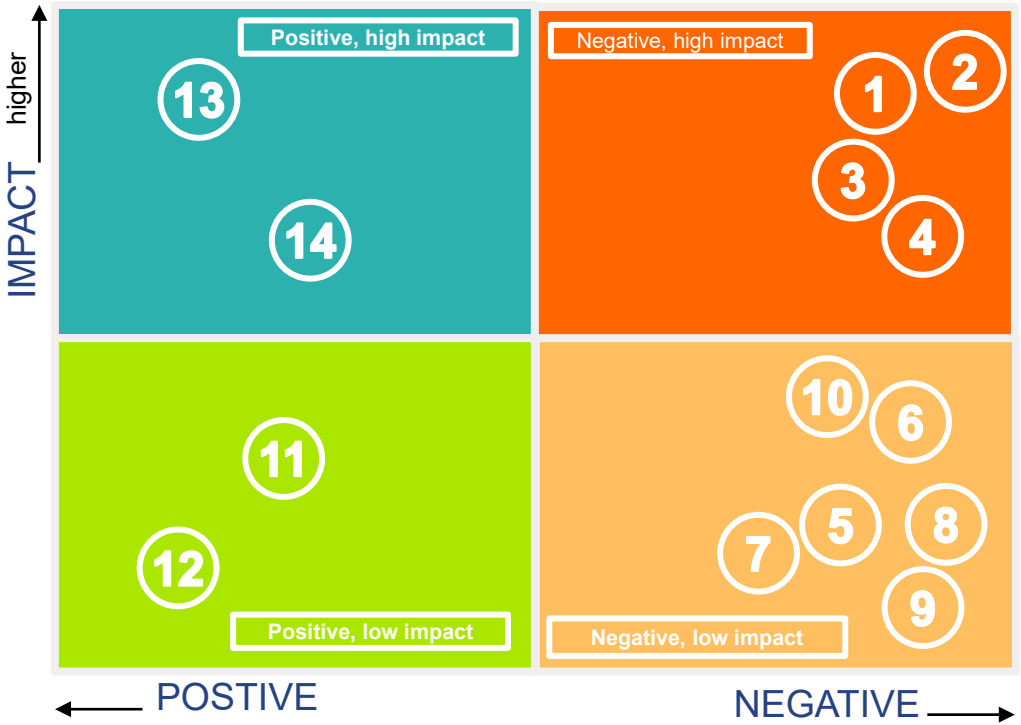
1- 1.5 hours face-to-face / phone interviews with targeted managers

List of respondents are provided by AAHA or free find by Kynetec and approved by AHA

Challenges faced with regulatory bodies/regulation : Bringing products to market

The pain-points are related to high standard set for regulation of AH products! PIC/S requirement/compliance is the main headache for some companies.

The general consensus is TH regulatory bodies had made big (positive) leap in meeting regulation timeline and increasing the standard of AH products.



IMPACT refers to the impact of this development/topic/change to the AH industry

POSITIVE refers positive development/topic/change, whilst

NEGATIVE refers to negative development/topic/change

1. Difficult GMP clearance
2. Unattainable standard = as human pharma
3. Inconsistent guideline across different authorities
4. Lack of staff with AH expertise
5. High product registration fees
6. Stringent requirement for stability data
7. Short time given for first review
8. Difficult to register Innovative products
9. Issue with product form change
10. Challenges faced with FSC
11. Communication between authorities & manufacturers
12. Waived import tax for vaccine
13. Shorter time for product registration
14. Enhancing standard of AH products

Thailand AH regulatory framework was revamped in the recent years and considered relatively advanced. Having said that, PIC/S compliance is said to 'create' most issues to some manufacturers…

Negative, high impact

Difficult GMP clearance (if not PIC/S compliance)

>> Thai FDA implemented GMP accreditation in 2012 and joined PIC/S in August 2016. Many MNCs faced numerous challenges to get the GMP clearance. First of all, PIC/S members mainly formed by human product organizations so it is harder for AH companies. Also, the companies with vaccine approved by EU will be fine but not those approved by USDA as USDA is not a member of PICS. However, US FDA is the member of PICS.

Thai FDA classified the manufacturers into 3 categories: ASEAN Listed Inspection Service (certified by PIC/S), PIC/S, and non-PIC/S. Non-PIC/S manufacturers will required to submit more documents, extra procedures, longer processing time and higher fees before they are bring their products to Thailand.

Documents and payment required during GMP clearance:

- Certified PIC/S – GMP Certificate OR GMP Audit Report, QA Agreement; 5,000 Baht
- PIC/S - GMP Certificate, GMP Audit Report, QA Agreement and Site Master File; 10,000 Baht
- Non-PIC/S - GMP Certificate, GMP Audit Report, QA Agreement, Site Master File, list of SOP, on-site GMP inspection and etc.; 150,000 Baht

The companies need to arrange a suitable time for the Thai officers for site inspection and pay 200,000 Baht as inspection fees. Officers' expenses during the inspection is borne by the companies.

