Drug Development in Asia: Scattering the Mist

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This article discusses misconceptions and their causes, surrounding drug development in Asia, and explains the region’s current drug development landscape.

Introduction

Asia is a huge landmass with contrasting physical and human geographies. The economic panorama within this rich milieu of human geography has become one of Asia’s most prominent features, and many major pharmaceutical companies are acquainting themselves with the unique regulatory and medical landscape and aggressively aiming to create ‘beachheads’ for drug development in Asia. They are doing this by carefully implementing strategies to optimize their “resource-benefit-risk.” Many also are trying to separate Asian drug development fact from misconception.

This article addresses some current misconceptions about drug development in Asia. To clear up misconceptions is akin to “scattering the mist” to see the clear blue sky and with this metaphor, this article intends for readers to gain clarity, insight and appreciation of the regulatory systems in Asia. Furthermore, readers should be able to avoid extrapolating from the practices of major countries, accepting dictates from influential lobbies as truths, and “over expecting” what major institutions can accomplish.

Misconceptions

1. “Data exclusivity” means the same to the US and EU as it does to other countries, so if one country implements data exclusivity, generics cannot enter that market during that period.
2. The “Tripartite Cooperation on Clinical Research” arising from the China/Japan/Korea collaboration is finalized and guidelines are in place, so clinical trial
activities can be pursued to take advantage of the mutual harmonization currently in place.

3. Besides the Tripartite Working Group of China, Korea and Japan, there are no other intra-Asian initiatives pertaining to regulatory cooperation.

4. To be successful in Asia, it would be best to copy what successful innovators (or follow-on products) have done in terms of formulating patient numbers and clinical trial design. In other words, it is easier to “cut-and-paste” from successful, proven programs.

5. Ethnic sensitivity needs to be shown in all markets, especially given racial or genetic diversity in Asia. As a consequence, local clinical trials are mandatory for most countries in Asia.

6. The therapeutic class of drug is a major factor in determining the regulatory pathway of a drug developed in Asia.

7. If we include ethnic Chinese patients or subjects from territories outside China, this could fulfill the requirements for drug development in China.

Background

Asia hosts 60 percent of the world’s population and claims 30 percent of the globe’s total land. It has the world’s highest mountains and the world’s second longest coastline. The Asian climate is one of extremes, yet tropical conditions temper its equatorial region.

In addition, Asia is a collection of human geography in terms of ethnic, social, cultural, economic, historical, regulatory and government elements, as well as political entities spread across its landmass. Asia’s economic promise remains one of its most alluring features and is currently enjoying one of its highest economic growth rates. China, Japan, Korea, Singapore and Taiwan are economic superpowers, while India and the Association of South-East Asian Nations (ASEAN) region also are experiencing growth spurts.

Pharmaceutical companies are looking to Asia for investment, timely collaborative research and development and to commercialize their products. Scientists also are studying and distilling potential therapeutic possibilities from Asia’s verdant forests and from age-old traditional practices.

Strategic Drug Development (Asia) is a department within Quintiles East Asia Pte Ltd, which aims to partner with and help client companies by leveraging its strong Asian footprint to accomplish the following:

- Accelerate strategy development with comprehensive and balanced best-in-class solutions
- Provide scientific and medical expertise to create a customized integrated, engaging approach
- Assure continuous alignment of goals
- Help clients navigate developmental complexities
- Focus on speed-to-market and cost savings

Misconception #1

“Data exclusivity” means the same to the US and EU as it does to other countries, so if one country implements data exclusivity, generics cannot enter that market during that period.

Reality

“Data exclusivity” means different things to people in different countries.

The Facts

Developing a drug candidate is an expensive and complicated process, costing an average of $2.6 billion and taking more than 10 years. The costs take into account the company’s other failed drug candidates, and costs associated with doing research in the chemical, pharmacological, pharmaceutical, toxicological and clinical domains.
Generics (a term usually reserved for chemical molecules) generally enter the market after a patent expires. Generic drug applicants, by legal privilege afforded by existing regulations, typically do not have to repeat toxicological and clinical research that innovator companies have conducted and paid for. In many cases, generic applicants just need to prove their drug has the same active ingredient, possess a similar dissolution profile or at the very most, demonstrate bioequivalence with the innovator drugs.

