REVIEW ARTICLE

Medicines development in the Asia Pacific region

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Abstract: The Asia Pacific region is an extremely diverse region, characterized by heterogeneity from a number of aspects, including culture, religion, economics, landscapes, and languages. This also applies to the standard of medical care and the regulatory requirements for approval of drugs in the region. Developed economies such as Japan and Australia have requirements which are not dissimilar to those of the EU and USA, but still have their own unique requirements. The developing economies all have their own requirements. In the ASEAN region there is harmonization of the dossier format, but each country still has local requirements. The region has seen significant growth in clinical trial activity, both to satisfy local registration and safety requirements and to help accelerate global trial patient recruitment. There is a clear need for training in all aspects of medical, regulatory, clinical and safety aspects of medicines development, which is being addressed through several organizations and at different locations in the region.

Keywords: Asia Pacific; medicines development; drugs; biologics; clinical trial regulatory; safety; CPP; stability; ICH; dossier; ASEAN; CTD

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1. Introduction

The Asia Pacific (APAC) region is an extremely vibrant, fast moving region, characterized by its extreme heterogeneity from a medical, regulatory and economic perspective. The region covers a wide geographic area, stretching from Mongolia in the North to New Zealand in the South. It has diverse cultures, societies, economies, landscapes, climates and religions. Over half the world's population lives in this region with India and China being the two most populous countries globally. Many people still live on less than a dollar a day. However, due to its diversity the region has enjoyed remarkable economic growth in the last 4 decades, and could become a growth center for the world in the coming decades[1].

The region includes both developed economies – South Korea, Australia, New Zealand, Taiwan, Hong Kong, Singapore, Japan, and developing economies – China, India, Vietnam, Philippines, Indonesia, Malaysia, Thailand, and others. There are 35 countries in the region, each with their own culture and language; in many countries such as India and China, there are multiple regional languages.

Despite the rapid economic growth, there remain several pressing unmet medical needs. These include neglected diseases in the less developed parts of the region, an epidemic of diabetes and cardiovascular disease due to Westernization of diet, increases in environmentally related diseases due to rapid industrialization and environmental degradation and a rapidly aging population putting additional strain on health services. In addition, there are a number of diseases which are more prevalent in the region than in other parts of the world[2,3].

2. Medicines Development Overview

From a medicines development perspective, the region

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is unique in that several countries in the region require specific stability data and local clinical data in their own populations in order to register compounds, and also have mandatory requirements for post-marketing surveillance studies (Tables 1 and 2). This can offer opportunities for regional development strategies.

All countries in the Asia-Pacific region require a New Drug Application (NDA) to contain sufficient data to support the efficacy, safety and quality of a pharmaceutical product before their regulatory agencies can approve its marketing authorization. Many require a Certificate of Pharmaceutical Product (CPP) from the country of origin (Table 1). A key critical challenge is the ability to keep abreast of the often rapidly changing regulations, and to be able to interpret the often 'grey' zones in the regulations. For many of the developing economies, there are opportunities to partner with the regulators in critical improvement projects, leveraging internal expertise. This requires depth and breadth of knowledge in the region, and excellent relationships with regulators.

3. CPP and Stability Data

However, there are certain specific considerations that need to be taken into consideration when preparing for NDA filing in countries in this region. Many APAC countries require that the prior marketing authorization approval in a reference country/countries and/or the country of origin of a pharmaceutical product has been obtained, before they in turn issue their approval based on a summary review complemented by such a reference approval. As such, the CPP is required as part of the NDA dossier in these countries. Some countries will require the CPP at the time of submission while others can accept an initial submission dossier without a CPP and start their review first, but require that the CPP be furnished at a later period so that they can issue their approval after their summary review. There is little harmonization between the regulatory systems in each country.

4. Clinical Trials

The number of clinical trials performed in the region has increased steadily over the last decade, due to several factors. Initially global multinational companies (MNCs) recognized the region as an opportunity to have less costly and easier access to patients, with most of the strategies being driven from the US and Europe. The early quality issues are becoming less significant as more companies are carrying out clinical trials in the region, and native investigators with experience in the US, Australia and Europe return to the region. Many of the agencies are also now carrying out inspections, which also add to improvement in quality. There are also many clinical research organisations (CROs) in the region driving quality and

Table 1. Requirements for CPP and local clinical data in APAC countries

NDA Requirements	Group 1	Group 2	Group 3
Reference country approval or CPP at time of submission	No	Yes — Approval letter from reference country	Yes — CPP from reference country
Local clinical data at time of submission	No	No	Yes
Countries	Australia New Zealand Singapore (full review)	Singapore (summary review), Malaysia, Thailand, Philippines, Indonesia, Hong Kong	China, Korea, Taiwan, India, Japan

