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CHAPTER 10

The Importance of Ethnicity Definitions and Pharmacogenomics in Ethnobridging

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OBJECTIVES

1. Emphasize the complexity of defining ethnicity and the need of a standardized definition for scientific research
2. Outline the ethnic intrinsic and extrinsic factors in determining outcome of treatment
3. Identify the factors considered in acceptability of foreign clinical data for drug approval
4. Highlight the role of pharmacogenomics in global drug development
The ethnicity effect on variability of pharmacological outcome is well established and has been described extensively. This is one of the major considerations for any local drug regulatory authority when considering applications for new drug approval using foreign clinical data in their region. Bridging studies were proposed to provide supplemental data on a drug’s pharmacokinetics/pharmacodynamics, safety, efficacy, dosage, and dosage regimen in a new country or region to determine whether the foreign clinical data can be applicable to the new region. Discussions on the (de)merits of doing bridging studies based on ethnicity are not new. Many arguments have been put forth for various reasons, and one of the main reasons for dispute is that the terms “ethnicity” and “race” are very poorly defined. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) E5 guideline [1] was drafted to facilitate registration of medicines in ICH-affiliated countries by providing a framework to evaluate ethnic factors on the outcome to medical treatment(s). It was intended to hasten drug approval process while minimizing clinical trial duplication with swift delivery of new medicines to needy patients. Although fully adopted by some countries in East Asia, not all have followed suit, especially in developing nations like the Southeast Asian nations, due to inadequacies in experience and resources. Even in the countries where it has been adopted, there were appreciable differences in the way the bridging concept has been applied. Approaches that may be a solution to this dilemma are the multiregional parallel bridging method or the process of simultaneous drug development. Apart from having the advantage of reducing the lag time in drug approval significantly, these approaches allow for prospective bridging of the data in various regions. The integration of pharmacogenomics and biomarkers in drug development is also seen as a positive attempt to better characterize ethnic factors. In the end, it is hoped that better risk-benefit consideration for drug treatment can be achieved through more relevant population data.

In this chapter, the relevance of ethnic-based bridging studies is examined in three different parts. The first part reviews the difficulties in the definition of ethnicity and the ambiguous ways in which the term has been applied. Next, ethnic factors as defined by the ICH E5 contributing to variability in drug response are examined, with emphasis on the effects of dietary and use of herbal medicines in various population groups. Finally, approaches by different nations on acceptability of foreign clinical data for drug marketing approval are reviewed.

Ethnicity is a sociocultural construct with very vague scientific definition. On many occasions, however, ethnicity becomes politically defined or nationality-based rather than representing true ethnicity. The tendency to overgeneralize ethnic population groups also reduces the validity of many analyses based on ethnic stratification.

The relationship between self-identified race or ethnicity and disease risk has been depicted as a series of surrogate relationships between genetic and nongenetic factors [2]. The nongenetic component includes social, cultural, educational, and economic variables,
all of which can influence disease risk. The distinction between the terms race and ethnicity are also very controversial and varied, as highlighted in an editorial: Census, Race and Science published in the year 2000 [3]. Several examples of dictionary definitions of race and ethnicity were exemplified as follows:

**Race:**
- A vague, unscientific term for a group of genetically related people who share certain physical characteristics
- A distinct ethnic group characterized by traits that are transmitted through their offspring
- Each of the major divisions of humankind, having distinct physical characteristics
- A group of individuals who are more or less isolated geographically or culturally, who share a common gene pool, and whose allele frequencies at some loci differ from those of other populations

**Ethnic group:**
- A population of individuals organized around an assumption of common cultural origin
- Individuals with a common national or cultural tradition
- A social group or category of the population that, in a larger society, is set apart and bound together by commonalities of race, language, nationality or culture

Although the definitions are ambiguous, it can be deduced that race and ethnicity give an insight to cultural, historical, and perhaps socioeconomic and political status, as well as ancestral geographic origins. Because race and ethnicity are different mixtures of biological with social constructs, they are highly dynamic in nature.

Defining race and ethnicity accurately is obviously difficult, given its dynamic nature and the fact that the genetic pool for a population would most likely be heterogeneous in nature. This issue makes any assumptions about purity and accuracy of the definitions fallacious.

**Ethnicities Are Rarely Homogenous in Any Nation**

There is often a presumption that certain nations are ethnically homogenous in nature and that extrapolation of clinical data can be made to certain nations this way. In most circumstances, such reference to population groups are not actually ethnicity based but rather, nation based. Even though this is understandable because regulatory agencies are nation-based entities, such practices are fundamentally erroneous, given the ethnically heterogeneous nature of almost all nations. Some examples are discussed in this section.

**Japan**

The word “Japanese” is used collectively for three ethnic groups known as the Yamato (Hondo-Japanese, or mainland Japanese), Ainu, and Ryukyuan (Okinawan). Even in the national census [4], actual ethnicity (minzoku) is not measured but rather Japanese nationality (kokuseki). However, the Ainu people in particular, who are regarded as the aborigines of Japan living in Hokkaido, differ from the rest of the broader Japanese group physically, linguistically and culturally [5]. Genetic studies evaluating ancestral origins of the Japanese people have shown that they originate from two distinct groups: the Ainu and Ryukyuan populations are direct descendants of the Neolithic Jomon people, and the Hondo people...
are derived from the northeast of continental Asia [6]. Ancient mitochondrial analyses sug-
ggested that the gene flow was from South Eastern Siberia to the Jomon/Epi-Jomon people of
Hokkaido, Sakhalin, and the Kuril archipelago, with the Okhotsk people being intermedi-
aries [7]. Phylogenetic analyses comparing the three ethnic groups also suggested that the
Ainu and Ryukyuan samples are clustered together, and the Hondo-Japanese and Koreans
were clustered together in the neighbor-joining genetic tree [6].

When a Japanese person leaves Japan and migrates to some other country, the definition of
Japanese assumes a slightly different context. This issue is important to recognize, especially
if recruiting for bridging studies. The Japanese then will be categorized as [8]:

- First-generation Japanese (Issei): Subject born in Japan
- Second-generation (Nissei): Subject born elsewhere, both parents born in Japan
- Third-generation (Sansei): Subject and one or both parents born elsewhere, grandparents
  born in Japan

To be eligible for the studies, a Japanese person must have at least all four grandparents
born in Japan with no mixed descent. Thus, a Japanese person of up to the third generation
would be eligible to represent the Japan—Japanese populations [8].

China

Although Han Chinese is the largest ethnic group in China, there are 55 officially recog-
nized ethnic minority groups [9] totaling about 105 million people in China. An equally
diverse number of languages—up to 200—are being spoken in China, from seven linguistic
families: Altaic, Austroasiatic, Austronesian, Daic, Hmong Mien, Sino-Tibetan, and Indo-
European [9]. Furthermore, even within the Han Chinese ethnic group, there is significant
genetic heterogeneity.

Han Chinese is possibly the largest ethnic group in the world, making up about 20% of the
human population. It is also the most prevalent ethnic group in China, accounting for more
than 90% of its total population [10]. Although the Han people are now spread all over the
country, the formation of the Han people began with the ancient Huaxia tribe in northern
China, which spread southward over 200 years [9]. Expansion of the Han ethnic group is
the result of integration of multiple tribes and ethnic groups [11]. Studies on Han-Chinese
mitochondrial DNA (mtDNA) from six provinces in China have suggested interesting vari-
ations within the Han population with obvious geographical differentiation, primarily on
a north—south axis [11]. As a consequence, it may be necessary to cluster the Han Chinese
population according to geographic origins. Today, there are several subgroups of Han
Chinese, speaking different dialects or, arguably, different languages and in fact living in
different parts of the world. It is uncertain whether a clinical study done in Han Chinese
from the northern part of China can adequately represent the rest of the global Chinese ethnic
group. Similarly, it is uncertain that clinical data derived from overseas Chinese who are
primarily derived from a southern Chinese group can be taken to represent a generic Han
Chinese population in China.

Apart from the heterogeneity in the Han Chinese, there is evidence of west Eurasian and
northern east Asian (along the Silk Road) genetic admixture with the northwest Chinese pop-
ulations [12]. It is further confirmed in later mtDNA studies from ethnic groups in Xinjiang
that Central Asia is the main location of genetic admixture between east and west [13].
Malaysia

Malaysia is a multiethnic nation, consisting of Malays (42.1%), Chinese (24.6%), Indians (7.4%), and native Sabah and Sarawak (24.8%). The majority of the Sabah and Sarawak native ethnic groups are the Iban and Kadazan/Dusun ethnic groups [14]. Similar to the Han Chinese in China, heterogeneity can be observed within the Malays in the Peninsular Malaysia itself. The Malay race has been defined as members of indigenous people inhabiting the Malay archipelago and nearby islands, which consists of Malaysia, Singapore, Indonesia, and the Philippines. The migration history of the Malays suggests the Malays have several ancestral origins [15]. The Melayu Bugis (Bugis Malay) and Melayu Jawa (Javanese Malay), who are mainly in the southern peninsula, as well as the Melayu Minang (Minang Malay) in the western peninsula, are historically and culturally related to Indonesia (Sumatera and Java), and the Melayu Kelantan are related to Thailand (Siam). In fact, the states of Kelantan and Terengganu were part of the ancient Siam kingdom, and the rest of the Malay peninsula were part of the Majapahit and then Srivijaya empire, which were strongly influenced by Hinduism and Buddhism, in contrast to the Malacca empire, which was essentially an Islamic empire with Arab influences [16]. Genetic admixture with the Chinese and Indians also occurred when they were brought in large scale in by the British colonizing the Peninsular. These are the main ethnic population groups that may play important parts in the genetic heterogeneity in the Malays [17] of the peninsular of Malaysia. Genetic differences among the four Malay subethnic groups within Peninsula Malaysia were studied by Hatin et al., using 54,794 genome-wide single-nucleotide polymorphisms (SNPs) from the four Malay subethnic groups and compared to the genetic profile of 11 other populations’ data obtained from the Pan Asian database [17].

