PhAMA Position Paper on Value Recommendations for ASEAN Joint Assessment Procedure

1. Background and Challenges

In the current pharmaceutical regulatory environment, patients continue to benefit from great advances in medical care. Sophisticated regulatory review systems have also evolved to ensure that safe and effective medicines are approved. However, these systems are not optimized in all countries. Gaps in individual regulatory agency capabilities together with duplication in non–value added national regulatory requirements can slow down regulatory approvals and therefore impede patient access to new medicines. These gaps exist despite the achievements in both regulatory convergence and harmonization of technical requirements by bodies such as the International Conference on Harmonization (ICH). There is a pressing need to strengthen regulatory review systems in emerging market economies as highlighted by the World Health Organization (WHO).[1]

In 2015 the ASEAN Product Pharmaceutical Working Group (ASEAN PPWG) started a project, with the support of WHO, aimed at strengthening the implementation of harmonized regulatory requirements (SIAHR). In the frameworks of the SIAHR Project at the PPWG - the ASEAN Joint Assessment Coordinating Group (JACG) was established with the task **to** lead the development of an ASEAN Joint Assessment (AJA) procedure and to proceed with the joint assessments of the application for marketing authorization for priority medical products.[2]

The first pilot joint assessment started in 2017 with an antimalaria drug and the participation of seven (7) member states with the support from WHO. The learnings from this pilot joint assessment include the following:[2]

- To make the activities of the JACG more formal and sustainable there is a need for further advocacy for the importance of the JACG using all possible means and mechanisms. A clear commitment to move this procedure forward beyond the pilot process would be helpful.
- The concerns and reservations of the industry in submitting the applications for joint assessment by ASEAN JACG need to be addressed to ensure there is added value for all parties.
- Despite all positive developments and support from WHO, the ASEAN Joint Assessment Procedure remains at large not known to the industry. To attract broader Industry participation, there needs to be a clear communication about the benefits and the importance of Industry's investment into the future.

The industry and other concerned stakeholders must see the potential benefits that the ASEAN Joint Assessment Procedure could provide in facilitating access to the priority medical products for the populations in the ASEAN Member States (AMS).To date, only two known applications have been made; eluding that more concerted efforts are needed to make the ASEAN Joint Assessment Procedure more appealing and attractive to industry. Thoughtful measures to optimize the procedure will surely inspire greater confidence and trust among regulators and industry. Beyond the initial pilot process, an appropriate governance structure and adequate resources must be provided for a sustainable and scalable mechanism.

While international regulatory cooperation on convergence and harmonization are in place, some best practices may be adopted to encourage the utilization of the ASEAN Joint Assessment Procedure.

2. Value Recommendations

We would like to propose the following value recommendations to improve ASEAN Joint Assessment (AJA) Procedure:

- Allow minimum of TWO (2) participating ASEAN Member States (AMS)
- Expand ELIGIBILITY list to all diseases and product types
- Consider WORK-SHARING in review procedure
- Streamline administrative work process
- Consider use of PUBLIC assessment report
- Consider option for PRIORITY Review
- Consider option for PRE-SUBMISSION Meeting

These value recommendations are mostly adopted as best practices observed from the success of other international collaborative procedures such as EU Decentralised Procedure (DCP), ACCESS (formerly known as ACSS) Consortium and Project ORBIS. Majority of the EU, ACCESS Consortium and Project ORBIS-eligible authorities are recognized as Stringent NRAs and Reference Authorities by WHO and ASEAN Member States (AMS), respectively. Hence, these collaborative procedures offer great role model examples and best practices for consideration by ASEAN Member States (AMS).