Innovator companies are facing increasing pressure to recoup investment costs afforded by the remaining patent period. The product’s patent duration is often not long enough; hence, the concept of “data exclusivity” has been introduced.

Article 39.3 under “Section 7: Protection of Undisclosed Information” of the World Trade Organization (WTO) “Trade-Related Aspects of Intellectual Property Rights” (TRIPS) Agreement of 1993 provides the following:

“Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public or unless steps are taken to ensure that the data are protected against unfair commercial use.”

According to a prominent lobby (typified by advanced countries, such as US and nations in the EU and frequently called TRIPS Plus), during the period known as “data exclusivity” in the US, and called “data protection” or “regulatory data protection” in the EU, regulatory authorities of the WTO’s member countries (which had enacted the appropriate laws) cannot rely on or use the data submitted by the originator for the approval of pharmaceutical “copycats” or generics without the permission of the originator.

This means, authorities cannot accept abbreviated generic product applications during this period because acceptance would inadvertently mean making reference to disclosed or undisclosed innovator’s data, such as the preclinical and clinical data. Unless data is re-generated, generics will be considered persona non grata during this exclusivity period, beginning with and extending from the date of the product’s marketing approval. While the period differs from country to country, it is typically five or six years.

Not every TRIPS member country accepts the description of data exclusivity as defined by the influential lobby. A second school of thought, followed by countries, such as Malaysia, have stated in their “Directives of Data Exclusivity,” they will protect the pharmaceutical test data that is undisclosed, unpublished and not in the public domain.

The above camp maintains they are complying with the original spirit and intent of TRIPS Article 39.3 under “Section 7: Protection of Undisclosed Information,” which says regulatory authorities and generic applicants can rely on data already published, disclosed or otherwise placed in the public domain. These generic applicants do not rely on undisclosed data from the originator’s registration file, but use their own pharmaceutical development data and also rely on what is already in the public domain for information regarding toxicology and clinical research. These generic drugs can be approved on their own merits, in keeping with the original spirit and intent of TRIPS Article 39.3.

Many countries also state in their data exclusivity laws, that protection will be given to submitted data considered confidential or trade secrets, which is not available to the public. These countries include Australia, New Zealand, China, Taiwan, Bahrain and Egypt.

The TRIPS Plus lobby also has created a concept known as “marketing exclusivity,” which raises the bar even higher for introducing generic products. In the case of marketing exclusivity, all generic products cannot be placed on the market, even if the product has already received a marketing authorization. The TRIPS Plus lobby says the data exclusivity clause (or marketing exclusivity) should be followed according to their tighter definition, and it specifically spells out this commitment to be followed when it enters into free trade agreements with other countries.

As explained above, where data exclusivity is concerned, this term does not necessarily mean the same to industry in the US or EU as it does to other countries.
Misconception # 2
The “Tripartite Cooperation on Clinical Research” arising from the China/Japan/Korea collaboration is finalized and guidelines are in place, so clinical trials activities can be pursued to take advantage of the mutual harmonization currently in place.

Reality
The China/Japan/Korea “Tripartite Cooperation on Clinical Research,” initiated in 2007,(6) has been on the “back-burner” since October 2011(7) and not much has been accomplished in terms of harmonized, actionable plans. However, one company has claimed success in leveraging the Tripartite Cooperation to implement an accelerated development strategy for its anti-cancer drug in Japan.(8)

Facts
Following the issuance of the ICH-E5 guidelines in 1998,(9) (Guidelines on “Ethnic Factors in the Acceptability of Foreign Clinical Data”) ethnically-similar Asian countries with local clinical requirements for drug development, such as Japan, China and Korea, collaborated to achieve regional consensus. Taiwan, with similar requirements, was not involved, possibly due to political sensitivities.

In 2007, the Health Ministers of Japan, China and Korea started the Tripartite Working Group (WG) to facilitate information sharing to enhance understanding of the impact of ethnicity on drug development and to explore possibilities to harmonize systems and procedures pertaining to multi-regional clinical research. The three major activities and their country leads are:

- Research on ethnic factors (Japan)
- Information sharing (Korea)
- Guidelines on regional clinical trials (China)

The WG had four meetings with the last held on 31 October 2011. Recent geopolitical developments or a re-assessment of national priorities may have contributed to a halt in the talks.