The study showed that the Kelantanese Malays were genetically distinct from the other three groups of Malays, who showed high resemblance to the Indonesian Malays. Not surprisingly, the results showed that the Malays could be assigned to three different clusters, with the Melayu Minang and Melayu Bugis in Cluster I, Melayu Jawa in Cluster II and Melayu Kelantan in Cluster III. The Melayu Kelantan formed an independent clade, suggesting a more divergent ancestry compared to the other two clusters.

There are also instances of political and religious bias in the definition of ethnicity. Take, for example, the definition of the Malay ethnicity in Malaysia. The Malaysian Constitution (article 160) [18] defines the Malays as:

- Malaysian citizen born to a Malaysian citizen
- Professes to be Muslim
- Habitually speaks the Malay language
- Adheres to Malay customs
- Resides in Malaysia or Singapore

It is obvious that the Malay ethnicity definition in Malaysia is a completely sociocultural and political construct and does not have any biological reference whatsoever. Apart from that, a Malay person in Malaysia is no longer considered Malay by law if the person converts out of Islam.

It should be noted, though, that only the difficulties in defining the Malays has been described here. Any attempts to carry out ethnobridging studies in Malaysia must also take into account the other ethnic populations, as described earlier. Although the situation...
in neighboring Singapore is not discussed here, it should be noted that the ethnic definition of Malay differs between the two countries and complicates attempts to generalize ethnic data from one country to another.

**Indonesia**

Indonesia is the fourth most populous country in the world. It is made up of 17,000 islands and is home to more than 240 million people with an immensely diverse admixture of more than 750 languages and 300 ethnic groups [19]. To promote nationalism and sense of unity in the postcolonization era, the *Pancasila* ideology was introduced in 1945, which underlines the nation identity as culturally neutral, along with the use of *Bahasa Indonesia* (the Indonesian language) by all people in Indonesia. National census between 1961 and 1990 was devoid of ethnicity data because ethnicity and race was deemed too sensitive to be discussed or recorded [20]. The first ethnicity data were recorded only in the year 2000 census. According to this census, there are more than 100 self-identified ethnic groups in Indonesia. However, most of these ethnic groups are small in number, and only 15 groups have more than one million people [20]. The majority of the Indonesian people are of Javanese ethnic group, which constitutes 41.7% of the total population. Table 10.1 lists the major ethnic groups in Indonesia, which makes up more than 81% of the total population percentage.

The majority of the nonnative Indonesians is of Chinese ethnicity. In the year 2000 census, it was reported that less than 1% of the population described themselves as Indonesian Chinese. It is believed that the figure was a gross underestimate and that the real figure was perhaps three to four times larger [21]. With the advent of assimilation of the Chinese with the native Indonesians, there is doubt that even the 1% self-reported Chinese were homogenous with no genetic admixture with the native Indonesians.

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<tr>
<td>Sundanese</td>
<td>15.41</td>
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<tr>
<td>Malay</td>
<td>3.47</td>
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<tr>
<td>Madurese</td>
<td>3.37</td>
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<td>Batak</td>
<td>3.02</td>
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<tr>
<td>Minangkabau</td>
<td>2.72</td>
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<tr>
<td>Betawi</td>
<td>2.51</td>
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<tr>
<td>Buginese</td>
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<tr>
<td>Bantenese</td>
<td>2.05</td>
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<tr>
<td>Banjarese</td>
<td>1.74</td>
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<tr>
<td>Balinese</td>
<td>1.51</td>
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<tr>
<td>Sasak</td>
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TABLE 10.1 List of Major Ethnic Groups in Indonesia [20]
Thailand

Thailand became the official name for the kingdom once known as Siam in 1939. It is often perceived as unique and homogenous in culture and ethnicity [22]. The 2000 census collected spoken language and religion data but not ethnicity data [23]. The official demographics report stated that 94% of the population are Thai-speaking Buddhists and 4% are Muslims [24]. In Thailand, there are over 30 distinct ethnic groups, including the Chinese, who migrated into Thailand in the nineteenth century to form significant urban communities [22]. Many have become significant political and economic figures and assimilated into the Thai society. Due to the lack of official figures, it is exceptionally difficult to get a reliable estimate of the actual numbers of ethnic groups and its composition in Thailand. The ethnic groups in Thailand can be categorized into five large groups based on the language groups, as below [25]. It is not clear to what extent language groups reflect different genetic heritages, but this population diversity needs to be acknowledged.

- Tai-Kadai [26]
  - Yuan, Lue, Khuen, Yong, Thai-Korat, Thai-Khon Kaen, Thai-Chiang Mai, Phu-Thai, Lao-Song
- Austroasiatic [26]
  - Mon, Lawa, Paluang, Blang, H’tin, Khmer, Ching, Thai-Korat
- Sino-Tibetan [26]
  - Lisu, Mussur, han-Yunnan, Han-Guangdong, Han-Wuhan, Han-Qingdao, Han-Liaoning, Han-Xinjiang, Tibetan-Qinghai
- Hmong-Mien [25]
  - Hmong, Mien
- Austronesian [25]
  - Malay, Cham

Ethnicity and Race as Defined by the U.S. FDA

There is a pressing need for standardization of terminologies for the collection of ethnicity and race information in biomedical research. Differences in response to medical products have also been observed in racially and ethnically distinct subgroups of the U.S. population. The U.S. Food and Drug Administration (FDA), mandated by the National Institutes of Health (NIH), prepared the Guideline for Industry: Collection of Race and Ethnicity Data in Clinical Trials [27], which is relevant in determining the safety and effectiveness of a drug or medical product, as well as addressing the issue of lack of inclusion of woman and minorities group in NIH-sponsored clinical research. However, much criticism has been arisen over the racial and ethnic categories, as they are not anthropologic or scientifically based designations but sociocultural categories as described by the Office of Management and Budget (OMB). In this guideline are

- Five race categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, and White
- Two ethnicity categories: Hispanic or Latino and Not Hispanic or Latino

The OMB standards also mention explicitly that “the racial and ethnic categories set forth in the standard should not be interpreted as being primarily biological or genetic in
Thus, when these categories are used in a defined biological or genetic context, it creates confusion in the biological and sociocultural meaning of race and ethnicity [28]. The broad categorization of race—for example, Asian—is also arbitrary, as it combines very heterogeneous groups of people together (although the guideline does allow for more detailed information such as Japanese or Indian). Likewise, “White” is defined as a person having descent from any of the original peoples of Europe, North Africa, or the Middle East [8]. This definition includes Scottish, Greek, Welsh English, Moroccan, and Iranian, which completely abandons ethnic or cultural definitions altogether but rather groups these populations together based on skin color.

The rapid rise in immigration and interracial marriages are on the increase, not only in the USA but also globally. This development creates populations with a very wide geographical and sociocultural background. If ethnicity and race were to serve, to a certain extent, as a surrogate for genetic variations, grouping people along racial and ethnic lines to study functional differences in their drug metabolizing capacity or to interpret results of research and clinical trials relating to various drugs has proven to be complex and challenging [29].

Conclusion

Ethnicity is a highly ambiguous and imprecise sociocultural and sociopolitical construct. Careful considerations should be given so as to not confuse ethnicity and nationality definitions because doing so could lead to fallaciously drawn conclusions, especially when considering risks and benefits of pharmacological treatment based on more biologically related processes. A useful way to describe ethnicity in scientific research would perhaps be to combine elements of geographic origins and the sociocultural context. For example, an ethnic group could be identified as Indonesian Chinese, Malaysian Chinese, American Chinese, and so on. This dual element in defining ethnicity would be better able to take into consideration the extrinsic components of ethnicity interacting with the intrinsic components.

ETHNIC FACTORS AFFECTING DRUG RESPONSE

The definition of ethnicity has both elements of biology and the environment. These have been described in the ICH E5 document as intrinsic and extrinsic factors [1]. Figure 10.1 summarizes the intrinsic and extrinsic factors, as outlined in the ICH E5 guidelines. It is often difficult to ascertain which of the intrinsic or extrinsic factors are causing differences in drug response. All intrinsic and extrinsic factors play important roles in influencing pharmacological outcome to treatment. In the following section, the genetics aspect of the internal factor and food and traditional medication intake as well as medical practices aspect of extrinsic factors are discussed.