Each value recommendation is further described as below:

Value Recommendation #1: Allow minimum of <u>TWO (2)</u> participating ASEAN Member States (AMS)

Currently, the ASEAN Joint Assessment main guideline does not explicitly state the minimum number of participating AMS. However, the FAQ section indicates a minimum of three (3) AMS in order to initiate the procedure. We believe a minimum of TWO (2) is more viable and henceforth, our recommendation based on the justifications below:

- Successful international collaborative procedures such as EU DCP, ACCESS Consortium and Project ORBIS allow a minimum of TWO (2) National Regulatory Authorities (NRAs) to initiate and participate in the collaborative review of a new product application. This is also very much aligned to WHO's initial recommendation to AMS for the ASEAN Joint Assessment. Early ACCESS collaboration typically begins with two countries and subsequently, the number increases as the pact stabilizes and strengthens with trust and experience gained among the regulators *(see Figure 1 below).*
- ASEAN Joint Assessment is a relatively new pathway for both AMS and industry. Hence, starting small with minimum of two participating AMS will allow AMS the opportunity to work more closely, better understand and familiarize with the process. The review process involving TWO NRAs is easier to manage in the beginning. This also helps to ease communication and coordination efforts among the participating AMS; which ultimately results in greater review efficiencies. Such progress inspires confidence and trust among the industry who will be more

motivated to participate in the collaborative procedure. With the increased uptake and utilization, both AMS and industry will gain much needed experience, expertise and trust; critical elements to drive successful collaborative procedures.

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ACCESS Approvals

Regulators	TGA	Health Canada	HSA	Swissmedic
Standard Timelines (days)	225	240	270	360

Date	Product (active)	Indication	Regulatory Agencies	Review Duration (days)
July 2018	**Erlyand** (AU) & **Erleada** (CAN) (apalutamide)	for prostate cancer:		
April 2019	**Verzenio** (abemaciclib)	for the treatment of metastatic breast cancer		
June (HC) /July (TGA) 2019	**Zejula** (Niraparib)	PARP-inhibitor for some ovarian, fallopian tube, or peritoneal cancers:		
February 2020	**NUBEQA** (darolutamide)	treatment of non-metastatic castration-resistant prostate cancer in men		185
February 2020	**Vyndaqel** (tafamidis meglumine) & **Vyndamax** (tafamidis)	for transthyretin amyloid cardiomyopathy (ATTR-CM):		187
March 2020	**Xofluza** (Baloxavir marboxil)	for treatment of uncomplicated influenza in patients ≥ 12 years		265
May 2020	**Sarclisa** (Isatuximab)	for the treatment of multiple myeloma		166
February 2021	**Kesimpta** (ofatumumab)	for the treatment of adult patients with active, relapsing-remitting forms of multiple sclerosis		243

Figure 1

- It can be challenging to secure participating interest from three or more AMS for a specific product application. Resource constraint, different national priorities or other internal conflicts may hinder AMS participation. Similar limitations may also apply to industry aside from commercial and/or regulatory strategy considerations. Given these concerns, flexibility to reduce the minimum to TWO (2) participating AMS will allow more opportunities to AMS and industry alike to benefit from the ASEAN Joint Assessment procedure.

It is important to note that while the minimum of TWO (2) participating AMS is highly recommended given the current challenges and significant benefits to both AMS and industry, this minimum number is subject to periodic review and revision as deemed fit by ASEAN-JACG; depending on the evolution and progress of the ASEAN Joint Assessment Procedure.

Value Recommendation #2: Expand ELIGIBILITY list to all diseases and product types

The ASEAN-JACG in consultation with AMS, has published a list of 11 priority products/diseases for their next joint assessment. The focus of this next joint assessment is primarily on medicines for HIV/AIDS and hepatitis, with additional calls for lung and breast cancer, Crohn's disease, pustular psoriasis, and treatment-resistant depression treatments.

We would like to propose an expansion of the current published list to encompass ALL disease areas for NCEs, Biologics and Vaccines based on the justification below:

- While we appreciate the list was developed with intention to focus on key diseases in ASEAN region, the list is restrictive and limits participation from industry as not all companies have R&D assets that fulfill current eligibility criteria.

- The list also limits opportunity for new products in other important diseases be submitted via the ASEAN Joint Assessment procedure. This potentially impedes early and simultaneous access of innovative products to patients in the region. The current evaluation timeline (after successful acceptance of Expression of Interest) as stipulated in the joint assessment guideline may be shorter than standard pathway timeline in some AMS.