Like some of its neighbors, the standard set for AH product registrations are similar to human health. This lead to delay in registration.

Negative, high impact

Unattainable standard – based on human pharma product registration

>> Thai FDA regulate both human and animal drug using the same drug law. Some requirements are not meant to apply for AH product! Regulations are getting stricter (more procedures, higher fees, etc) after every new announcements!

Both MNC and local expressed their concern on the strict regulation as this can stop the companies from introducing innovative products.

There are numerous challenges that faced by the companies, such as:

- New chemical entity on label – A suffix “NC” new drug with conditional approval is labelled on new products that registered in the country, this restricted them to sell the products freely…
- Feed classified as drug in Thai FDA – Some products are classified as feed in their origin country but Thai FDA classified it as drug. Thus the companies cannot meet the requirement in FDA for registration.
- INN (International Non-proprietary Names) on label – This is human standard. Many chemicals used in animal health products are not used by human so companies are not able to provide the INN to Thai FDA as INN only available for human.
- Requirement for variation - apply ASEAN variation guideline for human, some documents are not available.

Although there had been significant improvements, AH manufacturers found that there are still lacking of expertise amongst the regulators and inconsistency of AH registration protocol….

Negative, high impact

Inconsistent guideline across different authorities

>> Companies agreed that the guideline is unclear as the checklist requirement is highly dependent on the officer that review their dossiers. Their understanding or perception of the products can affect the requirement/guideline for the registration.

Local companies also mentioned that Thai FDA do not have a clear protocol for product testing for AH products. This discourages the local manufacturers to introduce new drug as there is no clear guideline/protocol for R&D activities.

We have doubts on some aspects that prevent us to do things due to unclear regulations, or they give an answer which sounds as if it is their own decision. In other words, there is no clarity. The obstacle lies in the indefiniteness on the part of the regulatory. - Local

Lack of staff with AH expertise

>> Both MNC and local agreed that the Thai FDA do not have enough officers to do all the work. Every registration comes along with thick dossiers that need huge amount of time and labor.

Moreover many officers in Thai FDA is pharmacists not veterinarians so their knowledge on AH is limited. This lead to them asking for documents/tests that are not AH related as they refer back to human health standard and processes. This once again, will cause delay…

With the aim to be more efficient and have AH products registered in a timely manners, some changes made – higher fees, strict regulation and short review time posed challenges to some companies….

Negative, low impact

High product registration fees >> Thai FDA increased the fees for product registration drastically in order to approve the product license in a timely manner. Most of the MNC companies are fine with it, but the high registration fees created some negative impact on the local companies.

In the past we pay only 60 dollars for both pharmaceutical and biologics but now separate. Vaccines we pay about 4,000 dollars. From 60 to 4,000 dollars for vaccine. For new vaccine, you will need to pay 5,000 dollars. For me, I am okay with fee but what I heard from the local company, they say, oh, it's too expensive. - MNC

Stringent requirement for stability data >> Few mentioned the Thai FDA required stability data Zone 4B for all products. The products especially vaccine will need to be kept in 2 to 8 °C and the stability temperature need 2 – 3 years' record. Thai FDA requires 3 batches per presentation but most country including Europe or US require 3 batches in total presentation, thus they have to plan in advance to prepare 3 batches stability record for Thailand's registration.*

Short time given for first review >> Majority of AH companies said the time given to prepare the documents for the first review is too short. Some documents are hard to obtain in a short time, and due to the strict registration process, the checklist is long.

To fasten registration process, Thai FDA will only review documents once. They gave the companies 15 working days – 2 months time to submit the documents for the first review or else their application will be canceled without any refund.

Additional information on stability data. This is validated and confirmed with respondent….

- It is really a big challenge to provide for Thailand and basically for Thailand only stability data for 3 batches PER PRESENTATION.
- In EU, indeed, in most cases, only need 3 batches IN TOTAL…
- Example:

Presentation	EU	TH
500 doses	1 batch	3 batches
1000 doses	1 batch	3 batches
2000 doses	1 batch	3 batches
Total	3 batches	9 batches

With the aim to be more efficient and have AH products registered in a timely manners, some changes made – higher fees, strict regulation and short review time posed challenges to some companies….