Intrinsic Factors: (Pharmacogenetics)

Interethnic differences have been demonstrated in the allele frequencies of various drug metabolizing enzymes, transporters and pharmacologic targets. The clinical relevance for the known variants are not fully understood—some have very clear relevance, and some
are still unknown. Pharmacogenetics of drug target, drug metabolism, drug transport, disease susceptibility, and drug safety have been discussed extensively elsewhere [30]. Thus, this chapter will only briefly review some examples of pharmacogenetics of DMEs and pharmacologic targets.

**CYP2D6**  
CYP2D6 is involved in the metabolism of approximately 25% of all drugs [31]. The first CYP polymorphism was discovered for CYP2D6, which is perhaps one of the most studied and best characterized CYP gene. More than 50 alleles have been described for this gene [32], with approximately 20 affecting metabolism of CYP2D6 substrates. CYP2D6 polymorphisms result in to four phenotypes: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs) and ultra-rapid metabolizers (UMs) [33]. Allelic variants that have been associated with the phenotypes are listed in Table 10.2.

The bioavailability, systemic exposure, area under the curve (AUC) and half-life of relevant drugs for the PMs, relative to the EMs have been reported to be between two- to sixfold, with metabolite clearance between 0.1- to 0.5-fold [34]. Meanwhile, UMs experience the extreme opposite, rapidly accumulating metabolites at the highest possible doses. Clinical effects of CYP polymorphisms have been reported for various drugs and are particularly serious with the use of tricyclic antidepressants, which are primarily metabolized by this enzyme. Tricyclic antidepressants are very toxic drugs, with potentially fatal adverse effects secondary to cardiac complications [35]. In vulnerable subpopulations like the CYP2D6 PMs,
as well as the elderly and adolescent, very low initial doses are recommended [36]. Table 10.3 lists some of the clinical consequences with the use of CYP2D6 substrates for persons with the PM and UM phenotypes.

> Interethnic differences in CYP2D6 allelic frequencies and phenotypes have been shown in many studies. The PM phenotype occurs in about 7 to 10% of European populations compared to 1% of East Asians, with *3, *4, and *5 being most commonly implicated in this
The *4 variant allele is the most common variant allele in Caucasians, with almost 21% frequency and, interestingly, the *4 variant is almost absent in Chinese. The most common variant allele in Chinese is the *10 (~50%), which is virtually absent in Caucasians. Other examples of differing CYP2D6 allele variant frequencies include the CYP2D6*3 allele (no enzyme activity phenotype), which is not found to be present in the Eastern to Southern Asian regions [38,39,40] but present in Western Europeans with frequencies from 0.9% to 1.7% [41,42,43]. However, in some populations—for example, Japanese, Koreans, and Chinese—studies have found small differences in the allele frequencies for most of the CYP2D6 variants (<10% difference), except CYP2D6*10 between Japanese and Chinese, with 14.7% difference. For the same variant, the difference between Japanese and Koreans as well as between Koreans and Japanese are 7.6% and 7.1%, respectively [44].

**CYP2C9 and VKORC1: Warfarin**

Warfarin is one of the most widely used oral anti-coagulants globally. It acts by interrupting the regeneration of dihydroxyquinone (KH2), the reduced, active form of vitamin K by targeting vitamin K epoxide reductase complex 1 (VKORC1), leading to decreased carboxylation and activation of the vitamin K-dependent clotting factors. Warfarin use is hampered by the more than tenfold variability in dosing requirement [45,46] to achieve the target international normalized ratio (INR) in different patients. Overcoagulation causes bleeding episodes, with intracranial hemorrhage being one of the most catastrophic. The effects of genetic polymorphisms in its metabolizing enzyme, CYP2C9, as well as the VKORC1 gene on sensitivity to warfarin have been shown in many studies to significantly affect the dosing requirements [47,48,49,50,51], with the CYP2C9*1/*1 genotype associated with a higher maintenance dose compared to the genotype containing CYP2C9*2 or *3 alleles. There are about 28 known polymorphisms for the VKORC1 gene to date, with the 1639G>A polymorphism being most clinically significant. The −1639 AA genotype is associated with a significantly lower warfarin dose requirement [36]. Subsequent clinical studies incorporating the use of a pharmacogenomics algorithm containing CYP2C9 and VKORC1 genotypes demonstrated better overall predictions for the appropriate warfarin dosage needed to achieve the target INR versus standard management approaches [52,53,54]. Table 10.4 shows allele distribution for CYP2C9 and VKORC1 variants and stabilized warfarin dose according to ethnicity [51].

**CYP2C19: Clopidogrel**

Clopidogrel is an antiplatelet agent of the thienopyridine group used in the secondary prevention of myocardial infarction and ischaemic stroke and also in existing peripheral arterial disease, among other indications. It is a prodrug, which is activated mainly by the hepatic enzyme CYP2C19, although other CYP enzymes such as the CYP1A2, CYP2B6, CYP2C9, and CYP3A4 are also involved. Apart from polymorphisms in CYP2C19, effectiveness of clopidogrel has also been associated with polymorphisms in the P-glycoprotein (P-gp) efflux pump, ABCB1—particularly the c.C3435T variant [56], which will not be discussed here. Variant CYP2C19 alleles have been associated with a range of differing activities, including UM, EM, IM, and PM. This finding has clinical implications whereby, for loss of function alleles, there is reduced activity of CYP2C19 rendering clopidogrel ineffective. In contrast, alleles with increased enzyme activity such as *17 may be associated with increased risk of bleeding. The CYP2C19*1 allele is the allele related with normal functionality, and the
A; rs4244285) is most commonly associated with loss of function and is observed in up to 30% in Europeans and Africans (3 to 4% homozygotes) and 70% in Asians (10 to 15% homozygotes) [57]. The cumulated evidence for \textit{CYP2C19} genotyping from clinical studies appears confusing, possibly due to differences in the role of \textit{CYP2C19} in patients with varying degree of disease risk, with greater importance in those at higher risk for poor outcomes, such as patients undergoing percutaneous coronary intervention (PCI) [57]. Studies who enrolled patients at lower cardiovascular risk (e.g., atrial fibrillation or acute coronary syndrome managed medically) mainly found no association between \textit{CYP2C19} genotype and treatment outcome with clopidogrel [58,59] and those who selected patients at higher risk found significant association [60,61]. The FDA approved a boxed warning on the product label regarding the risk of lack of clinical effect of clopidogrel in patients who are poor metabolizers in March 2010 [57]. The labelling does not, however, mandate genotyping for all patients who will be prescribed the medication. Several institutions are starting to embrace genotyping for loss-of-function alleles for all possible clopidogrel candidates [62].

### Extrinsic Factors

Although intrinsic factors, especially genetic factors, are critical determinants of drug response, the impact of extrinsic factors may also be profound. Nutritional, dietary factors, intake of over-the-counter drugs, as well as use of traditional or alternative medicines all have the potential to alter treatment outcome with drugs. Not surprisingly, drugs with narrow therapeutic index and high potency are among those that have been documented to give rise to significant pharmacokinetics and pharmacodynamics alterations.

**Table 10.4** Stabilised Warfarin Dose According to Ethnicity, Allele Distributions for \textit{CYP2C9}, Genotype Distributions for \textit{VKORC1} [55]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>African American</th>
<th>Caucasian</th>
<th>Hispanic American</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (mg/day)</td>
<td>5.2</td>
<td>4.3</td>
<td>4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>\textit{CYP2C9*1} (95% CI)</td>
<td>94 (89–99)</td>
<td>74 (66–82)</td>
<td>93 (85–100)</td>
<td>95 (89–100)</td>
</tr>
<tr>
<td>\textit{CYP2C9*2} (95% CI)</td>
<td>1 (0–3)</td>
<td>19 (12–26)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{CYP2C9*3} (95% CI)</td>
<td>1 (0–3)</td>
<td>6 (2–10)</td>
<td>7 (0–15)</td>
<td>5 (0–10)</td>
</tr>
<tr>
<td>\textit{VKORC1 GG} (95% CI)</td>
<td>82 (74–90)</td>
<td>37 (28–46)</td>
<td>32 (18–46)</td>
<td>7 (0–13)</td>
</tr>
<tr>
<td>\textit{VKORC1 GA} (95% CI)</td>
<td>12 (6–18)</td>
<td>45 (36–54)</td>
<td>41 (25–56)</td>
<td>30 (18–42)</td>
</tr>
<tr>
<td>\textit{VKORC1 AA} (95% CI)</td>
<td>6 (1–11)</td>
<td>18 (11–25)</td>
<td>27 (14–49)</td>
<td>63 (51–75)</td>
</tr>
</tbody>
</table>
Many different types of food and drugs are substrates of CYPs enzyme, particularly CYP3A4 as well as the membrane efflux transporter protein, P-gp. Both CYP3A4 and P-gp are constitutively expressed in the enterocytes and, as such, affect the bioavailability of many drugs such as digoxin, cyclosporine, midazolam, and verapamil. As chemicals contained in foods are present in high concentrations in the gut, food types which affect CYP3A4 as well as P-gp would have a significant effect on the bioavailability of many drugs [63]. Expressions of P-gp and CYP enzymes at target tissues could also be affected by drug–food interactions in similar manner. Table 10.5 lists examples of food–drug interactions.

