International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR |Volume 6 | Issue 1 | Jan - Mar - 2018
www.ijamscr.com

Review article *Medical research*

A review of consideration of ethnic factors during drug approval process

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ABSTRACT

Purpose

To determine feasibility of drug registration for the selected drugs at USFDA based on the ICH E5 guideline.

Methods

Methodology involves two steps, they are 1. Determination of ethnic sensitivity of the selected drugs based on factors such as pharmacokinetics (PK), pharmacodynamic (PD), therapeutic range, and metabolism etc., given in appendix D of ICH E5 guidelines. 2. Determination of the need for the bridging studies after determining ethnic sensitivity of the selected drugs based on the ICH E5 guidelines.

Results

After the extensive analysis of the selected drugs, ethnic factors found to have profound effect across all classes of drugs like Analgesics and Anti-Inflammatory Agents, Central Nervous System Agents, Antihypertensive Drugs, Anticoagulants, Metabolism and Endocrine Agents, Immunomodulators, Anticancer Agents, Gastrointestinal Agents, Antiparasitic Agents and Genitourinary Agents.

Conclusion

Some drugs may be ethnically insensitive and some other drugs may be ethnically sensitive among the selected drugs based on the ICH E5 guideline.

Drugs which are ethnically insensitive may be approved by USFDA (United States Food and Drug Administration) without need of bridging studies where as drugs which are ethnically sensitive and they need bridging studies before they can be approved.

INTRODUCTION

There is need for study of ethnic factors when a drug has to get approval in the foreign locations where the clinical trials of drug have not been conducted to avoid duplication of the clinical studies, which are already done with lot of expenses because, for the development of a single drug it take years and 802 million dollars [1]. In this context, The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued ICH E5 guidance in February 1998 regarding the ethnic factors in the acceptability of foreign clinical data. The ICH E5 guideline provide a general frame work for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data, with the underlying objective of minimizing duplication of clinical data and it also describes the requirement of bridging study for extrapolation of foreign clinical data to a new region.

NEED FOR THE STUDY

All countries acknowledge the desirability of utilizing foreign clinical data that meet the regulatory standards and clinical trial practices acceptable to the region considering the application for registration.However, concern that ethnic differences may affect the medication's safety, efficacy, dosage and dose regimen in the new region has limited the willingness to rely on foreign clinical data. Historically, this has been one of the reasons, therefore, the regulatory authority in the new region has often requested that all, or much of, the foreign clinical data in support of registration be duplicated in the new region. Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions. Requirements for extensive duplication of clinical evaluation for every compound can delay the availability of new therapies and unnecessarily waste drug development resources.

The purpose of ICH E5 guidance is to facilitate the registration of medicines among ICH regions by recommending a framework for evaluating the impact of ethnic factors upon a medicine's effect, i.e., its efficacy and safety at a particular dosage and dose regimen. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies, cost, time and supplying medicines expeditiously to needy patients for their benefit [2].

To realise full potential of ICH E5 guideline goals, there is need to identify and register more drugs which are approved for their efficacy and safety in one country and prescribed in the millions of the patients for the decades and not approved in the another country based on the ICH E5 guideline by appropriate institutions like World Health Organisation (WHO), Non-Governmental Organisations (NGOs'), pharma companies etc., to realize the goals of ICH E5 guideline.

Overview of the drug development process

The discovery and development of safe and effective new medicines is a long and complex process. Pharmaceutical companies typically spend 9-15 years of research and hundreds of millions of dollars into this effort; a low rate of success has historically been achieved. A progression of research activities and regulatory filings must operate in parallel, often under severe time constraints. The success of a drug development program depends upon a number of favorable selections, such as targeting a therapeutic area in which an identified drug compound offers outstanding efficacy, identifying the optimal chemical structure of the drug molecule that yields the most favorable absorption, distribution, metabolism and elimination profiles, demonstrating safety, satisfying regulatory needs, as well as cost effective manufacturing and extensive sales support in the marketplace [4].