Table 2. Requirements for local clinical data

Local Data Requirements	China	Korea	Taiwan	Japan	India
Local Ph I/ PK requirements	Yes — local PK and it may be conducted in parallel with Ph III study Phase I – 20 subjects	Not required	Not required If bridging study evaluation (BSE) accepted	Yes, and may be conducted In parallel with Phase II/III	Not required
Local subject number in Phase III	Per regulations: Ph III — 100 (small molecules) and 300 (biologics) in active arm + statistical significance	30 to 50 in active arm (in practice)	Per regulations: If total $n > 200$, 5% or 30 whichever is lower, If total $n < 200$, 10% or 10 whichever is lower	Negotiable	100 in total
PMS	Usually	Yes	No	Yes	Yes

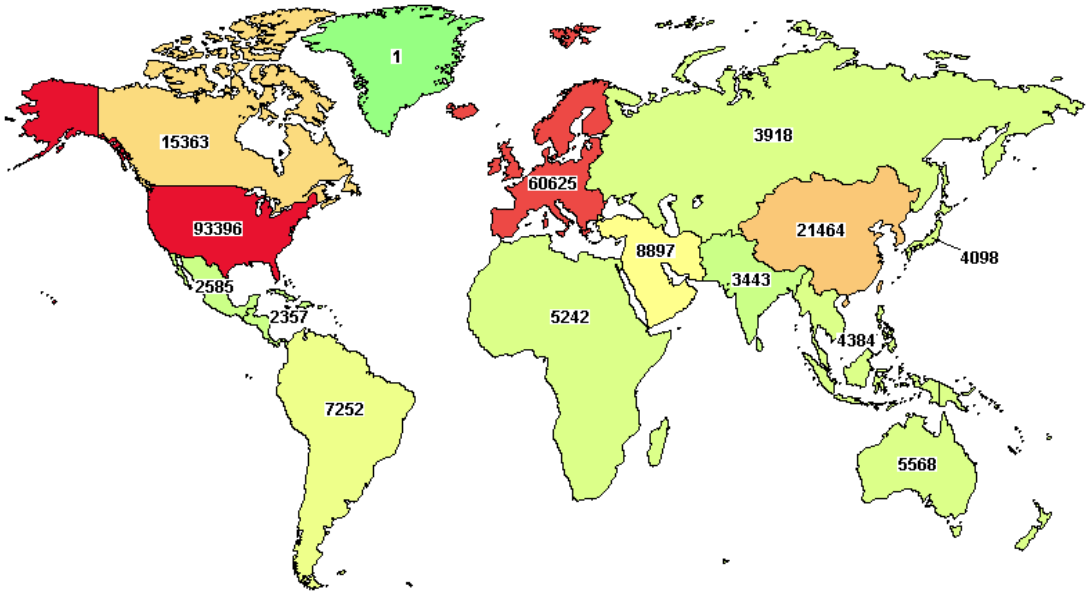

Figure 1. Current numbers of clinical trials on clinicaltrials.gov[4], viewed June 2, 2016.

standardization. The growth in Asia Pacific is rapidly changing the strategic focus and many MNCs include the regional input at an early stage in development. There are also many emerging Asian bio-pharmaceutical companies who are developing products for commercialization on the global arena. The diseases prevalent or more common in Asia, such as hepatocellular carcinoma, gastric cancer, dengue fever and others, are driving innovation. Biomedical R&D expenditure has increased in the region compared to that of US and Europe, driven primarily by Japan and China[2].

Clinical data submitted to support efficacy and safety of the pharmaceutical product should be generated from well-designed trials conducted in accordance to Good Clinical Practice (GCP). They should be robust enough to stand up to reviews by well-established regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Key agencies in the region, such as the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Health Sciences Authority (HSA) in Singapore[5] and the Therapeutic Goods Administration (TGA) in Australia have links and communicate frequently with each other and with FDA and EMA. These agencies also provide training for other agencies in the region. In some cases, bridging studies performed locally can fulfil the requirement for local data, or participation in a global trial may also suffice, if the subject numbers are sufficient.