- The restrictive list also decreases opportunity to build a greater network of collaboration among AMS. As we recall, the primary purpose of this endeavour is to strengthen the technical capacity of ASEAN NRAs and to foster mutual trust and reliance among AMS. Technical capacity building and good reliance practices are some important considerations in WHO's Global Benchmarking Tool (GBT) – a toolkit developed for their assessment of the maturity level of each NRA and subsequently listing into the appropriate categories within the WHO Listed Authority (WLA) list. Therefore, the ASEAN Joint Assessment procedure is an excellent platform that should be capitalized by AMS as each NRA strives to achieve WLA-Cat 3 or Cat 4 status and be recognized as Reference Authority.

- The ACCESS consortium does not have a specific product/disease list and hence, allows equal opportunity for new products indicated for different diseases be considered for submission. Although the disease list for the ASEAN Joint Assessment can be reviewed and updated, the process takes time, requires deliberation and consensus by AMS during ASEAN-JACG meeting which happens once or twice a year.

Value Recommendation #3: Consider WORK-SHARING in review procedure

WHO defines work-sharing as a process by which regulatory authorities of two or more jurisdictions share activities to accomplish a specific regulatory task. Work-sharing also entails exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other regulatory authorities.[3]

During the ASEAN Joint Assessment, each participating AMS reviews the country specific ancillary documents and common technical dossier (Quality, Non-Clinical and Clinical) individually. Subsequently, all participating AMS will convene to discuss, deliberate and finalize the joint assessment report. Indeed,

there is still opportunity to streamline duplicate assessment and better leverage leverage peer resources through work-sharing among AMS .

Work-sharing allows smarter utilization and sharing of resources among AMS. This leads to improved focus and efficiency in the assigned regulatory tasks which ultimately may translate to shorter review procedure timeline. More importantly, work-sharing facilitates better use of available expertise and knowledge among participating AMS and promotes capacity building.

Hence, we would like to propose enhanced work-sharing elements for incorporation into current ASEAN Joint Assessment Procedure. Taking ACCESS Consortium as a example, work-sharing has helped the participating regulators to use best scientific and technical expertise and resources for assessing the scientific and technical information. The national regulatory decision is then based on these assessments.. The process flow for an ACCESS application is outlined in Figure 2.

Figure 2

Participating regulators will discuss the division of labour and joint-review timeline. For example, Module 3 (+BE) will be reviewed by Agency A, Module 4 (+ impurities) will be reviewed by Agency B and Module 5 (PK, clinical pharmacology) will be reviewed by Agency C or in the case only 2 agencies participating, may be taken up by Agency A or B.[4]

Since 2018, the Therapeutic Goods Administration (TGA) has granted approvals through ACCESS Consortium participation. Figure 3 shows the division of the review by agencies for each of the applications. [4]

Submission	Indication	Module 3 Quality	Module 4 Non-clinical	Module 5 Clinical	Approval
ERLEADA (apalutamide)	Prostate cancer				July 2018
VERZENIO (abemaciclib)	Breast cancer				April 2019
ZEJULA (niraparib)	Ovarian cancer				June 2019
XOFLUZA (baloxavir marboxil)	Anti-viral (influenza)				Feb 2020
NUBEQA (darolutamide)	Prostate cancer				Feb 2020
VYNDAQEL (tafamidis)	Cardiomyopathy				March 2020
SARCLISA (isatuximab)	Multiple myeloma				Apr 2020

Figure 3

In summary, moving from joint review to work-sharing reduces duplication in the review procedure, allows sharing of resources and expertise among the participant regulators and promotes collaborative approach to decision making; ultimately facilitating early and simultaneous regulatory access of innovative products to patients.