ETHNIC DIFFERENCES IN EXPOSURE AND RESPONSE TO DRUGS

All drugs exhibit significant intersubject variability in pharmacokinetics and pharmacologic response. Such differences vary considerably among individual drugs and depend on a variety of factors, which are often separated into extrinsic and intrinsic factors. Typical extrinsic factors include food and dietary factors that may affect systemic availability, concomitant drugs that may cause drug interactions, and tobacco and alcohol use. Typical

intrinsic factors, on the other hand, include the individual's body weight, age and gender, the presence of diseases affecting elimination (e.g., renal and hepatic insufficiencies), absorption (e.g., certain gastrointestinal disorders) and distribution (e.g., certain cardiovascular disorders), and genetic factors determining drug metabolism and pharmacologic response.

One potentially important determinant of drug responsiveness is ethnicity. The influence of ethnic factors on drug disposition and pharmacologic response has been extensively reviewed in the literature. Considering underlying molecular mechanisms of ethnic differences, it is often unclear how to interpret differences in functionally significant polymorphisms of individual cytochrome P450 (CYP) isozymes with respect to drug development and registration of individual drugs since most of these exist in all ethnic groups, albeit with different frequencies, and most drugs are eliminated by more than one metabolic pathway. In addition to intrinsic factors as potential sources of ethnic differences in drug disposition and pharmacologic response, extrinsic factors (e.g., diet, environmental and cultural factors) have also been identified as potential sources of ethnic differences in drug responsiveness.

The International Conference on Harmonization (ICH) is charged with developing approaches to harmonize global drug development and thus facilitate the availability of new medicines to patients. A key consideration for global drug development and registration therefore involves the acceptability of foreign clinical data in the different regions. To address this issue, the ICH developed guidelines on ethnic factors in the acceptability of foreign clinical data, which was approved in 1998 by the three parties of the ICH: the European Union (E.U.), Japan, and the U.S. Food and Drug Administration (E5 ICH Guidance, 1998).

The sources and classes of drug where the variation in drug responses are reported are presented as below.

ANALGESICS AND ANTI-INFLAMMATORY AGENTS

Glucocorticoids

Methylprednisolone are synthetic glucocorticoid used as anti-inflammatory or immunosuppressive agents. A study on methylprednisolone in Black and White renal transplant patients found an almost 50% lower clearance in the Black population and suggested that these interracial differences should be considered in methylprednisolone therapy. In a later study, the same investigators reported race-dependent clinically significant adverse effects in that 5 of 9 Black patients had steroid-associated diabetes while only 1 of 8 White patients manifested this adverse effect. The Black patients with diabetes also had higher cortisol Area Under the blood Concentration-time curve (AUC) with lower methylprednisolone clearance than the White patients.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen is an oral NSAID with analgesic and antipyretic properties as well as anti-inflammatory and antiplatelet properties. Their pharmacokinetics in Blacks and Whites has been investigated in the presence and absence of the histamine H_2 receptor antagonist ranitidine. Ibuprofen steady-state peak concentration in the presence of ranitidine increased by 54% in Blacks, while it decreased by 15% in Whites. It was suggested that Black patients should be monitored for an increase in adverse effects of NSAIDs in the presence of histamine H_2 receptor antagonists, while use of H_2 receptor antagonists in White patients may reduce the effects of NSAIDs.

Opioid Agonists

A study comparing the pharmacologic effects of morphine in Caucasians and Chinese reported that Caucasian was more sensitive to the cardiovascular and respiratory effects of morphine than Chinese, although the former were less sensitive to its gastrointestinal side effects. In a later publication, the same investigators reported that the apparent clearance of morphine was significantly higher in Chinese than in Caucasians, possibly providing an explanation for the previous findings. However, another study found no difference in the respiratory response to carbon dioxide between the same ethnic groups.