Cruciferous vegetables such as cabbage, broccoli, cauliflower, and Brussels sprouts are consumed by people worldwide. They are rich in glucosinolates, which can endogenously be converted to biologically active indoles, such as indole-3-carbinol (I3C) and sulforaphane (SFN) [64]. I3C, in nontoxic doses, has been shown to enhance chemo-resistant K562 human leukemic cells in an experimental in vitro study [65]. The K562 cells were also cross-resistant to other chemotherapeutic drugs, such as doxorubicin and vincristine. The Western blot analysis in this study further showed that the P-gp expression was down-regulated when the cells were treated with I3C, suggesting that I3C could alleviate chemo resistance in patients taking these drugs for treatment. This development could potentially give rise to differences in chemo resistance profiles among populations consuming high amounts of I3C-containing foods versus to those with lower consumption. The Koreans are among the largest cabbage consumers worldwide. The Korean population consumes a traditional fermented, spicy cabbage dish, kimchi, almost on a daily basis, totaling about 56.5 kg/person/year [66]—more than 10 times the average consumption of Americans, who consume an average of 4.2 kg/person/year [67]. Similarly, there are marked differences in some parts of the world with regard to consumption of various foods with the ability of modulating P-gp function.

Grapefruit and grapefruit juice intake and drug interactions have been widely studied. Interactions with many drugs are mediated mainly through physical interactions with CYP P450 inhibition, specifically the intestinal CYP3A4, resulting in complete inactivation of this enzyme. This causes prolonged inhibition of the intestinal clearance of specific drug substrates of this enzyme, such as felodipine [68], as well as other drugs metabolized by this pathway. Furthermore, grapefruit has also been shown to inhibit P-gp mediated efflux, potentiating drugs used in HIV treatment and chemotherapy [69]—for example, vinblastine and saquinavir [70]. However, due to significant overlap in the substrates for P-gp and CYP3A4, studies to particularly isolate P-gp mediated interactions have been challenging. The consumption of grapefruit is highest in Eastern Asia, with Japan making up a significant portion, followed by the Americas and European Union nations. However, it should be noted that CYP3A4/P-gp is affected by a large number of phytochemicals. The potential differential effects in different regions should also be considered when potential drugs are being evaluated for market registration. The consumption of such phytochemicals, which are not all related to grapefruit, are highly ethnic specific as they relate to dietary exposures. In some parts of Asia, although grapefruit is not consumed regularly, the pomelo, a related citrus fruit, is consumed in great abundance. The CYP3A4 inhibitory effect of the pomelo has been reported to be as potent as that of the grapefruit [71].
### TABLE 10.5  Examples of Food—Drug Interactions and Their Mechanisms

<table>
<thead>
<tr>
<th>Food type</th>
<th>Drug interaction</th>
<th>Mechanism of interaction</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peperine (black pepper constituent)</td>
<td><em>In vitro:</em> Digoxin, Cyclosporine A, Verapamil</td>
<td>Pg-p efflux inhibitor, CYP3A4 inhibitor</td>
<td>[127]</td>
</tr>
<tr>
<td>Capsaicin (red chili constituent)</td>
<td><em>In vitro:</em> Digoxin</td>
<td>Pg-p efflux inhibitor</td>
<td>[128]</td>
</tr>
<tr>
<td>Curcumin (turmeric constituent)</td>
<td><em>In vitro:</em> Digoxin</td>
<td>P-gp efflux inhibitor</td>
<td>[129,130]</td>
</tr>
<tr>
<td>Green tea</td>
<td><em>In vitro:</em> Doxorubin, Vinblastine</td>
<td>P-gp efflux inhibitor</td>
<td>[131–134]</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td><em>In vitro:</em> Vinblastine, Vincristine</td>
<td>CYP 1A2, 3A4 inhibition P-gp modulation</td>
<td>[135,136]</td>
</tr>
<tr>
<td>Orange juice</td>
<td><em>In vitro:</em> Vinblastine</td>
<td>P-gp efflux inhibitor</td>
<td>[136]</td>
</tr>
<tr>
<td>Pomelo juice</td>
<td><em>In vitro:</em> Tacrolimus</td>
<td>CYP3A4 inhibitor P-gp modulation</td>
<td>[137,138]</td>
</tr>
<tr>
<td>Russian green sweet pepper (Anastasia Green)</td>
<td>Verapamil</td>
<td>P-gp inhibitors</td>
<td>[139]</td>
</tr>
<tr>
<td>Tangerine</td>
<td><em>In vitro:</em> Nifedipine, digoxin</td>
<td>Stimulates CYP3A4 activity and inhibits P-glycoprotein</td>
<td>[149–151]</td>
</tr>
<tr>
<td>Grapes</td>
<td>In humans: Cyclosporine</td>
<td>Inhibits: CYP3A4 and CYP2E1</td>
<td>[152,153]</td>
</tr>
<tr>
<td>Cranberry</td>
<td>In humans: warfarin</td>
<td>Inhibits: CYP3A and CYP2C9</td>
<td>[154–157]</td>
</tr>
<tr>
<td>Pomegranate</td>
<td>Animals: carbamazepine</td>
<td>Inhibits: CYP3A and phenolsulfotransferase activity</td>
<td>[158,159]</td>
</tr>
<tr>
<td>Mango</td>
<td><em>In vitro:</em> Midazolam, diclofenac, chlorzoxazone, verapamil</td>
<td>Inhibits: CYP1A1, CYP1A2, CYP 3A1, CYP2C6, CYP2E1, P-glycoprotein (ABCB1)</td>
<td>[160–162]</td>
</tr>
<tr>
<td>Guava</td>
<td>No data available; possible P-gp mediated drug uptake inhibition</td>
<td>Inhibits: P-glycoprotein (ABCB1)</td>
<td>[163]</td>
</tr>
<tr>
<td>Black raspberry</td>
<td><em>In vitro:</em> midazolam</td>
<td>Inhibits: CYP3A</td>
<td>[164]</td>
</tr>
<tr>
<td>Black mulberry</td>
<td><em>In vitro:</em> midazolam, glibenclamide</td>
<td>Inhibits: CYP3A and OATP-B</td>
<td></td>
</tr>
</tbody>
</table>

10. THE IMPORTANCE OF ETHNICITY DEFINITIONS AND PHARMACOGENOMICS IN ETHNOBRIDGING
Use of Alternative, Complementary, and Traditional Medicines

According to the World Health Organization (WHO), some Asian and African countries use almost 80% of traditional medicine for primary health care. In fact, even in developed countries, the use of alternative or complementary medicine is very prevalent. Herbal and other natural products use were reportedly taken by 1 in every 5 American adults [72]. A follow-up study in the United States that evaluated the use of herbal and natural products revealed that the use was lowest among African Americans, compared to Hispanics and non-Hispanic whites, with the Hispanics using the most number of products [73].

In Asia, the use of traditional medicine systems dates back to the twelfth century B.C. Almost every nation in this region has its own use of traditional medicine, and the practice of some of these systems has spread worldwide. The traditional systems use many remedial methods, and for this chapter, only remedies using herbs and natural products will be mentioned. Some of the systems used in Asia include [74]:

- Traditional Chinese medicine (TCM)
- Ayurveda, from India
- Siddha, from south Tamil India
- Unani medicine, from Persia/Middle East, popular in India
- Kampo, Japanese herbal medicine

### Table 10.5 Examples of Food—Drug Interactions and Their Mechanisms—cont’d

<table>
<thead>
<tr>
<th>Food type</th>
<th>Drug interaction</th>
<th>Mechanism of interaction</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>In vitro: fexofenadine</td>
<td>Inhibits: CYP1A1, OATP family</td>
<td>[165]</td>
</tr>
<tr>
<td>Broccoli, cauliflower</td>
<td>No data available; possible ABC transporters and CYP 1A1, CYP2B1/2, CYP3A4, CYP2E1 substrates modulation</td>
<td>Inhibits: CYP1A1, CYP2B1/2, CYP3A4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, glucoronytransferases, sulfotransferases, quinone reductases phenolsulfotransferases induces: UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and quinone reductases (QRs)</td>
<td>[166–168]</td>
</tr>
<tr>
<td>Watercress</td>
<td>In humans: chlorzoxazone</td>
<td>Inhibits: CYP2E1, P-glycoprotein, MRP1, MRP2, and BCRP</td>
<td>[168,169]</td>
</tr>
<tr>
<td>Spinach</td>
<td>In vitro: heterocyclic aromatic amines</td>
<td>Possible inhibition of CYP1A2</td>
<td>[170]</td>
</tr>
<tr>
<td>Tomato</td>
<td>In vitro: diethylnitrosamine, N-methyl-N-nitrosourea, and 1,2-dimethylhydrazine</td>
<td>Inhibits: CYP1A1, CYP1B1, UGP (Wang and Leung 2010) Increases: UGT and CYP2E1</td>
<td>[171]</td>
</tr>
</tbody>
</table>
Southeast Asian region share many common herbs for medicinal uses, possibly because of the natural distribution of the available plants. This regions’ use of herbal medicine is also greatly influenced by the Ayurveda, Unani, Siddha, and TCM, and thus certain similarities in the use of herbs are often seen. However, it is also important to note that use of herbal medicine is usually specific to ethnicity [75]; for example, the Chinese ethnic groups from various countries tend to use herbs from TCM, rather than Ayurvedic herbs, and Indians tend to use herbs from Ayurvedic/Siddha and Unani medicines, while the Malays tend to use more herbs from the Unani system, apart from the use of folk medicine herbs unique to the ethnic Malays, such as the Tongkat Ali (Eurycoma longifolia) [76].