Negative, low impact

Difficult to register innovative products	>>	One MNC said that obtaining the efficacious result for new innovation takes time and effort…as regulators wanted 'proof of concept' for innovate products. *The innovator (MNC) usually the original, if we do not follow their route we will fall into the new drug category which will be a major affair where we need to pay high amount of money, invest more time and more documentation for innovative product registration. - Local*
Issue with product form change	>>	One local company said if they want to change the application method of a product to be more innovative (e.g. from oral to injection), they will require to register the product as new product. This is costly and time consuming. Various paperwork needs to be resubmitted as FDA considered this as a new product! *There are 2 things. One is innovation while the other one is a development on existing forms; for instance, previously it maybe tablet or injection forms but when we introduce a patch form it will be considered new by FDA. Anyway, it is difficult because there has to be supportive information of its effectiveness. - Local*
Challenges faced with FSC (with innovative products)	>>	Some MNCs mentioned that the registration is delayed when they need to wait for the FSC from the origin country as Thailand usually is not the first country to register for innovative products. *We have to delay everything because FSC is required with each documentation so we have to wait until some country selling the product. We prefer to invest or work together with the FDA in doing a trial or anything to submit the dossier without FSC, by running parallel without the FSC and get the registration approval. Until the product gets the FSC from some country, we will submit later on. - MNC*

The willingness of Thai AH regulatory bodies to have open dialogue and discussions with companies is a positive development.

Positive, low impact

Open communication between authorities & manufacturers

>> According to both local and MNC manufacturers…although there are strict process to adherent, authorities are relatively open for discussion and explanation if there are certain documentation that these companies are not able to provide.

The companies or their association(s) have opportunity to try to explain and convince regulators to be flexible or compromise on some part of the regulations.

Waived import tax for vaccine

>> Only one MNC mentioned that the import tax for vaccine has been waived to 0% to support the farmers.

Even the registration, like release the product, they're trying to help us, like last time, they try to waive the tax of imported vaccine, because we want the farmer to have very high margin but low cost production of the vaccine. So, then there's no import tax on the vaccine, still the same. Normally the government support the farmer, because we're agricultural country, so the export is the main. - MNC

Although AH manufacturers at times a caught off guard with the rigid regulatory requirements, many professed that the reasons behind the regulations helps to elevate the standard of AH products

Positive, high impact

Shorter time for product registration (with PIC/S GMP)

>> As the Thai FDA is currently following the new regulation by military intervention laws (CC. Liberation Law), they committed to approve animal health generic product's product license within 1 to 1.5 year (MNC) or within 5 months (Local) but with much higher charges charged on the companies for product registration.

This increases the no. of AH products registered in the market.

In the past, we have to take about 9 to 12 months to have a first batch imported after getting the approval from the FDA. But today we can do that in just only 3-4 months. That's why it requires more collaboration among our people not only here in Thailand, but also with the planning and manufacturing side. - MNC

Enhancing the standard of AH products (due to strict regulation)

>> MNC agreed that the implementation of stricter registration for AH products brought many benefits. It prevents low quality / illegal products from entering the market easily.

This will also able helps to protect the patent (IP protection) of the companies' producing the products as it will harder for the counterfeits to get in Thailand.

Normally they follow the high standard of US FDA or European FDA. When there's some report, there's something maybe residue, will be.. have the problem of cancer, in human, sometimes they can even send a letter to us, if you've this program or stock maybe. - MNC

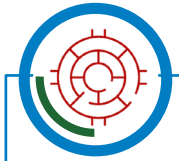
The major headache (in terms of cost and challenges) for AH companies in Thailand tends to be related to meeting PIC/S compliance. It can be costly and delay registration process….

Most expensive

- Manufacturer site inspection (if not PIC/S compliance)

  If regulators needs to do site inspection, companies will need to pay 200,000THB for site inspection. Besides that, the companies are responsible to make the schedule and also sponsor the trip of 2 officers for this inspection.
- Drug registration & scientific (dossier) review – feedbacks from local companies

  New registration fee is most expensive, increased a few fold compared to previous registration fees. Local manufacturer also said that the price for scientific (dossier) review is increased nearly 30 folds.



Most challenging

- Most challenging part is the guideline being unclear in registration for AH as Thai FDA follows human regulations.

  Some local manufacturers faced issues in manufacturing new drug as some protocols do not exist for veterinary products, only for human drugs. Thus very few is keen to invest in new product production.

Thai AH regulatory bodies are putting lots of emphasis on product safety. Hence, Pharmacovigilance compliance is now in place for AH products….

No major challenges for most companies with regulation requirement for selling / marketing their products once the products obtain registration.

Negative development ⟷ Positive development

Restricted advertising

Companies cannot advertise product publicly especially for vaccine and antibiotics. They can only advertise on specific channels and sell to veterinarians with license.

Labelling

The product is mandatory to have Thai labelling, companies need to have bilingual (if English is requires). The custom will only release the product if the label align with CoA registered.

Pharmacovigilance (PV)

Companies need to record performance of their products -- PV report. They will need to send the report to FDA if any complaints or adverse effect is observed to ensure safety.

Predictable timeline for sales planning

With new regulations that are predictable in registration timeline, AH companies are able to make precise and timely marketing decision for their business.

Patent protection and copyright control

Thailand has a surveillance/patent protection system like other countries to protects the copyright of innovative products. Thus encourage the innovation in the country.

Assessment on: safety, manufacture/quality, efficacy & R&D activities

None faced issue with safety. With respect to manufacture/ quality, the issue is not in the production but providing suitable documentations to authorities to prove they meet the required standards.