Japan had issued the guidance: “Basic Principles on Global Clinical Trials” on 28 September 2007. An addendum guidance: “Basic Principles on Global Clinical Trials (Reference Cases)”(10) was issued on 5 September 2012 as a result of scientific updates and accumulated experience, partly from the collaborative efforts among the Tripartite regulatory authorities up until then.(11) This document offers guidance to industry on how to include Japan in global clinical trials or how to accept data generated from global clinical trials conducted in East Asia.

Other than the guidance created by Japan for local use, there are no official tripartite guidelines harmonized across the three participating countries.

However, in January 2015, HUYA Bioscience International announced the Pharmaceutical and Medical Devices Agency (PMDA) had accepted its accelerated development strategy for the novel cancer drug HBI-8000, based on the Tripartite Cooperation. (12) This industry news is exciting and may pave the way toward greater tripartite cooperation. However, until official Tripartite consensus and guidelines are in place, pharmaceutical companies will have to continue to navigate and implement drug development and regulatory strategies appropriate to the nature of the drug and according to the needs of each country.

Misconception #3
Currently, there are no notable intra-Asian regulatory collaboration activities other than APEC initiatives (and follow-on Tripartite Working Group of China, Korea and Japan, currently on the backburner), and the ASEAN harmonization activities on pharmaceutical products.
Reality
Besides the Tripartite Agreement and the ASEAN harmonization, there are other intra-Asian regulatory collaborations, such as the “Comprehensive Economic Cooperation Agreement (CECA)” between India and Singapore, and the “Cross-Straits Economic Cooperation Framework Agreement (ECFA)” between Taiwan and mainland China.

Facts
In May 2010, Singapore and India launched the second review of the India-Singapore “Comprehensive Economic Cooperation Agreement (CECA),”(13) which established the fast-track registration program of Indian generic medicines in Singapore. The Health Sciences Authority (HSA) will grant accelerated approval to Indian generics meeting the set criteria, which includes having obtained product approval in the US, Canada, the EU, Britain or Australia.

On 29 June 2010, China and Taiwan signed a landmark trade pact known as the “Cross-Straits Economic Cooperation Framework Agreement” (ECFA).(14) One of the strategic initiatives of this agreement involves the “Cross-Strait Cooperation Agreement on Medicine and Public Health Affairs” between Taiwan and mainland China, seeking to enhance cooperation in drug regulatory matters.

Within the space of a few years, projects under ECFA have moved forward much faster than the 2007 Ministerial level Japan-China-Korea Tripartite Agreement which, as of August 2015, is still on the ‘backburner.’

The first drug under the ECFA, Taigexyn (nemonoxacin) from Taiwan’s Taigen Biotechnology Co., submitted to both the Taiwan Food and Drug Administration (TFDA) and China Food and Drug Administration (CFDA) in May 2013,(15) was approved by the Taiwan FDA in March 2014,(16) and is currently under review by CFDA. Taigexyn is the first pharmaceutical product to fall under the Cross-Strait Cooperation Agreement on Medicine and Public Health Affairs of the Economic Cooperation Framework Agreement (ECFA) between Taiwan and mainland China. It also is the first new drug from Taiwan to meet the requirements of CFDA’s Category 1.1, which is New Chemical Entities (NCEs) that have never been approved anywhere in the world,(17) and developed according to the rules in China.

It was reported on 7 August 2015(18) CFDA had completed an on-site inspection of the manufacturing site of Taigexyn (nemonoxacin) capsule formulation and was satisfied the manufacturing practices conformed to GMP standards. This on-site inspection is the final step in the approval of the Drug Manufacturing Certificate which authorizes the marketing of a new drug in China.

Misconception #4
To be successful in Asia, it would be best to copy what successful innovators (or approved “follow-on” products) have done in terms of formulating patient numbers and clinical trial design. In other words, it is easier to “cut-and-paste” from successful, proven programs.