CENTRAL NERVOUS SYSTEM AGENTS

Tricyclic Antidepressants

Tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline) have a narrow therapeutic index and are metabolized by *CYP2D6*. Poor metabolizers and ultra extensive metabolizers may have clinical problems when these drugs are taken at usually prescribed doses. Poor metabolizers often develop elevated blood concentrations that may result in adverse effects. These side effects are rarely life threatening, but they are sufficiently unpleasant that problems with patient compliance ensue. Ultra-extensive metabolizers, on the other hand, may not respond to recommended doses because drug concentrations are too low to be efficacious.

Benzodiazepines

The benzodiazepine diazepam is an important drug affected by *CYP2C19* polymorphisms. However, there have been relatively few studies of ethnic differences in response to diazepam or other benzodiazepines. Asian psychiatric patients often require lower doses of diazepam, but this may be because of differences in body fat rather than to genetic differences in drug metabolism. The clearance of alprazolam, which is metabolized by the *CYP3A4* system, is significantly higher in Whites than in Asians.

Table 2: Racial and Ethnic Differences in Response to Central Nervous System Agents

Drug	Comparison groups	Exposure*	Clinical response
Clomipramine	Asians, (Indian, Pakistani) Vs. Whites (English)	Greater in Asians (AUC)	Higher incidence and severity of side effects in Asians
Nortriptyline	Japanese Vs. American	Greater in Japanese (AUC)	N/A
Benzodiazepines			
Alprazolam	Asians Vs. Caucasians	Lower for Asians (CLs)	N/A
Clozapine	Korean Americans Vs. Caucasians	N/A	Clinically adjusted dose lower in Koreans, and higher rate of anticholinergic side effects
	Orientals (Chinese, Japanese, Filipino, Korean, Vietnamese) Vs. Caucasians.	No difference	Neuroleptic dose and optimal response threshold lower for Orientals.
Haloperidol	Chinese Vs. Non-Chinese (Caucasians, Hispanics, Blacks).	Higher mean blood levels in Chinese than in Americans (When given same dose).	Clinically adjusted dose lower for Chinese than for non-Chinese.
	Caucasians Vs. American-born Asians Vs. foreign-born Asians (Chinese, Filipino, Japanese, Koreans)	Higher for Asians than for Caucasians (C_{max}). Similar for American-born and foreign-born Asians.	No difference in side effects

Statistically significant differences in exposure, i.e., a measure of the blood concentration: either the area under the blood concentration-time curve (AUC), the peak blood concentration (C_{max}), or systemic clearance (CLs).N/A, not available.

ANTIHYPERTENSIVE DRUGS

Hypertension is disproportionately prevalent in the Black population and is associated with higher incidences of cerebrovascular and renal complications and left ventricular hypertrophy. However, the overall risk of coronary artery disease in the Black male population is lower than in White males, particularly in Europe and the Caribbean, and to a lesser extent in the United States. There

are general differences in the pathophysiology of hypertension between the Black and White populations. Black hypertensives exhibit enhanced sodium retention, a higher incidence of salt-sensitive hypertension, expanded blood volume, more frequent proteinuria, and a higher prevalence of low blood renin activity (although the majority of renin may reside in vascular tissue).

Table 3: Racial and Ethnic Differences in Response to Cardiovascular Drugs[6]

Drug	Comparison groups	Drug exposure*	Clinical response
ACE inhibitors	Blacks Vs.	N/A	Hypertension and
Enalapril	Whites		hospitalization for heart failure reduced in Whites but not in Blacks with left ventricular dysfunction
Captopril	Blacks Vs. Whites	N/A	Antihypertensive effect greater in Whites
Beta-blockers	Black Vs. White men	N/A	Vasodilation response to isoproterenol markedly lower in Blacks
Isoproterenol	Chinese Vs. Caucasians	Lower in Chinese	Chinese twice as sensitive to effects on blood pressure and heart rate
Propranolol			
	Blacks Vs. Whites	N/A	Antihypertensive effect greater in Whites
Nifedipine	South Asians Vs. Caucasians	Threefold higher in South Asians	N/A
		Greater in Koreans	
	Koreans Vs. Caucasians		N/A
		Greater in Nigerians	
	Nigerians Vs. Caucasians		N/A
Diuretics	Blacks Vs.	N/A	71% of Blacks achieved blood pressure goal vs.
Hydrochlorothiazide	Whites		55% of Whites in Veterans Administration study