Safety

- Most of the companies (MNC and local) do not face any major issue in terms of safety with their products. Their product is imported from developed countries with high safety assurance. Both local and MNC able to hand in documents and comply with the high standard of safety required by FDA.
- Pharmacovigilance is implemented in October 2016 by the Thai FDA where the companies agreed that this move is positive move to keep track of the adverse events.

Actually, right now we also encourage our people to monitor or to pharmacovigilance, but I think to make this data useful we should have a database and I think the most importance thing is that we should use this data to integrate into our direction of research and development. - MNC

Manufacture/Quality

- Majority MNC has their own specific problems with the manufacture or quality. The stability data, CoA requirement requested by authorities and strict GMP declaration are the issues that were mentioned.
- One MNC mentioned the trouble with the stability data happens when the authority is been inconsistent on stability guidelines by changing the requirement frequently. Besides that, CoA requirement is challenging when authority asking for certificate from the original manufacturer which is beyond the companies' ability to get.
- MNC hoping that the authority will has a clear and consistent guideline to follow and explanation rejections they received…

Generally, companies, both local and MNC do not faced issue with product efficacy. R&D activities are challenging for local manufacturer due to strict criteria from regulators!

Efficacy

- MNC and local companies do not face any major efficacy problem as they are mostly imported/produced well-developed AH products. Only one MNC mentioned possible issue with generic/"old' products where the data is not as well developed or updated as the new products.
- Another MNC suggested to hire more experts in Thai FDA to read stability data correctly and consistently as the stability data requirements (either strict or lenient) highly dependent on the experts reviewing it.

R&D activities

- As expected, there are not many issue raised by the MNC as most of the R&D activities are not carried out in Thailand but imported (and have complete dossiers). Only one MNC mentioned the problem where their > 10 years old products was requested for the product trials using the newly implemented Good Regulatory Practices (GPR) which is impossible for the company to comply.
- Local faced numerous challenges when trying to carry out R&D activities in their business.
  For example, it will require them 2-3 years to get the stability data of their product's formulation.
  Furthermore, if companies used their own analytical methodology (instead of official pharmacopoeia), the fees they need to pay will be THB10K higher.

There are no major issues with the PIC/S, GMP and FSC unless the manufacturing plant in non-PIC/S compliance

- Thailand officially became a PIC/S member in 2016.
- It is a positive when the companies tried to register EU products. But it can be problematic for companies that want to registered US or other non-PIC/S compliance AH products.

Even you pass the GMP, you need data support for PIC/S. That's why people who bring products from the US face this issue. For the others in the market, more than 50% of the products came from the US. Any product, after 2014 /15 you have to submit this PIC/S. - MNC

- As Thailand became the PIC/S member, the GMP needs to part of PIC/s standard.
- There are few issues raised for non-PIC/S compliance manufacturing plants. They will need to undergone many procedures, documents and huge amount of money to get their products registered. As USDA for US vaccine authority is not PIC/S member, many faced trouble in this.
- For PIC/S compliance manufacturer plants, the burden is relatively minimal as requirements / documentations needed are lesser. All agreed that the high standard of PIC/S GMP ensures (good) product's quality.

- All products irrespective of local or imported products needs FSC
- There is no major issue with the FSC for both local and MNC companies on generic product. FSC is easy to apply – just need to request the paper from the origin…and generally easy to obtain.
- The only issue with FSC is parallel register or registering brand new AH products that were tailor-made only for ASEAN (or Thailand) market. These products do not have FSC from manufacture country. The time lost (several years) and obstacles to register is hard to overcome!

Importance & feasibility of ASEAN technical harmonization

ASEAN technical harmonization is an aspiration for all as companies. But their perception is that such concept is difficult to implement in the region….

Progress

- There is no AH ASEAN technical harmonization to follow now.
- Currently, AH industry follow human pharma standard (Compliance with ASEAN Harmonization) for product registration, and it is not practical!

Challenges & benefits to the industry

- AH technical harmonization will be hard to achieved as every countries will want to protect their own practice and 'ego'. It will take time and effort for alignment across ASEAN countries as products might be classified differently, with different procedures and protocols.
- Without doubt, many support the idea of harmonization.
- Why? AH products exportation and importation will be easier as there are standardization in guidelines across all countries in ASEAN – e.g. 1 registration and 1 set of dossiers for all countries. This imply less time and effort wasted in product registration.

For me, harmonization is not a problem for us, it's good, because the requirements will be clear. There will no need to talk to Thai FDA to try to understand their requirement as the documents will be standard and we can meet them, and we can get quick approval….. - MNC

AAHA is not unknown in Thailand. But the complain is – actions from AAHA tend to be slow. Local associations tends to focus their attention on local manufacturers (lesser on MNC companies)

- Both local and MNC heard about AAHA. It is considered a voice for the MNC importing companies. BUT many mentioned AAHA reactions and actions are quite slow compared to the local associations.
- By the time getting the translation done and collected signatures from all members, it is too late to take effective action!