Value Recommendation #4 Streamline Administrative Work Process

Aside from advocating the "divide and conquer" approach for the technical review of the dossier, we also would like to recommend an assessment of the administrative duties required for the entire ASEAN Joint Assessment Procedure; particularly in Step A ASEAN JA Candidate Product Selection which is the anticipated longest step in the procedure. It is observed that the Lead AMS is tasked with many responsibilities e.g. coordinating meetings, facilitating retrieval of assessment reports, developing draft joint assessment report – on top of the actual assessment of the dossier. It is worthwhile to examine if some administrative tasks could be shared with another participating AMS or a certain administrative step can be omitted if there are other alternative approaches. Alternatively, there should be dedicated resources for administrative and project management tasks which are provided by each participating Agency. Specific funding for those additional resources might be allocated from ASEAN development initiatives. The WHO coordinator assigned to the ASEAN Joint Assessment Procedure could also be a source that AMS can leverage upon for additional support in some of the administrative process.

There is opportunity to explore on a common technology infrastructure that allows sharing of information; thereby reducing administrative work burden. The infrastructure can range from basic tools such as Microsoft TEAMS space and shared folder to more advanced and sophisticated platforms like Accumulus. These can facilitate online review of dossier and share posting of observations or questions. Aside from technology infrastructure, there is also opportunity to develop common templates that can assist with more efficient review. Moving to work sharing approach as described in *Value Recommendation #3 Consider WORK-SHARING in review procedure* above can contribute to reduction of administrative duties. A Pre-Submission Meeting option which allows discussion and clarification on logistical matters can also help to ease administrative burden along the process work stream (please refer to *Value Recommendation #7 Consider option for PRE-SUBMISSION meeting*).

Value Recommendation #5: Consider use of PUBLIC assessment report

One of the ASEAN Joint Assessment Procedure criteria is the complete and unredacted assessment report from the chosen reference agency. This document would best be shared by the authoring agency to ensure there is an opportunity to ask questions on the review. While we support the concept of reliance and recognize the facilitating role which the assessment reports can play, there is still a lack of clarity on what type of information that can be provided for the ASEAN review and the level of redactions are dependent on each national legal system of the reference agency. There is no one size fits all for the definition of unredacted assessment reports given the differing laws, regulations and practices among the reference agencies.

Therefore, we would like to propose the use of **public assessment reports** instead given the additional considerations below:

- Public assessment reports provide a detailed summary of the basis of the regulatory decision. For example, the European Public Assessment Report (EPAR) contains in practice very few redactions, which have been reviewed and accepted by the EMA during the redaction process and is therefore very informative.
- We believe that public assessment reports are valuable as they provide key insights into the rationale of the regulatory decision-making process. These reports should be the primary source of information to support regulatory reliance.
- Public assessment reports are routinely available and accessible on website of major reference agencies. This is aligned to WHO's advocacy for NRAs to produce meaningful publicly available assessment reports, supporting the benefit-risk decision making for major approval decisions. The sharing of such documents will facilitate greater reliance, especially as WHO seeks to expand the pool of reference NRAs and institutions who can be relied upon.
- Non-public information exchange typically requires a confidentiality agreement, sometimes connected with a Memorandum of Understanding or Mutual Recognition Agreement be established between participating AMS and chosen reference agency – in order to safeguard the confidential nature of the document exchange, i.e. patient confidentiality & commercially confidential information. This is an administrative process that will take time, effort and coordination by the Lead AMS and WHO. This also adds on to the administrative responsibilities burden of the Lead AMS who is already occupied with Joint Assessment meeting preparation, coordination with stakeholders, development of draft report – on top of actual assessment of the product application.
- There is a provision within the ASEAN Joint Assessment Procedure for a meeting between participating AMS and chosen reference agency; in facilitation with WHO to address specific questions or deliberate further following completion of initial review by the participating AMS, This is an alternate platform to gain deeper insights which should be leveraged upon by AMS.
- While the physical product has to be the same, the essentially same dossier that was submitted to the chosen reference agency is provided to AMS. This is a good source of reference if additional details are required.