Many of the herbal medicines commonly used have been shown to have significant drug interactions. St. John’s wort has been traditionally used in the treatment of depression, concomitantly with other antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) and has been implicated in the incidence of serotonin syndrome by additive effect, and also CYP3A4 induction [77,78]. In vivo human studies have also reported a reduction in plasma concentration of drugs such as amitriptyline, cyclosporine, digoxin and fexofenadine, indinavir, methadone, midazolam, nevirapine, phenprocoumon, simvastatin, tacrolimus, theophylline, and warfarin, possibly due to CYP3A4 and P-gp induction [79]. Gingko biloba has been used to improve cognitive functions in Alzheimer’s patients. A report by Galluzzi [80] highlighted a case of an Alzheimer’s patient who became comatose after she was started on trazodone, an antidepressant which enhances release of GABA, and gingko biloba. In view of reversal of the patient’s clinical condition by flumazenil, a specific benzodiazepine (BDZ) antagonist, it was postulated that her condition was possibly due to a drug interaction as a result of an increase in GABAergic activity mediated directly by BDZ receptor. The usually subclinical increase in GABAergic activity of ginkgo biloba became clinically enhanced through an interaction with trazodone. A list of reported herb—drug interactions are given in Table 10.6.

It is important to keep in mind that a significant number of people regardless of ethnicity and geographical locations use herbal and natural products as remedies or daily supplements and that ethnic groups and subpopulations tend to use different types of herbal and natural products—based medicines. These medicines have the potential to interact with prescribed drugs and thus play a significant factor in determining outcome to treatment and should be given due consideration.

**Differences in Medical Practice**

An important extrinsic factor in determining outcome to treatment, as well as whether foreign clinical data can be extrapolated to a new region, is the evaluation of whether there are significant differences in medical practices between the two regions. Common examples in this respect would be the difference between medical practices in Japan to that in the United States and Europe. Studies have shown that there are differences in drug dosing between the United States, Europe, and Japan [81,82,83]. For 32% of drugs approved between 2001 and 2007, the maximum recommended dose in the United States was at least twice as high as in Japan [83]. However, it is not certain whether the differences were due to difference in intrinsic factors or due to differences in interpretation.
TABLE 10.6 Examples of Herb—Drug Interactions and Their Mechanisms

<table>
<thead>
<tr>
<th>Herb type</th>
<th>Drug interaction</th>
<th>Mechanism of interaction</th>
<th>Note on use and primary users</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypericum perforatum (St. John's wort; Seiyo-otogiri-so)</td>
<td>Interacts with selective serotonin reuptake inhibitors and duloxetine by additive effect</td>
<td>Induces CYP3A4, P-glycoprotein membrane transporters</td>
<td>Used as antidepressants; Western traditional medicine; also in Japan</td>
<td>[172–174]</td>
</tr>
<tr>
<td>Allium sativum (Garlic)</td>
<td>Saquinavir Ritonavir Warfarin Chlorpropamide</td>
<td>Induction of CYP3A4 and P-gp Additive effect Platelet dysfunction</td>
<td>Used as antidepressants; Western traditional medicine</td>
<td>[175–179]</td>
</tr>
<tr>
<td>Glycyrrhiza glabra (Licorice)</td>
<td>Prednisolone Hydrocortisone</td>
<td>Potentiation of oral and topical corticosteroids by inhibition of 11β hydrogenase of its metabolite (decreasing clearance)</td>
<td>Widely used in Western traditional medicine</td>
<td>[180]</td>
</tr>
<tr>
<td>Ginkgo Biloba (Ginkgo)</td>
<td>Thiazide diuretic Trazodone Warfarin Asprin Digoxin</td>
<td>Induce: CYP2C19 Metabolic Inhibition Increase of GABAergic activity Inhibition of CYP3A4</td>
<td>Widely used in TCM, U.S., Europe</td>
<td>[181–189]</td>
</tr>
<tr>
<td>Panax spp (Panax ginseng)</td>
<td>Alcohol (ethanol) Phenelzine Warfarin</td>
<td>Delayed gastric emptying and enzyme induction Additive effect</td>
<td>Widely used in TCM, East Asia, US</td>
<td>[186–189]</td>
</tr>
<tr>
<td>Silybum Adans (Milk Thistle)</td>
<td>Indinavir</td>
<td>Modulation of CYP3A4 and P-gp</td>
<td>Widely used in the Mediterranean, Northern Africa as liver tonic</td>
<td>[190]</td>
</tr>
<tr>
<td>Angelica sinensis (Dong Quai)</td>
<td>Warfarin</td>
<td>Contains coumarin</td>
<td>Widely used in TCM</td>
<td>[180]</td>
</tr>
<tr>
<td>Ephedra (Ma huang)</td>
<td>Monoamine oxidase inhibitors, caffeine, decongestants, stimulants</td>
<td>Enhanced sympathomimetic effects when used with other similar drugs</td>
<td>Used in TCM for respiratory ailments</td>
<td>[191]</td>
</tr>
<tr>
<td>Danshen (Salvia miltiorrhiza)</td>
<td>Warfarin</td>
<td>Increases bleeding tendencies by decreasing clearance and increasing bioavailability</td>
<td>Used in TCM for chronic renal failure, coronary heart disease</td>
<td>[192]</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Herb type</th>
<th>Drug interaction</th>
<th>Mechanism of interaction</th>
<th>Note on use and primary users</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eurycomia longifolia (Tongkat Ali, Asian Viagra)</td>
<td>Unknown; speculated to adversely interact with immunosuppressive drugs</td>
<td>No available data</td>
<td>Aphrodisiac, anti-malarial, anti-diabetic; used mainly by Malays in Malaysia</td>
<td>[193]</td>
</tr>
<tr>
<td>Labisia pumila (Kacip Fatimah)</td>
<td>No data available</td>
<td>Inhibits CYP2C8</td>
<td>Postpartum medication, treat menstrual irregularities; used mainly by Malays in Malaysia</td>
<td>[194,195]</td>
</tr>
<tr>
<td>Andrographis panniculata (Hempedu bumi)</td>
<td>No data available</td>
<td>Inhibits CYP2C8, weak inhibitor of CYP2C19</td>
<td>Treatment of infections, diabetes mellitus; widely used in Asia-South India, Sri Lanka, Malaysia, Indonesia &amp; South China, mainly by the Indians and Malays</td>
<td>[194,196]</td>
</tr>
<tr>
<td>Orthosiphon stamenesus (Misai kucing)</td>
<td>Possible interactions with CYP2C19 substrates: omeprazole, citalopram, proguanil, diazepam</td>
<td>Strong inhibitor of CYP2C19</td>
<td>Kidney and urinary disorders; used widely in Thailand, Malaysia &amp; Indonesia</td>
<td>[196]</td>
</tr>
<tr>
<td>Asparagus racemosus (Satavari)</td>
<td>Potential interaction with drugs interacting with cholinesterase and monoamine oxidase enzymes</td>
<td>Nonselective competitive inhibitor for cholinesterase and monoamine oxidase enzymes</td>
<td>Widely used in Ayurvedic medicine as galactagogue, aphrodisiac, diuretic, antispasmodic, nerve tonic</td>
<td>[197,198]</td>
</tr>
<tr>
<td>Commiphora mukul (Guggul)</td>
<td>Enhanced the efficacy of erlotinib, cetuximab and cisplatin (<em>in vivo &amp; in vitro</em>)</td>
<td>Induced decreased expression of both phosphotyrosine and total signal transducer and activator of transcription (STAT)-3</td>
<td>Used in Ayurvedic medicine to promote heart and vascular health and treat obesity &amp; rheumatism among others</td>
<td>[199,200]</td>
</tr>
<tr>
<td>Agricus brazei Murill (Ji Song Rong; Kawariharatake)</td>
<td>Diltiazem and other CYP 3A4 substrates</td>
<td>Inhibits CYP 3A4</td>
<td>Used in TCM and Japan</td>
<td>[174]</td>
</tr>
</tbody>
</table>
between risk-benefit balances between the regions. Differences in patient—physician relationships between Western and Asian culture have also been highlighted, in which the Japanese/Asian culture has been viewed as being more hierarchical and paternalistic [84]. The doctor is held in great respect to the point that patients sometimes do not report adverse effects so as to not be offensive to the doctor [85]. However, it should also be noted that recent findings in Japan shows that the Japanese patients now prefer the mutual “Western”-style relationship, which may also be considered ideal also in other Asian cultures [84].