5. Region/Country Overviews

In the ASEAN region — Singapore, Malaysia, Thailand, Vietnam, Brunei, Myanmar, Philippines, Cambodia, Laos, Indonesia — much work is ongoing to harmonize requirements and regulations. Most countries have adopted the ASEAN Common Technical Document (CTD) for submissions. The ASEAN CTD is similar in format to the ICH CTD, with local modifications. There are now no requirements for local clinical data for registration or for post marketing surveillance studies for New Chemical Entities (NCEs). Until recently, Vietnam required the collection and submission of local data for compounds which had not already been on the market for 5 years outside Vietnam, but this requirement has recently been removed for small molecules. The ASEAN region also has specific Zone IV (Hot humid/tropical zone) stability requirements.

India has updated its regulations recently, following accusations that there were many clinical trials being conducted in India without adequate protection for subjects. The new regulations mandate fixed compensation according to a specific formula, review of trials by the Drug Controller General of India (DCGI), and video taping of subject consent for specific vulnerable populations. Initially almost all trials in India stopped while the regulations were being updated, but in the last year the number of companies conducting clinical studies in India has increased (Figure 2).

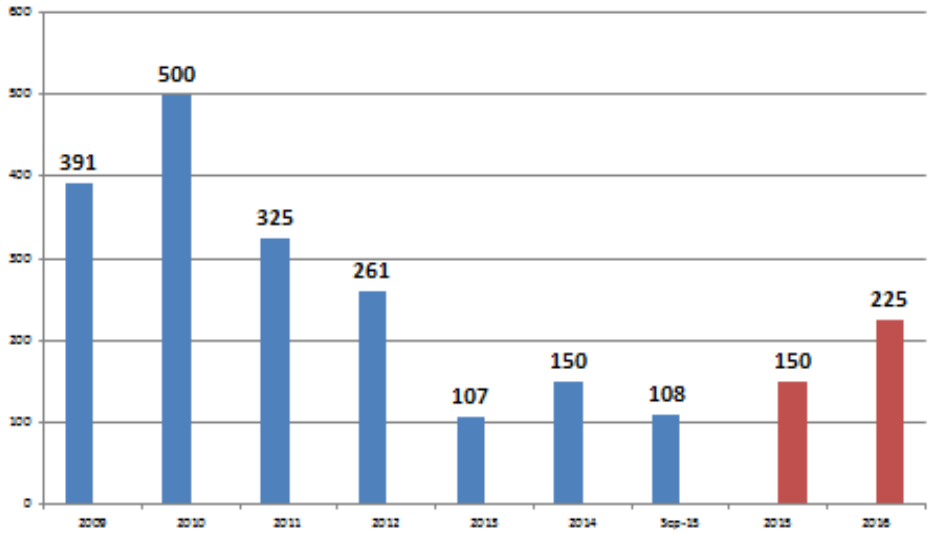

Figure 2. Clinical trial approvals in India 2009–2015[6].

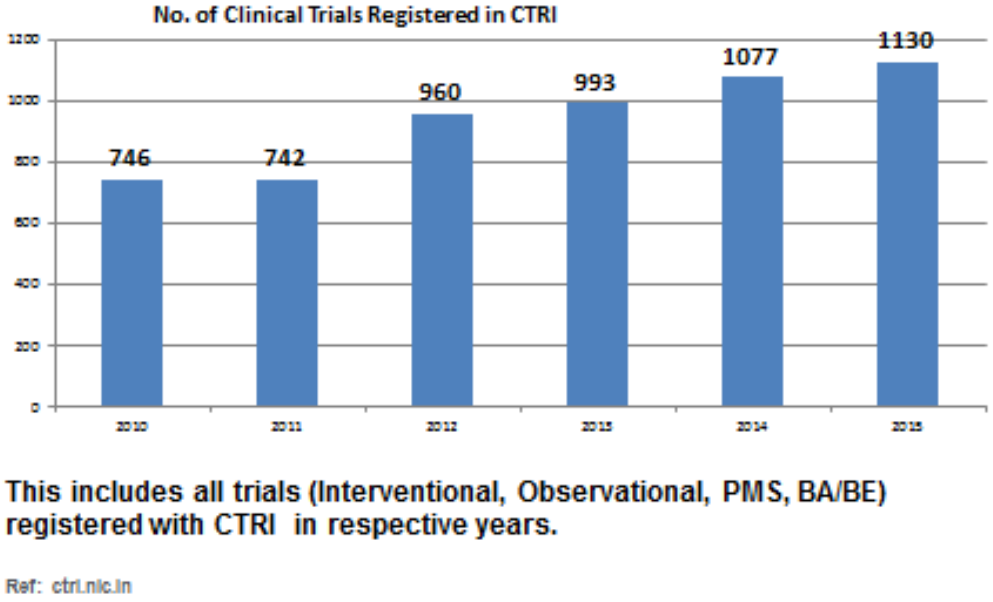

Figure 3. Number of clinical trials registered in the Clinical Trials Registry — India (CTRI) (includes all trials).