Value Recommendation #6: Consider option for PRIORITY Review

As cited at the beginning, one of the learnings from the pilot ASEAN Joint Assessment Procedure is that industry and other concerned stakeholders have to see the potential benefits that the procedure could provide in facilitating access to the priority medical products for the populations in AMS. Hence, timeliness in regulatory review and approval is an important benefit and source of motivation for industry to overcome reservations or concerns and actively participate in this collaborative procedure. There should also be a significant saving on the Industry resources through minimisation of national documents, harmonised dossier requirements, less requests for information and predictable and fast review timelines.

Currently, the entire ASEAN Joint Assessment Procedure can take up to 14-17 months; starting from Step A Candidate Process Selection (195 calendar days) to Step B ASEAN JA Review Process (180 calendar days assuming JA meeting is needed) and Step C Regulatory Decision-Making (30-90 Working Days). Indeed, there is opportunity to improve the timelines and in so doing, attract more participation interest from industry. More importantly, the increased uptake will transform this promising regulatory pathway and truly enable it to facilitate earlier access of high quality, effective and innovative medical products to patients in this region.

Therefore, we would like to propose the following for consideration:

- Introduce an option for Priority Review dedicated to important public health products akin to the practice by ACCESS Consortium. The eligibility criteria can include but not limited to diseases of high unmet medical needs.
- Consider adopting the shortest timeline among the participating AMS; similar to the practice by ACCESS Consortium.
- Consider work-sharing enhancement suggestions described earlier to speed up approvals.
- Appropriate resources to operate a good project management and collaboration across countries

Value Recommendation 7: Consider option for PRE-SUBMISSION Meeting

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We believe in value of Pre-Submission Meeting as an option to facilitate greater collaboration and efficiencies between AMS and industry (sponsor). As depicted in Figure 2, a Pre-Submission Meeting is the first step prior to Expression of Interest in the ACCESS procedure.

This is a platform for industry to raise and seek clarification on technical or logistical issues relating to the product application. As the ASEAN Joint Assessment Procedure is relatively new, the insights gained from such Pre-Submission Meetings will benefit industry (sponsor) to determine the appropriate regulatory strategy, highlight considerations and make better decisions. The benefits include but not limited to developing a Right-First-Time regulatory submission that fulfills technical requirements for a successful procedure outcome.

AMS can benefit from these interactions as there is additional time for resource management and prioritization; given the interest level and heads up on potential submission. Aside from this, AMS can clarify expectations and achieve more alignment which should ultimately result in mutual satisfactory outcomes. It can allow AMS a better planning and anticipation of required expertise and resources.

Conclusion

The ASEAN Joint Assessment Procedure is currently the only regional collaborative procedure involving all AMS. This highly promising regulatory pathway can potentially transform and facilitate earlier, simultaneous access of innovative medical products to ASEAN patients; if the value recommendations above are adopted and implemented. Political commitment, appropriate governance structures and funding and a well-functioning project management are key to support its implementation.

References:

[1]O'Brien et al, Building a Better Approach for the Benefit of Patients: 10 Pillars to Strengthen Regulatory Review Systems Globally; Therapeutic Innovation & Regulatory Science 2020, Vol. 54(2) 283-292

[2] Dr Samvel Azatyan, Current status, challenges and future activities of the ASEAN joint assessment procedure 27th ASEAN Consultative Committee for Standards And Quality – Pharmaceutical Product Working Group (ACCSQ-PPWG) Meeting, Penang, Malaysia, 24 - 27 June 2019

[3] WHO Good Reliance Practices Guideline: https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_good_reliance_practices.pdf?ua=1

[4] Michael Shum, TGA, Work-sharing, Reliance, and Other Novel Approaches to Accelerating Review, Approvals, and Access, An Australian perspective. RAPS Convergence2020

[5] Access Consortium Terms of Reference Version 1.1 Revision date: September 2020