**Conclusion**

Genetic variations causing differences in drug response are well established, accounting for some of the ethnic differences in drug response. Moreover, genomics on its own is yet unable to account for all population differences in drug response, and in many cases, despite its ambiguous definition, ethnicity—with related differences in extrinsic factors—is an important consideration for many of the differences.

**ACCEPTABILITY OF FOREIGN CLINICAL DATA**

According to the ICH E5 [1], it is possible to use foreign clinical data in drug registration, subject to the completeness of the data package, which should include:

- Adequate characterization of pharmacokinetics, pharmacodynamics, dose response, efficacy, and safety in the population of the foreign region(s).
- Clinical data of efficacy, dosing and safety from trials conducted according to regulatory standards (GCP standards), well controlled with appropriate endpoints as well as appropriate medical and diagnostic definitions acceptable to the new region.
- The foreign population in whom the clinical trials were conducted should be representative of the populations in the new region.

Once the clinical data package fulfills the local regulatory requirements, extrapolation of foreign clinical data to the local population should be considered. If a drug is deemed ethnically sensitive, some amount of pharmacokinetic data from local subjects would be required, in order to “bridge” the two sets of data from different regions or ethnic populations.

**Figure 10.2**, taken from the ICH E5 Appendix B, demonstrates an overview of the assessment of the clinical data package (CDP).

As can be seen from the figure, fulfillment of local regulatory requirements is mandatory; failing this fulfillment, additional clinical trials may be requested for this purpose, as well as a bridging study, should the drug be deemed ethnic sensitive. The outcome of the CDP assessment could then be:

- No bridging studies required
- If drug is not ethnically sensitive
- If drug is ethnically sensitive, but the population is ethnically similar to ensure that the drug will behave similarly in the two populations
Bridging studies required

- If drugs is ethnically different but with similar extrinsic factors
  - Usually requires a pharmacodynamic study (e.g., dose response) using acceptable endpoint to ensure safety, efficacy, dose, and dosage regimen are applicable to new region
- Pharmacokinetic measurements for data support
- Controlled clinical trials (CCT) required
- Dosage is uncertain
- Limited CCT in the new region
- Difference in medical practice
- Drug is not familiar in the new region

Safety bridging studies

- If there are safety concerns despite adequate foreign data addressing safety and efficacy issues, for example concerns regarding possibility of higher occurrence rate of adverse events in the new region; can be done together with efficacy studies, with adequate power
- Separate safety study may be needed if there are no efficacy bridging studies or if efficacy studies is not powered for this purpose

If pharmacodynamic data from bridging studies indicate that there is a difference in drug response between the two regions, a CCT will be required. If there is a difference in drug response between the two regions, a CCT will be required.

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**FIGURE 10.2** Assessment of the clinical data package for acceptability of foreign clinical data [1].
in pharmacokinetics, a dose adjustment may be all that is needed, without the need for a CCT.

**Ethnic Sensitive or Insensitive?**

The ICH E5 guideline indicates that a bridging study is necessary for drugs that may be ethnically sensitive. Table 10.7 lists some of the factors that may be used to evaluate whether a drug would have a high likelihood of being ethnic sensitive.

Due to the complex interaction among the drugs’ pharmacological class, indication, and demography of the population [86], the ICH E5 guideline does not provide a definitive criterion for evaluation of a drug’s ethnic sensitivity in terms of the evaluating the complete clinical data package or assessment of similarity of clinical results between regions [87]. Various statistical models and strategies have been proposed to assess sensitivities and similarities in ethnicities [87,88,89]; however, no gold standard has yet been established. Specific methodology for extrapolating foreign clinical data is not provided, either. This issue has resulted in marked heterogeneity in the conduct of bridging studies in many regions, notably

<table>
<thead>
<tr>
<th>TABLE 10.7</th>
<th>Factors Affecting a Drug’s Sensitivity to Ethnic Factors [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors</strong></td>
<td><strong>Ethnically sensitive</strong></td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Nonlinear</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>Steep curve for efficacy and safety in the range of recommended dosage</td>
</tr>
<tr>
<td>Therapeutic dose range</td>
<td>Narrow</td>
</tr>
<tr>
<td>Metabolism</td>
<td>High, especially through a single pathway. Enzymes known to show genetic polymorphism Administered as a prodrug; possible ethnically variable enzymatic conversion</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Low; susceptible to dietary absorption effects. High inter-subject variation in bioavailability</td>
</tr>
<tr>
<td>Potential for protein binding</td>
<td>High</td>
</tr>
<tr>
<td>Potential for interactions</td>
<td>High; use in multiple co-medications</td>
</tr>
<tr>
<td>Potential for inappropriatate use</td>
<td>Low</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Systemic</td>
</tr>
</tbody>
</table>
heterogeneity in the criteria for bridging evaluation, trial procedure, and statistical methods adopted.

**Acceptability of Foreign Clinical Data and Drug Regulatory Procedures in East and Southeast Asia**

Concerns about foreign clinical data from the drug regulatory agencies’ perspective vary by region. The ICH guidelines were initially intended to harmonize regulations governing drug registration in the ICH regions, but not all regions have adopted the guidelines. Some non-ICH countries such as Taiwan and Korea have fully adopted and integrated the bridging concept; others have not. Southeast Asian counties have not adopted the ICH E5 guidelines, although some technical aspects of evaluating the ability for foreign data to be extrapolated to their regions as outlined in the guidelines have been incorporated. The East Asian and Southeast Asian perspectives on and experiences with acceptance of foreign clinical data is reviewed in the following section.

**East Asia**

**JAPAN**

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA), under the Ministry of Health, Labour, and Welfare, is the regulatory authority responsible for the scientific review of marketing authorization application of pharmaceutical and medical devices [90]. Japan has a huge pharmaceutical market, second only to the United States, and third if the European Union (EU) is included. Various reports have been put forth to highlight the significant drug lag, which refers to a delay in the time it takes for a drug to be approved in Japan, as compared to the United States and the European Union. A survey of the 100 top-selling drugs in 2004 reported a drug lag difference of 2.5 years between the United States and Japan. Another report stated that Japan took an average of 3.9 years, compared to 1.1 years in the United States and the European Union, for drugs approved between 1999 and 2005 [91]. Japan has developed many strategies to improve the drug lag; one is based on the use of bridging studies. Figure 10.3 demonstrates Japan’s adoption of bridging strategies in the hope to expedite the drug approval process.

In Japan, foreign phase I results may be used to estimate the Japanese Phase I studies to enable an abbreviated study beginning with a dose lower than the maximum tolerated
dose (MTD) in the foreign region but higher than the starting dose. Foreign Phase II data using the new drug as a single agent may replace the requirement for one of the two late Phase II studies. At least one of the Phase II studies must be conducted in Japan, in addition to Phase I studies, although studies conducted elsewhere may be considered [92]. In this case, the foreign Phase II study must be of adequate size with dose, route, and schedule used in the study similar to those used in the Japanese studies. Otherwise, it will be necessary to prove that the difference will not give rise to a different clinical effect, based on a pharmacokinetic/pharmacodynamic studies conducted in Japanese subjects (local or abroad). Phase III studies conducted abroad may also be submitted to support a reexamination application, with the provision that one of the studies must be conducted in Japan [92].

Hirai et al. [91] performed a detailed study to analyze factors contributing to the drug lag and found that one of the major contributors to this was the significant delay in initiating clinical trials in Japan; that is, drugs developed in the United States and the European Union had longer lags in Japan. In about 60% of approved drugs in the United States and the European Union, a clinical development phase had not even been developed in Japan [91,93]. Apart from this, Japan’s review of their bridging experience highlighted several facts that support their meticulous procedure of acceptability of foreign data, including their bridging approach. This process includes several examples of final drug dose approved in Japan that is different than doses approved in the United States, occurrence of higher adverse events in the Japanese population, as exemplified by induced interstitial lung disease with use of certain chemotherapeutic agents, as well as differences in pharmacokinetic profile for tolterodine between Japanese and Koreans. Thus, the PMDA’s issuance of the Notification of Basic Principles on global clinical trials (GCTs) [94], which strongly recommends that clinical studies be done prior to or in parallel with global studies [96], was an effort to abolish the drug lag without compromising Japanese data. Japan initiatives also resulted in a revision of the ICH E5 guideline at the sixth ICH Conference, with a set of 10 questions and answers to facilitate the implementation of the E5 guideline. The set of questions and answers outlines concepts for planning and implementing GCTs or multiregional clinical trials (MRCTs).