Reality
Although patient numbers are often recommended by authorities through various guidelines, clinical trial design also depends on various factors, such as prevalence of the disease, disease sub-sets, ethnicity considerations, the drug’s Chemistry, Manufacturing and Controls (CMCs) and safety-efficacy profile, overarching set of statistical objectives (power of trial, superiority, non-inferiority, etc.) and defined clinical end-points. With so many variable factors to consider, it would be a mistake for a manufacturer (e.g., of a biosimilar), while aspiring to enter a certain market, to simply follow the clinical program of an already registered biosimilar.

Facts
Biosimilar drug development provides an example illustrating the complex development coupled with a demand for simplicity; yet there is no one-size-fits-all strategy.
One could expect “biosimilar-wannabes” could simply employ a “copy-and-paste” strategy of already marketed biosimilars, but that is not the case.

The “copy-and-paste” strategy is an exception rather than the rule. For example, there are various biosimilar filgrastims that have gained approval in the EU since 2008. Some of these biosimilar filgrastims are Tevagrastim® (Teva Generics GmbH), Nivestim® (Hospira UK Ltd.), Zarzio® (Sandoz GmbH), Gastrofil® (Apotex Europe BV). The manufacturers had different development approaches. (Figure 1)(19)

### Figure 1. Biosimilar Filgrastims to have gained approval in the EU since 2008

<table>
<thead>
<tr>
<th>Filgrastim Biosimilar</th>
<th>Phase I Studies</th>
<th>Phase III Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum Number of Studies</td>
<td>Minimum Number of Subjects</td>
</tr>
<tr>
<td>Tevagrastim (Teva Generics GmbH)</td>
<td>1</td>
<td>196</td>
</tr>
<tr>
<td>Nivestim (Hospira UK Ltd.)</td>
<td>2</td>
<td>92</td>
</tr>
<tr>
<td>Zarzio (Sandoz GmbH)</td>
<td>4</td>
<td>146</td>
</tr>
<tr>
<td>Gastrofil (Apotex Europe BV)</td>
<td>4</td>
<td>200</td>
</tr>
</tbody>
</table>

Although the “cut-and-paste” logic would seem to be the simplest approach for a manufacturer intending to enter a market (in Asia or elsewhere), everyone starts from a different point and the subsequent approaches need to be individually tailored.

### Misconception #5

Ethnic sensitivity needs to be shown in all markets, especially given the racial or genetic diversity in Asia. As a consequence, localized clinical trials are mandatory for most countries in Asia.

### Reality

Ethnic sensitivity as a topic does not just comprise genetics (intrinsic factors), but also that of culture and environment (extrinsic factors). Some countries have adopted approaches to address the impact of genetic diversity or ethnicity on the drug’s efficacy and safety.

Although some countries require ‘local’ clinical data to address the question of ethnic sensitivity, there may be room for flexibility afforded by local guidelines.

### Facts

The concept of ‘race’ as a valid biological category among Homo sapiens is questionable in medicine; however, the concept of ‘race’ has been used as an imprecise proxy for explaining assumptions about the frequency, causes, onset, expression and treatment of disease in diverse populations.(20)

There is a concern that a drug’s safety, efficacy, dosage and dose regimen as elicited from clinical programs conducted in different geographical regions with diverse ethnicities may vary with ethnic/genetic differences. This concern has led to the creation of the ICH E5 Guidelines on “Ethnic Factors in the Acceptability of Foreign Clinical Data.”(21)

In ICH E5, the concept of ethnicity is defined as not just limited to genetics and race. Factors affecting ethnic sensitivity are both intrinsic (genetic and physiologic) and extrinsic (cultural and environmental). Extrinsic factors take into account local medical practice and drug-diet interactions. Countries such as South Korea, Taiwan and Japan have officially adopted ICH-E5 guidelines on ethnic sensitivity. Criteria expressed in the guidelines are based on scientifically-based principles. These criteria will give a sense of the likelihood of ethnic sensitivity (or insensitivity as the case may be), and the degree of acceptability of
foreign clinical data. If the probability of ethnic sensitivity is high, a local ‘bridging study’ may be necessary to establish and validate the impact of ethnic sensitivity.

In general, for Certificate of Pharmaceutical Product (CPP)-dependent countries, local clinical trials are not mandatory. For Korea and Taiwan, a local study may not be necessary depending on the outcome of the bridging study evaluation or if the drug class has been determined by local regulations to be eligible for a local study waiver.