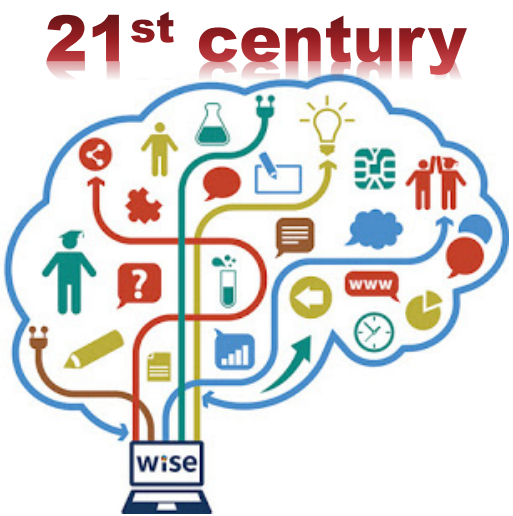
In the eyes of the authority, this association is not visible…Many times, we try to submit a letter in the name of AAHA but we can see that the Director or the representatives don't know the association. The name of this association is not present. Maybe they just don't realize that we have this association. - MNC

- AHPA is an influential local association for the AH companies in Thailand.
- However, this association tends to pay more attention to local issues faced by the local companies eventhough both international and local companies are members of the association. They only focus some issues faced by the MNC companies.

- RAPAT is the regulatory affairs association for human health. But AH companies sometimes submit their issues to regulatory via RAPAT.
- Besides that, the AH RA also form a group – VetRA, acting as a platform for the AH regulatory affairs in Thailand to communication easier on topics related to AH

Future outlook of ASEAN regulatory framework

Feedbacks are very positive…although there are improvement needed, Thai regulatory bodies are on the right path to meet 21st century framework.



Current view

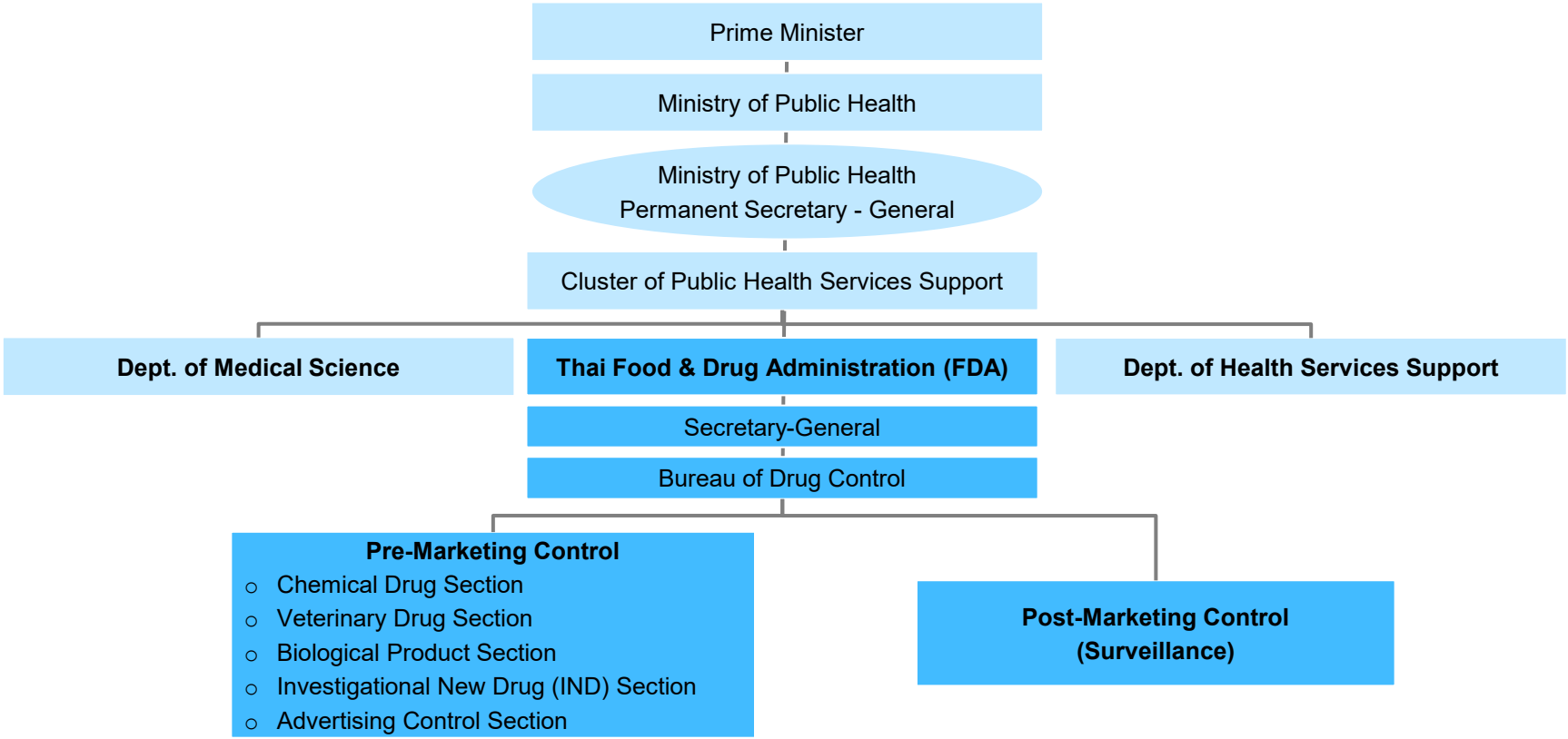
- Majority agreed that the current framework fits 21st Century. As the authority made a huge improvements by implementing high standard regulations, new technology and improving timeline for making AH industry better…Thailand AH industry is moving towards ‘modernization’.
- There are still rooms for improvement for the authorities in Thailand to perform better in AH industry. Areas of improvement are shown below.