Subsequent to the publication of the guidance, there has been a marked increase in the number of GCTs that includes Japan, with total numbers of GCTs conducted in 2007 (17) more than doubling as compared to those conducted in 2008 and 2009 (both 48) [96]. Data from GCTs conducted did highlight the fact that although there were differences in pharmacokinetics, efficacy, and safety, there were also undoubtedly similarities in the data obtained across several populations. Losartan Phase III trials showed superior effect when compared to placebo in overall population (Europe, Latin America, New Zealand, and North America-by region) including Japan, while almost no effect was seen in the U.S. population [96,97]. Global PK studies of tolterodine tartrate also showed some interesting values in the average ratio of the AUC between Japanese and Koreans, as well as the ratio between Japanese and Caucasians, which were 0.72 (95% CI: 0.62, 0.83) and 0.90 (95% CI: 0.78, 1.03), respectively. These results showed that the Japanese pharmacokinetic values were similar to those of the Caucasians and different from those of the Koreans [96]. This finding exemplifies the complexity involved in understanding the interethnic issues and in attempting to equate drug responses based on superficial ideas of ethnic differences or similarities.
The Korea Food and Drug Administration (KFDA) is responsible for monitoring safety, assessing clinical data, and granting approvals for pharmaceuticals. Korea adopted the ICH bridging concept of extrapolating foreign clinical data in 2001. The KFDA defines bridging studies as “a trial conducted in Koreans in Korea, for the purpose of obtaining bridging data, in case it is difficult to directly apply the foreign clinical data due to differences in ethnic factors related to safety and efficacy of a drug.” Bridging data, on the other hand, refers to “data of trials conducted on Koreans living in Korea or abroad, which are excerpted or selected from the clinical data package or obtained from the bridging study.” Bridging data may have already been included as part of the original drug approval application package of the drug, and can be used to extrapolate the foreign data. Otherwise, a bridging study must be carried out unless the drug falls into one of the seven waiver categories [98]:

1. Orphan drugs (or used to be orphan drugs)
2. Drugs for life-threatening disease or AIDS
3. Anticancer therapy for the following
   - No standard therapy
   - Therapy after failure of a standard therapy
4. New drugs for which clinical trials were conducted on Koreans
5. Diagnostic or radioactive drugs
6. Topical drugs with no systemic effect
7. Drugs that have no ethnic differences

Basically, bridging studies must be carried out when there is absence of or inadequate bridging data or if bridging data shows ethnic differences between Koreans and non-Koreans. Figure 10.4 summarizes Korea’s bridging concept.

**FIGURE 10.4** Overview of bridging concept in Korea [99].
In Taiwan, the Center for Drug Evaluation (CDE) under the commission of the Department of Health (DOH) evaluates and reviews all new drug applications (NDAs). It was one of the first non-ICH regions to embrace the ICH E5 guideline. The bridging strategy was implemented in stages, beginning with inclusion of local (Taiwanese) clinical trials in 1993 in the “double-seven announcement” [98]. Subsequently, the “double-twelve announcement” on December 12, 2000, recommended that sponsors first apply for a Bridging Study Evaluation (BSE) to assess the necessity of carrying out a bridging study in Taiwan, which was fully implemented in 2004.

The nine waiver categories requiring no verification of ethnic sensitivity are [98]:

1. Drugs for the treatment of AIDS
2. Drugs for organ transplantation
3. Topical agents
4. Nutritional supplements
5. Cathartics used prior to surgery
6. Radio-labeled diagnostic pharmaceuticals
7. The only available treatment for a serious disease
8. Drugs with demonstrated breakthrough efficacy for a life-threatening disease
9. Drugs for the treatment of rare diseases for which it is difficult to enroll enough subjects for a trial

Should the application not fall into the waiver category, in principle, Taiwan will accept all Asian data for consideration of NDA approval, including PK/PD study data that enable a reasonable estimation of efficacy and safety of the drug. Unless the data indicated that there are ethnic sensitivities that make extrapolation of data impossible, a bridging study would then be requested.

It is well known that China’s current and future pharmaceutical market is substantial. China’s 1.3 million people make up about 20% of the global population. It has grown to be the third largest pharmaceutical market and is still growing rapidly. The State Food and Drug Administration (SFDA) is in charge of drug registration and evaluation, and the Center for Drug Evaluation (CDE) is responsible for the evaluation of chemical drugs, traditional Chinese medicines and biologic products [100]. Article 11 in the Drug Registration Regulation [101] defines five types of drug registration application: (1) new drug application, (2) generic drug application, (3) imported drug application, (4) supplemental application, and (5) renewal application. A foreign applicant shall make application according to imported rule. For import drugs with a Certificate of Pharmaceutical Product (CPP) issued by the exporting country with a patent certificate and established GMP status [102], foreign clinical data would then be assessed for completeness, in line with GMP requirements as well as the Chinese regulatory requirements and ethnic sensitivity assessment. Subsequently, a pharmacokinetic study and a clinical trial of 100 Chinese subjects (per arm) will be required [85,102]. Alternatively, the foreign applicant could submit a clinical trials application, in accordance with Article 44 of the Drug Registration Regulation [101], which states that the drug should already be registered in a foreign country or in Phase II development (however, this does not
apply to applications for new vaccines, which are not registered in any country). Furthermore, the SFDA may also request that the applicant first conduct a local Phase I trial. There is no explicit definition of “Chinese” given in biological or geographical terms, other than it must be local.

CHINA-KOREA-JAPAN TRIPARTITE

The China-Korea-Japan Tripartite cooperation was formed in 2007, following the ICH E5 revision as well as Japan’s Notification of Basic Principles on Global Clinical Trials. The tripartite’s cooperation involved research into ethnic differences in pharmacokinetics/pharmacodynamics and genetic polymorphisms affecting them, information sharing to promote regulatory framework understanding, and creating a regional clinical guidelines protocol [103]. The pioneer activity of this group was a comparative pharmacokinetic study between China, Korea, Japan, and Caucasians for three drugs—moxifloxacin, simvastatin, and meloxicam—under the Kawai Project. The study demonstrated similar pharmacokinetics between all comparator populations (moxifloxacin), similar pharmacokinetics between some comparator populations (simvastatin between Japanese and Caucasians; meloxicam between Japanese and Chinese) and also differences among comparator populations [104]. This cooperation is at an early stage of development, which may be seen as an initial move towards genomics-based bridging as opposed to ethnic-based bridging.

Southeast Asia

SINGAPORE

Singapore is regarded as the country with the most well-developed drug regulations in the Association of Southeast Asian Nations (ASEAN) region [105], as well as the country with the best capacity for new drug development [106]. Nevertheless, it accepts foreign clinical data with no ICH E5 requirements, just as all the other countries in Southeast Asia.

In Singapore, the Health Sciences Authority (HSA) administers the provisions under the Medicines Act, which requires all western medicinal products to be registered by HSA before they can be marketed in Singapore. HSA has adopted an evidence- and risk-based approach in the evaluation processes for registration of western medicinal products. Although HSA performs independent review of all applications, HSA also leverages on the assessment by other regulatory agencies.

ASEAN COUNTRIES

The ASEAN has 10 member countries: Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar, and Cambodia. The population size is about 598.5 million, with a combined gross domestic product of US$1,850,855 million and a total trade of US$2,042,788 million [107]. The pharmaceutical market in southeast Asia is relatively small, but the region remains attractive to the pharmaceutical industry due to its growth potential. Among the ten ASEAN members, the five founding member countries (Singapore, Malaysia, Thailand, Philippines, and Indonesia) are more progressive with drug registration and drug development clinical trial activities. All ASEAN member countries are net pharmaceutical importers except for Singapore.

The ASEAN’s Pharmaceutical Product Working Group (PPWG) was set up in 1999 to “harmonize pharmaceutical regulations of the ASEAN member countries to complement
and facilitate the objective of ASEAN Free Trade Area (AFTA), particularly the elimination of technical barriers to trade posed by these regulations, without compromising on drug quality, safety, and efficacy. The topics selected for harmonization by the PPWG was safety, quality, efficacy, and administration data, which reflects the basis for drug registration approval. PPWG was instrumental in preparing key drug regulatory harmonization documents:

- The ASEAN Common Technical Requirements (ACTR) for pharmaceutical product registration
- The ASEAN Common Technical Documents (ACTD) for pharmaceutical drug registration
- ASEAN guidelines on analytical validation, bioavailability and bioequivalence studies, process validation, and stability study

Each set of guidelines gives cross-references to relevant ICH guidelines or pharmacopeia. It should be noted that although many of the ICH guidelines were adopted by PPWG, it was decided that the ICH E5 was not going to be adopted due to lack of experience and resources and to first make a scientific justification on the need for local clinical trials and to subsequently verify the actual efficacy of drugs in local situations. Instead, the ASEAN countries were strongly encouraged to participate in the Global Drug Development Programs. In general, ASEAN capacity for evaluating and assessing drug quality, safety, and efficacy are limited. For this reason, they require CPPs issued by the reference country as a surrogate assurance of the product reliability. Furthermore, most of the drug applications reviewed by ASEAN drug regulatory authorities are generic drugs, thus much more emphasis is given to evaluations relating to quality issues such as bioavailability/bioequivalence and stability studies. It should also be noted that Brunei Darussalam is the only ASEAN country that does not require regulatory approval for drugs to be marketed in the country.

The recent trend in the shift of clinical trials to Asian emerging regions, especially in Korea, Taiwan, China, Thailand, Singapore, the Philippines, and Malaysia, is an opportunity to provide a platform in addressing the issues of ethnic differences more objectively.