Appendix 1

List of priority products for next JA activity

Priority No.	Product type/ category	Brief justification
1	Products containing new active substances to treat Hepatitis C	• A new treatment option for treatment of patient with chronic hepatitis C virus genotype infection • National priority to eradicate Hepatitis C through scaling up of diagnosis and treatment
2	Products containing new active substances to treat specific cancer, i.e. breast cancer, lung cancer	• A new treatment option for some women with aggressive types of cancer e.g. treatment of HER2-positive tumours • Lung cancer have the highest reported rate among males in Asia, and there is difference in treatment outcomes (ORR, OS, toxicity) between Asian and Western patients
3	Products containing new active substances to treat HIV/AIDs, e.g. Efavirenz tablets 600 mg	There are products approved under WHO PQ/US FDA tentative approval/EMA Article 58. Efavirenz tablets 600mg has been registered in Thailand
4	Products containing new active substances to treat TB infection	There are products approved under WHO PQ/US FDA tentative approval/EMA Article 58
5	Products containing new active substances to treat Hepatitis B	Public health interest
6	Product containing new active substance to treat Treatment-Resistant Depression (TRD)	Major Depressive Disorder (MDD) is a common, serious, severely debilitating and recurrent psychiatric disorder. It affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide. Individuals with depression, including major depressive disorder, experience continuous suffering from a serious, biologically based disease which has a significant negative impact on all aspects of life, including quality of life and function. TRD is considered a subset of MDD and is defined as lack of clinically meaningful improvement to at least two different antidepressant agents prescribed in adequate dosages for adequate duration. It is the leading cause of disability (measured as years lived with disability) worldwide. Overall, patients with depression have a 7- to 10-year shorter life expectancy at birth compared to the general population. This compound is under evaluation by the US FDA where it received “break through therapy” and “Priority Review” designation.
7	Products containing new active substances to treat general pustular psoriasis	General Pustular psoriasis is a severe and potentially life threatening

Priority No.	Product type/ category	Brief justification
		skin disease characterized by the repeated occurrence of acute flares caused by systemic inflammation affecting the skin and internal organs. It is a disease with high unmet medical need and current treatment options for controlling acute GPP and maintenance of response are limited.
8	Product containing new active substances to treat interstitial lung disease	Causes of ILD are still largely unknown and local prevalence rates are not well-known. However, this disease often leads to respiratory failure and require lung transplant. As such, there is an urgent need to discover effective medications for this disease.
9	Product treating chronic kidney disease	Chronic kidney disease (CKD) is a major health problem for the underdeveloped countries of southeast Asia, home to more than 2 billion people. The majority of affected individuals are young and in the most productive years of their lives. CKD is associated with impaired quality of life and substantially reduced life expectancy at all ages. End stage renal failure (ESRD) is the most severe form of CKD, and is fatal if not treated by renal replacement therapy. Although patients with early CKD are more likely to die before they reach ESRD, the avoidance of ESRD is still highly desirable due to its adverse effects on quality of life and the substantial costs of dialysis and transplantation to healthcare providers. Although Renin-Angiotensin System (RAS) blockade with Angiotensin-converting enzyme inhibitor (ACEi) or Angiotensin receptor blockers (ARB) have been shown to reduce albuminuria and slow the rate of progression in proteinuric nephropathies, particularly in diabetic kidney disease, a substantial residual risk of ESRD remains. In summary, there is a high unmet medical need for new treatment options that can be added safely to current standard treatments in CKD, with a primary aim to slow the progression of CKD and reduce risk of CV death.
10	Products containing new active substances to treat Crohn's disease	Even there is approved therapies for Crohn's disease, active substances with new mechanism of action that address mucosal healing and show superior efficacy can potentially qualify as priority products.
11	Product containing new active substance to treat Alzheimer's disease	Alzheimer's Disease Dementia, a chronic progressive mental disorder caused by Alzheimer's Disease (AD), is the most common cause of dementia and accounts for 50 to 70% of all cases. More than 25 million people in the world are currently affected by dementia, most of them suffering from AD, with around 5 million new cases occurring every year. With an aging population, it is expected that these numbers will increase further in the future making AD to an important public health challenge.