There are excellent centres with investigators experienced in conducting trials. The ministry is also taking steps to accredit and register clinical trial centers[6].

Currently China is possibly the toughest regulatory environment, with imported NCEs taking up to 6 years for registration. The number of submissions (Figure 4) is very large compared to other agencies, driven mostly by generic submissions. Local clinical trials to collect local data are required for imported drugs, and the backlog of applications for Clinical Trial Permissions due to the high volume and relative under-staffing at the China Food and Drug Administration (CFDA) is proving frustrating for many companies. The CFDA recently released guidelines for the conduct of multi region clinical trials (MRCT) with at least three countries including China, for unmet medical needs and life threatening disease, which may help to speed up registrations. A new guidance was issued recently. This describes (i) launching a pilot program of a market authorization holder (MAH)

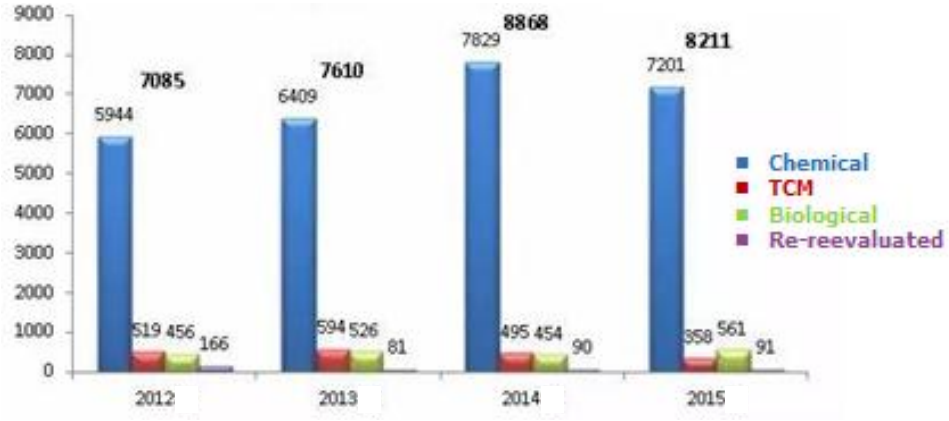

Figure 4. Annual drug submissions received by CFDA
TCM: Traditional Chinese Medicines

system for drugs, where the market authorization holder may be the marketing organization not just a manufacturing site, (ii) allowing synchronous in-country clinical trials for new drugs that have not yet been marketed overseas, and (iii) adopting qualified clinical data obtained directly from multicenter clinical trials. Four sites in Taiwan have also been qualified so that their data can be used in China.

Since July 2015, the CFDA has been conducting inspections on clinical trials and clinical trial sites in China, with the aim of improving the quality of clinical trial data. This has led to additional delays, coupled with the requirement since October 2015 for review and approval by the Human Genetic Resource Authority, which is adding 3–6 months to timelines.

Another new guidance was recently released with the objective of clearing the backlog of applications waiting for review. Drugs with significant clinical value will be given priority, including those for AIDS, hepatitis, rare diseases, cancer and pediatric populations. The classification of drugs has changed to a new definition for "new" drugs. Other measures include increasing significantly the registration fee for applications, and recruiting 300 new staff members to support reviews. The backlog was reduced from 23,000 to 17,275 by end 2015[7].

Overall, the reforms emphasize improving the efficiency of the review system, resolving the drug application backlog by the end of 2016, improving the quality of generic drugs, improving the quality of clinical trials, encouraging the development of innovative drugs and creating a more transparent review and approval process[8].

Many multinational companies have opened R&D centers in China, in order to capitalize on the wealth of talent and the opportunities in the region. It has been suggested that China has over the next 10 years will become a major force in global pharma[9].

Japan has required local data for many years, and has moved from requiring repeat of the entire development program in Japan to now being open to multi-region or global trials including Japanese patients, provided the number of Japanese patients is sufficient to meet the Japanese regulatory requirements. Japan is routinely included in global development trials by many MNCs. Last year, the Pharmaceutical Affairs Law was revised in order to strengthen safety of drugs and device registration[10]. It is now the third largest market in the world, after the US and China, and so remains very attractive[11].

Taiwan requires local data or a bridging study which may include Asian patients or provide pharmacokinetic justification, which is the path most commonly used. Taiwan is an increasing center for clinical trials in the region, given the short timelines for obtaining regulatory and ethics approval, and the high quality of data from experienced clinical trial centres[12]. Four centers have also been approved for use of the data to submit for inclusion in NDAs for China[13].