**Global Drug Development and Pharmacogenomics**

Currently, efforts are concentrated on developing biomarkers and pharmacogenomics information from clinical trial inception. Japan has proposed the multiregional clinical trials (MRCT) model, which incorporates special consultation on pharmacogenomics/biomarker qualification to facilitate utilization of this information for regulatory decision. This development was pioneered by the efforts from the FDA and the EMEA by first encouraging voluntary submission of genetic data (VGDS) (the scope was then expanded to include non-genomic biomarkers; hence, VGDS was renamed “voluntary exploratory data submission,” or VXDS, for inclusion of more diverse biomarkers) by pharmaceutical industries to allow for nonthreatening discussion between the industry and regulatory authorities. For this purpose, the FDA and the EMEA issued the Guidance for Industry: Pharmacogenomic Data Submissions in 2005. This platform has encouraged novel pharmacogenomics and biomarker integration in drug development. Subsequently, a harmonized submissions guideline was drafted by the ICH E16 working group for genomic biomarker qualifications in 2010.
A pharmacogenomics-based (biomarker) success through the conduct of MRCTs is perhaps best exemplified by trastuzumab. Trastuzumab is a monoclonal antibody targeting the extracellular domain of the HER2 protein, an epidermal growth factor receptor gene [113], which was found to be amplified 25 to 30 times in patients with an aggressive form of breast cancer, along with an increase in the expression of its protein in the malignant cells [114]. This biomarker identification, coupled with reliable laboratory testing using fluorescence in situ hybridization (FISH) assay, have enabled a more successful treatment of this subgroup of women with breast cancer, with improved disease-free survival as well as overall survival [115,116]. The design of the trial, which preselected women who were HER2-positive, has saved much time and patient numbers to provide the statistically significant benefit of trastuzumab [117,118]. Table 10.8 lists examples of drugs that have been approved in Japan based on the use of biomarkers in MRCTs.

All of these developments to exciting prospects for better risk-benefit judgment for regulatory authorities, as well as for making drug therapeutic effects more predictable, effective, and safe for the patients.

Pharmacogenomics and Ethnicity in Global Drug Development

The use of pharmacogenomics in global drug development may very well be the turning point for the realization of actual translational medicine. The adoption of the use of pharmacogenomics as a tool to evaluate differences in population groups has added tremendously to its initial value of merely looking at interindividual differences. Invariably, characterization of each and every causative factor and quantitative relationship of their combinations of variability in pharmacologic treatment outcome [120] would be needed to truly personalize medical treatment. Pharmacogenomics and biomarkers are undoubtedly significant parts of this understanding. Nevertheless, it cannot be ignored that there are other factors that constitute an integral part of drug response at a population level that cannot be defined merely by looking at genetics and biomarkers.

In the context of using MRCTs as a bridging study, one of the key points to address is a sample size calculation to enable extrapolation of the overall trial results to the particular population. Table 10.8 lists examples of drugs that have been approved in Japan based on the use of biomarkers in MRCTs.

**TABLE 10.8 Drugs Approved Based on the Use of Pharmacogenomics (Biomarkers) in Multiregional Clinical Trials in Japan [119]**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Indication</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Adjuvant therapy for Her2-positive breast cancer</td>
<td>Her2/neu</td>
</tr>
<tr>
<td>Panatimumab</td>
<td>Metastatic colorectal carcinoma with wild-type KRAS tumors</td>
<td>KRAS</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Newly diagnosed chronic myeloid leukemia in chronic phase</td>
<td>Ph chromosome</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Her2-positive metastatic gastric cancer</td>
<td></td>
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</table>
region. The ICH E5 (Q&A) 11 [1] emphasizes this point, and the Japanese MHLW have also provided a guideline on how to demonstrate drug efficacy in a particular region [121]. Two methods were proposed in this guideline for determination of sample size [121]:

- **Method 1**: $D = \text{difference between placebo and study group; } D_{\text{all}} = \text{difference in the overall study population across regions; } D_{\text{Japan}} = \text{difference within the Japanese subpopulation. The sample size is determined so that } D_{\text{Japan}}/D_{\text{all}} > 0.5 \text{ will achieve a probability of 80% or more.**}

- **Method 2**: $D_{\text{all}} = \text{difference between placebo and entire study groups across regions, assuming inclusion of three regions } D_1, D_2, \text{ and } D_3 = \text{difference between placebo and study groups in regions 1, 2, and 3. The sample size is determined so that } D \text{ for each region will show similar tendency. In the case in which } D > 0, \text{ the number of subjects is determined so that } D_1, D_2, \text{ and } D_3 \text{ will exceed 0 with a probability of 80% or higher.**}

It has been argued that genetic clustering (which is being used in genetic ancestry) defines a population in a more robust manner than do ethnicity and geographical approaches [120]. However, Risch et al. [122] pointed out a very important point of how data analyses evaluating genetic clusters in isolation and ignoring race and ethnicity may lead to conclusions that are seriously confounded. As an example, they illustrated how, in a study comparing the efficacy of ACE inhibitors between African American patients and Caucasian patients, there was a significantly better outcome to treatment in white patients. Had the study used a genetic clustering method, the direct inference made from this study would be that this difference was due to the difference in the genetic clusters between the two groups. Although it has been shown in other studies that genetic clustering is highly correlated with self-identified ethnicity/race [123], a direct inference as shown in this example could lead to a grossly confounded conclusion simply because the difference in treatment may very well be other extrinsic factors that are related more to the ethnicity, rather than to the actual genetics. Thus, it should be highlighted that one should not be blinded to ethnicity information while carrying out studies with genetic or even nongenetic biomarkers in order to have a more complete understanding of the given scenario.

The approval of isosorbide dinitrate and hydralazine combination for the treatment of heart failure in African Americans by FDA in 2005 illustrates that race and ethnicity are indeed very much relevant. The initial application for the marketing of the isosorbide dinitrate/hydralazine combination for all patients was rejected as the original trial, Vasodilator Heart Failure Trial I and II (V-HeFT) failed to demonstrate required statistical significance [124]. Subsequently, when the data was reanalyzed, it was found that the drug may be selectively effective in the black population. Subsequently, the FDA recommended a new trial, named the A-HeFT trial (African American Heart Failure Trial), which demonstrated a 43% reduction in the rate of death from any cause, 33% relative reduction in the rate of first hospitalization for heart failure, and an improvement in the quality of life [125]. This study demonstrates how the inclusion of different specific subpopulation identification and definition can result in a different outcome.

The potential for deriving less expensive, more effective, and safer drugs using pharmacogenomic stratification certainly has a special appeal for developing countries that are in desperate need of more cost-effective health care strategies. Thus, close cooperation between nations for amassing and sharing genotyping data can be significantly beneficial. The HUGO
Pan-Asian SNP consortium is an example of such a cooperative effort [126] to provide a platform for disease population studies or pharmacogenomics research for investigators and can be leveraged on by regulators alike.

**CONCLUSION**

Although ethnicity is very challenging to define, it is of utmost importance that ethnicity be defined in a standardized manner so that accurate scientific conclusions can be derived from any analysis that uses ethnicity/race as a variable. It remains a useful tool for regulatory authorities, practitioners, and researchers for providing a certain degree of insight to the risk-benefit consideration to outcome of pharmacological treatment. Bridging strategies have been useful in addressing some of the concerns about variability in drug response, as well as expediting drug approval in some countries. The advent of bridging strategies using MRCTs has made it possible to address the issue of variability in drug response in a more global manner. However, to be able to answer specific ethnic-related questions, population selection must be clearly defined with protocols specifically catered to the target population. The incorporation of pharmacogenomics and biomarkers in drug development may allow the stratification of patient populations in a more objective manner and further characterize some of the variability observed in different ethnic populations.

**DISCUSSION QUESTIONS**

1. Discuss the challenges of incorporating different ethnic groups in pharmacogenetic and pharmacogenomic research.
2. Describe how foreign clinical trial data are utilized for drug approval in other parts of the world.
3. Describe culturally related extrinsic factors that might influence the design of pharmacogenomic studies and the interpretation of study data.

**References**


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<thead>
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<th>Reference</th>
<th>Title</th>
<th>Publication Details</th>
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DISCUSSION QUESTIONS


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10. THE IMPORTANCE OF ETHNICITY DEFINITIONS AND PHARMACOCENOMICS IN ETHNOBRIDGING


DISCUSSION QUESTIONS


Abstract:
Concerns about ethnicity-related differences have resulted in a significant “drug lag” in regulatory approvals. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) document on Ethnic Factors in the Acceptability of Foreign Clinical Data, ICH E5, provides guidelines for assessing ethnicity as a cause of differences in drug treatment, and the use of bridging strategies to avoid unnecessary duplication of clinical trials without compromising the quality, safety and efficacy of the drug, with the goal of expediting the drug approval process. These guidelines have however not been fully adopted by all countries, and there are differences in the way the bridging concept is applied. An approach, which may provide the resolution to this dilemma, is the multi-regional parallel bridging method, or simultaneous drug development. However, the definition of ethnicity is currently too vague and imprecise for clinical trial data to be easily understood and extrapolated across borders. The integration of pharmacogenomics and biomarkers in drug development may provide greater clarity to the characterization of drug response variability between populations.

Key words:
ethnicity, pharmacogenomics, ethnobridging, variability in drug response, global drug development