**Misconception #6**

The therapeutic class of drug is a major factor in determining the regulatory pathway of a drug developed in Asia.

**Reality**

Regulatory pathways are distinct from and not largely dependent on therapeutic classes in Asia. By and large, the therapeutic class of drug is not the main factor for determining regulatory pathways in Asia.

**Facts**

In Europe, the therapeutic class of the drug can determine its regulatory pathway. For example, the centralized procedure is mandatory for human medicines for the treatment of HIV/AIDS, cancer, diabetes and neurodegenerative diseases.

In the US, review divisions are divided according to therapeutic classes, such as cardiovascular, renal and neurology; however, regulatory pathways are not usually classified by therapeutic class. Also, there are a number of approval pathways, such as fast-track, priority review, accelerated approval and breakthrough product designations. It was reported there were plans to introduce a pathway for greatly needed drugs in certain medical settings, such as newer antibiotics for treating life-threatening conditions caused by antibiotic-resistant bacteria.(22) However, with the subsequent draft guidance issued by the United States Food and Drug Administration (US FDA): “Guidance for Industry, Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases”(23), it was expressly stated it was not intended to establish a new approval pathway or standard for such drug products.

With a few exceptions, regulatory pathways in Asia, by and large, are not dependent on therapeutic classes. These pathways are:

- Accelerated pathways dependent on medical needs, including “unmet needs,” life-saving needs and rare disease or orphan drug designation
- Chemical drug pathways
- Biological drug pathways: drugs produced from living cells
- Advanced cellular therapy pathways such as for stem cell therapy
- “Copy” drug pathway, including generics and biosimilars
- Prescription drug and OTC drug pathways

Although most regulatory pathways in Asia are organized as listed above, there are exceptions, such as in China(24) and Indonesia.(25) Due to the countries’ unique medical needs, these authorities may impose different sets of regulatory criteria or clinical trial requirements for drugs belonging to specific therapeutic classes, such as oral contraceptive drugs.

**Misconception #7**

If we include ethnic Chinese patients or subjects from territories outside China, this could fulfil the requirements for drug development in China.

**Reality**

Unless there are special circumstances or permission granted, CFDA will only accept Asian data from territories outside China as supportive data. The data in and of itself,
even if consisting purely of overseas ethnic Chinese, will be insufficient for fulfilling local requirements.

Facts

The regulatory system in China is unique and has a reputation of having very long Clinical Trial Application (CTA) or Investigational New Drug (IND) and New Drug Application (NDA) review timelines. However, the regulatory system in China is constantly evolving and continues to change. This evolution is propelled by a mission to modernize and increase home-grown innovation and pursue world standards on the international stage. Chinese authorities continue to adopt innovative approaches and follow international standards, such as ICH, where appropriate.

Drug development in China generally necessitates local clinical trials engaging locally-qualified researchers, Chinese institutions and the local populations. The CFDA does accept clinical trial data from three qualified centers in Hong Kong, e.g., Prince of Wales, Queen Mary and Hong Kong Eye Hospitals, in certain therapeutic areas.

As a consequence of the ECFA between mainland China and Taiwan, an agreement was signed between the two parties in December 2014 allowing new drug clinical trials to be conducted simultaneously in both regions.\(^{(26)}\)

In China, subtle nuances may result in a reality contrary to expectations, and one should approach any apparent good news with caution. Unless the CFDA has expressly agreed (e.g., in consultations) or if there are already well-recognized precedents, there is still a small risk to include data (e.g., pharmacokinetic data) only from Hong Kong centers or Taiwan centers in lieu of data from mainland patients for eventual FDA purposes. Other than this officially-recognized “flexibility,” which is still not free of difficulties, the CFDA has not formally agreed to accept any other overseas Chinese data or other Asian patient data in lieu of local Chinese data.

Conclusion

This article attempted to address some misconceptions prevalent in Asia regarding drug development. It intended to “scatter the mist” of misconceptions resulting from an over-simplification of the region and an under-appreciation of the nuances and forces catalyzing Asia toward an exciting future.

References


19. Data from public sources collected by Quintiles for the purpose of understanding biosimilar study design.


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