Action needed

- Provide training to officers – Make sure well prepared before new regulations
- Hire more experts and veterinarians – Not pharmacists to review the work of AH
- More e-technology – speed up procedures using well developed e-submission
- Focus more on post marketing – field sampling using caution system to monitor products sold (whole process including import, storage and etc.)
- Public hearing and discussion before putting in place new rules or regulation
- Separate human and AH regulations – Different departments to manage AH as AH needs to be more lenient on the dossiers

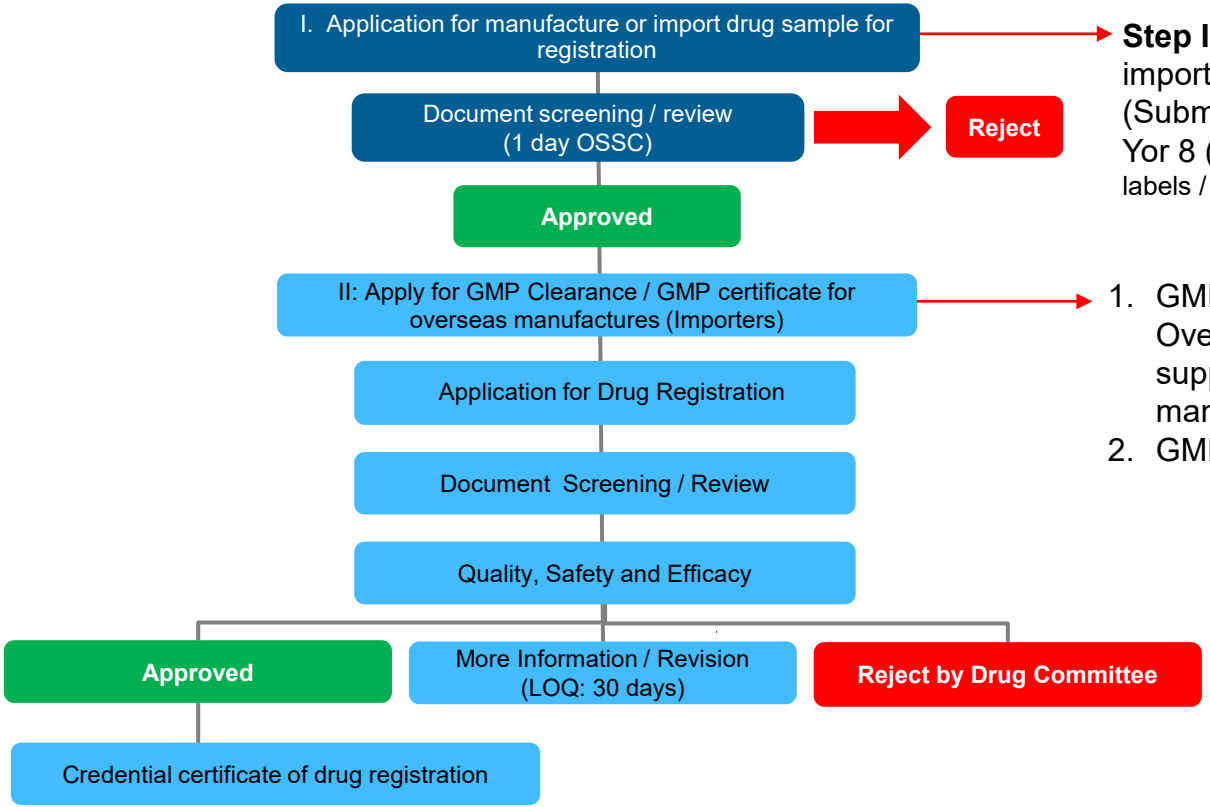
APPENDIX: Desk Research

There is only 1 regulatory body involved in the registration and approval of AH products - - FDA