Statistically significant differences in exposure to drug expressed in terms of a measure of the blood concentration—in these examples, the area under the blood concentration-time curve (AUC).
N/A, not available.

Anticoagulants

Race has been reported to contribute to variability in dosing requirements for warfarin in anticoagulation, with African Americans requiring higher doses and Asians requiring lower doses than whites. CYP2C9 is the enzyme primarily involved in warfarin PK. Variant CYP2C9 genotypes are associated with an increased risk of major hemorrhage, and the frequency of variant genotypes is significantly higher in European Americans than in African Americans. Variations in the *VKORC1* gene that encodes for the pharmacologic target of warfarin, vitamin K epoxide reductase, contribute to differences in sensitivity to warfarin. One of the variants in VKORC1 associated with lower dose requirements is 1639 G>A. the AA genotype is found in warfarin-sensitive patients. The frequency of the warfarin-sensitive AA genotype is higher in Chinese than in whites, with frequencies of 82% in Chinese and 14% in whites. A genomic basis found in recent mechanistic studies supports the previously observed ethnic differences in warfarin dose requirements. This serves as an example of the need to understand potential reasons for pharmacokinetic or pharmacodynamic variability in clinical pharmacology or phase II studies so that dosing can be adjusted for relevant populations in later clinical studies.[7]

METABOLISM AND ENDOCRINE AGENTS

HMG-Coa reductase inhibitors

The pharmacologic activity of rosuvastatin (a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor) in treating dyslipidemias is due primarily to the parent compound. Approximately 10% of a radiolabeled dose is recovered as metabolite, which is formed primarily by CYP2C9. Because of the small contribution of CYP2C9 to rosuvastatin exposure, and because the most common variant alleles of CYP2C9 are not found in the Asian population at a higher frequency than in whites, a higher systemic exposure in Asians than whites on the basis of P450-mediated metabolism would not be predicted.

IMMUNOMODULATORS

Immunosuppressants

Immunomodulators are used in the prophylaxis of tissue rejection in organ transplant patients. Cyclosporine, sirolimus, and mycophenolic acid are often used in combination with steroids for this purpose. Tacrolimus, cyclosporine, and mycophenolic acid are all substrates for CYP3A4 and P-glycoprotein. Individual dosing regimens are prepared using therapeutic drug monitoring for cyclosporine, sirolimus, tacrolimus, and mycophenolic acid to maintain target trough concentrations or exposures. In the use of cyclosporine for the prophylaxis of tissue rejection in organ transplant patients, it was found that Black patients had higher rates of organ rejection than Caucasians when using the same dosing regimen. Assessments of the bioavailability of various oral formulations of cyclosporine in different ethnic groups have shown lower bioavailability in Blacks and higher bioavailability in Hispanics as compared to Caucasians. However, similar bioavailability between Blacks and Caucasians has also been reported for the microemulsion formulation. Observed differences in bioavailability are likely due to differences in intestinal CYP3A4 activity.

The absolute bioavailability of tacrolimus was lower in Blacks (11.9%) and Hispanics (14.4%) as compared to Caucasians (18.8%). Differences in intestinal CYP3A4 and/or P-glycoprotein were suggested probable reasons for the observed differences [5].