South Korea is also a major center in the region for clinical trials, due to the regulatory, political and demographic favorable conditions. The government has established clinical trial training centers, improved and streamlined the clinical trial approval process within the regulatory framework. The quality of trials,

ease of the regulatory framework and medical infrastructure, along with the requirements for local data for product registration, have attracted many MCNs to do trials in Korea. Clinical trial data generated in South Korea can be accepted in Japan, which allows an Asian strategy for product development[14–16].

In Australia, current data suggests that around 1000 new clinical trials are commenced in Australia each year by pharmaceutical, biotechnology and medical device companies, representing a $1 billion investment, the top 10 global pharmaceutical companies being responsible for 20% of this investment[17]. There has been a shift in trend in the type of clinical trial activity conducted in Australia. Historically, Phase III studies have dominated. However, since 2008, there has also been a significant increase in early-phase activity, reflecting global trends, along with local capabilities in early-phase clinical research.

Australia boasts a quality medical research infrastructure and a skilled workforce, a world-class healthcare system, a stable socio-economic environment, an ethnically diverse population and a strong intellectual property regime. An efficient regulatory system, including a rapid clinical trials approval system, its proximity to Asia, a strong mechanism of support services, streamlined processes and globally competitive tax incentives for research and development (R&D) investment, all contribute to making it attractive for conducting trials[18].

The TGA is responsible for the regulation of medicines and medical devices in Australia. In December 2011 a comprehensive package of TGA reforms, drawn together by the Australian Government, were announced in the *TGA reforms: A blueprint for the TGA's future*. The blueprint reforms aim to improve community understanding of the TGA's regulatory processes and decisions, enhance public trust and confidence in the safety and quality of therapeutic goods. A four-year implementation plan was put into place, focusing on the areas of communication and stakeholder engagement, advertising of therapeutic products, complementary medicines (or traditional and alternative medicines), medical devices and promotion of therapeutic products[19].

There is a national focus on continuous improvement of the industry through government reform and policy innovation. Two significant examples are the Therapeutic Goods Administration (TGA) reforms and the Australian Government Clinical Trials Initiatives[20]. The Australian Government, in partnership with industry and other stakeholders, is currently undertaking initiatives (Australian Government Clinical Trials Initiatives) to improve the clinical trials environment in Australia, whilst maintaining the highest quality and ethical standards. These include a focus on reducing study start-up times, working towards a nationally consistent approach to clinical trials, boosting patient recruitment and developing a standard list of costs for clinical trials[20].

6. Post-marketing Surveillance (PMS)

Japan, Korea, India and China have specific requirements for PMS studies in order to collect data for license renewals. There are specific requirements and guidelines from each country regarding number of patients, length of study, study design, etc. The data should be submitted as part of the license renewal application[21].

7. Strategic Development Options

Given the number of countries requiring local data for registration, there are several strategic options in the region to obtain approval. These include stand-alone trials in each country, inclusion of the countries into global trials, and regional multi-country trials. The region is also increasingly being included to achieve recruitment numbers for global trials, in Australia for example, even if local data is not required. The advantages of having experienced investigators and local data which can be leveraged for publications and reimbursement are not to be underestimated. The best option will depend on the individual compound, the number of patients to be recruited and the timelines to be met.

8. Education

It is critical to have well trained staff who are able to manage the complexities in the region. Regulatory affairs, drug safety, medical and clinical affairs staff all need to be informed and abreast of the changing environment and are able to have the knowledge base and critical and strategic thinking skills to leverage.

There are a number of ongoing activities aimed at advancing education in pharmaceutical medicine in the region. There are courses already available in Beijing, China, Osaka, Japan and at the University of New South Wales, Sydney, Australia[22]. Education of this kind is a critical need to keep pace with the growth in the industry, and in particular the growth in clinical

trials and medical affairs activities, needing experienced, well-trained personnel.

9. Conclusion

The region is fast moving with a constantly changing environment, with many countries taking steps to improve their healthcare, including strengthening registration and safety requirements. The opportunities abound, and this is being increasing recognized by MNCs who are focusing their efforts and setting up regional offices and R&D centers in the region. There are new regulations, new guidance and changes in the regulations happening continuously. It is therefore critical to have experienced people on the ground that keep abreast of the changes and provide key inputs as required to leverage the knowledge base and experience of MNCs and local companies. With this in place, it will be possible to leverage the possibilities and help shape the environment in order to bring much needed therapies to patients in the region[23].

Conflict of Interest and Funding

The author declares that there is no funding or conflict of interest associated with this work.

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