Source: http://www.fda.moph.go.th/sites/fda_en/SitePages/Organization.aspx

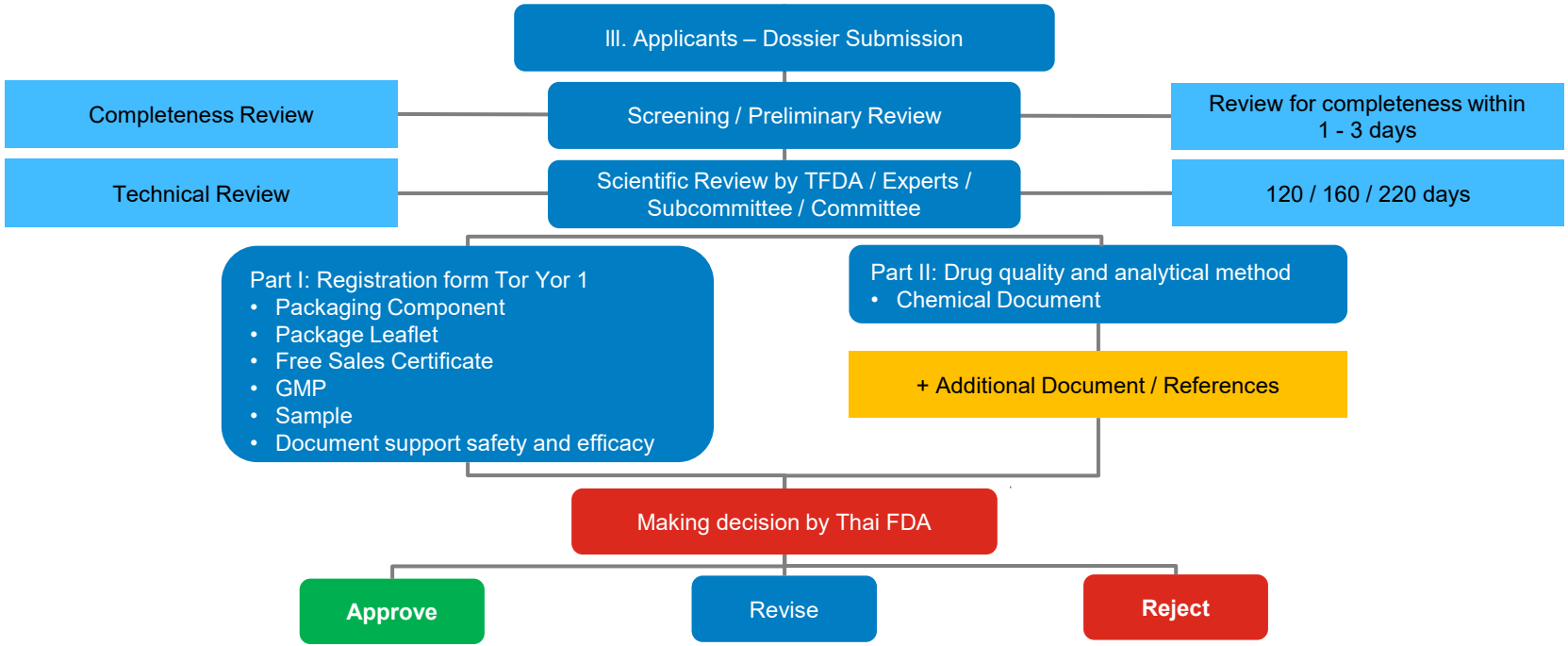
The regulation framework for veterinary drug registration in Thailand



Step I: Apply for permission to manufacture or import of a drug sample for registration. (Submit an application: Application form Nor Yor 8 (import) / Por Yor 8 (manufacturer) and labels / packaging inserts)

1. GMP clearance (document review) Overseas manufacturer are required to support evidence to demonstrate that the manufacturing site is acceptable.
2. GMP certificate – on-site inspection

The regulation framework for veterinary drug registration in Thailand (cont'd)



Future trend: HIGHER FOCUS ON ANITIMIRCROBIAL RESISTANCE (AMR) WITH THE NATIONAL STRATEGIC PLAN (NSP) THAILAND: 2017-2021

DLD appointed Residue Monitoring Committee to manage the residue monitoring plan and collection data to evaluate the results and the residue control system. The National Strategic Plan (NSP) aimed to reduce 30% of antimicrobial use in animal.

Surveillance of AMR in animal pathogens conducted by the DLD includes:

i. Samples from slaughterhouses (E.coli, Salmonella spp., Campylobacter spp. Staphylococcus aureus, Clostridium perfringens, Listeria monocytogenes, Enterococci)
ii. Samples from diagnostic cases (E.coli, Salmonella spp.)

Action Plan

i. Thai FDA set up new committee to re-evaluate the status of AM drugs, this committee comprises both medical doctors, veterinarians and pharmacists. The first non – official meeting will be held on May 2013
ii. DLD set up committee of MRR to collect and collate AMR data
iii. DLD set up new regulation to control and eliminate Salmonella in poultry farms by stamping out
iv. DLD and Thai FDA amended drug law especially the part of veterinary drug to focus on Medicated Feed, farm mixing and pharmacovigilance

With respect to this, all importers, manufacturers, farm veterinarians and farms must comply with the decision of FDA and DLD.

The major regulatory updates in Thailand for the past five years is the revision of law done on Article 44 in 2016.

The few amendments after the Article 44 had been invoked by the PM of Thailand:

1) **DLD and Thai FDA amended drug law especially the part of veterinary drug to focus on Medicated Feed, farm mixing and pharmacovigilance**

2) **Drug Act 1967 : Thai FDA : MOPH**
   i. Thai FDA disallows antimicrobials to be registered under the growth promoter
   ii. Reclassification and control distribution channel of antimicrobials
   iii. Thai FDA will reject any application of new antimicrobials that are used in humans (e.g. carbapenems) to be used in animal

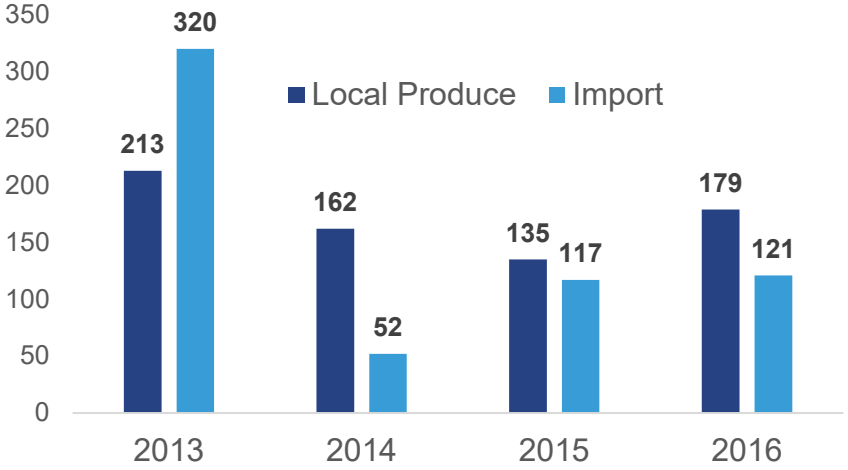
3) **Feed Quality Control Act 2015: (DLD : MOAC)**
   i. In 2006 : The use of antimicrobials as growth promoter was banned in poultry/Partial banned since 2000
   ii. In 2015 : all antimicrobials are prohibited to be used as growth promoters
   iii. Regulation on Medicated Feed

In December 2016, Prime Minister of Thailand invoked Article 44 under the interim constitution to establish a panel to oversee national reform agencies which will ensure their work does not overlap. He will also exercise Article 44 to fast-track drug registration with the Food and Drug Administration (FDA). The order aims to help process the registration of thousands of drug lists with the agency as the lists had been put on the back-burner under several governments.

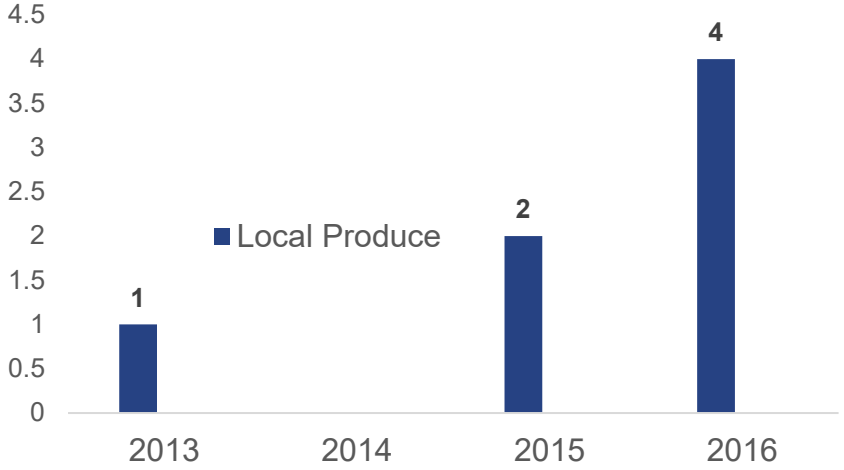
The drug registration move will help Thais buy drugs at lower prices as well as boost the herbal medicine industry. Since FDA is short of staff to examine a number of products for approval, the order will allow the FDA to collect additional fees from those operators to hire experts from both Thailand and overseas to examine the products…

Number of veterinary product registered in 2013 - 2016

CONVENTIONAL VETERINARY PRODUCTS



TRADITIONAL VETERINARY PRODUCTS



Source: Thai FDA

TIMELINE FOR NEW PROUDCTS	▪ New Drug: Standard: 210 – 280 days
	▪ New Generic Drug: Standard: 110 days

Note: It normally takes minimum two years to register a pharmaceutical product with Thai FDA.

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