ANTICANCER AGENTS

Cytotoxic Agents

Amonafide and 6-mercaptopurine (6-MP), metabolic pathways involving polymorphically regulated enzymes (N-acetyltransferase [NAT] and thiopurine methyltransferase [TPMT], respectively) have provided some guidance regarding potential ethnic differences. As it relates to Amonafide, acetylator phenotype affects the generation of the active N-acetyl-Amonafide metabolite such that fast acetylators experience greater toxicity and thus should receive lower doses. Known ethnic differences in the NAT genotype suggest that Amonafide would likely have a differential therapeutic profile across different ethnic groups.

Extrinsic Factors

Among extrinsic factors, the effects of food ingestion with drug administration are the most extensively studied. The effects of food on drug disposition have been recently reviewed. Co administration of food with selected drugs can affect the rate and degree of drug absorption; this can involve enhancing, decreasing, or delaying absorption. It is further recognized that different types of food (e.g., the so-called high-fat and low-fat food used in food effect studies) can have different effects on absorption [5]. Grapefruit juice inhibits Metabolism of alprazolam, atorvastatin, cisapride, cyclosporine, midazolam and Triazolam [9]. There are numerous examples of the effect of food ingestion on drug disposition, including antimicrobials, hypoglycemics, and hypocholesterolemic agents, just to name a few.

Ethanol use has been shown to affect the elimination of many drugs, including diazepam, lorazepam, chlorazepate, oxazepam, meprobamate, pentobarbital, chlormethiazole, and rifamycin, based on induction of hepatic enzymes. Tobacco smoking has also been shown to affect the metabolism of several drugs, including theophylline, tacrine, imipramine, haloperidol, pentazocine, propranolol, flecainide, and estradiol, also through enzyme induction. While major cultural or regional differences in the composition of meals and in ethanol and tobacco use may

potentially affect population drug exposure and thus explain ethnic differences, it is not clear to what extent such effects are population specific. While socioeconomic status in different geographic regions of the world is an important determinant of access to pharmacologic therapy, the role such factors may play with respect to acceptability of foreign clinical data is less obvious. Socioeconomic and cultural factors may be important in determining expectations and efficacy of specific pharmacologic therapies specifically, psychotropic medications. Differences in regional medical practices do exist, and to the extent these influence outcomes from global clinical development programs, they need to be considered when determining acceptability of foreign clinical data. Variations in compliance have also been cited as factors explaining ethnic differences.Other possible extrinsic factors cited in the ICH E5 guidelines, such as exposure to pollution and sunshine, remain largely unexplored as factors responsible for ethnic differences. In general, therefore, it appears there are only a limited number of documented cases in which extrinsic factors are responsible for ethnic differences, and we are not aware of any systematic examination of these issues.

Given all these, there are a few examples of suspected ethnic differences in pharmacokinetics or pharmacodynamics. Noteworthy examples include the following: Chinese are more sensitive to the cardiovascular pharmacologic effects of propranolol than Caucasians, Chinese have lower daily warfarin dose requirements than Caucasians, and slow acetylators (more common in Caucasians and Blacks than Asians) are more likely to experience adverse events than fast acetylators of drugs that are eliminated by N-acetylation due to greater exposure. In most of these cases, the underlying molecular mechanisms are not known; in some cases, body weight appears to be at least a contributing factor, and in a few cases, documented CYP polymorphism difference does not appear to provide an explanation.

The ICH E5 guidelines of 1998 are intended to facilitate drug and biologics registration in the different ICH regions by recommending a framework for evaluating the impact of ethnic factors on a drug's safety and efficacy at a particular dosage and dose regimen, involving regulatory and development strategies that will enable appropriate evaluation of ethnic factors, minimize unnecessary duplication of clinical studies, and expedite the drug approval process. However, considering the general nature of these guidelines, there is clearly the potential for different regions or countries to apply different interpretations, thus potentially defeating some of the goals of the guidelines [5].

Impact of ethnic factors and ICHE5 guideline

There has been significant impact of ethnic factors on drug development after release of ICHE5 guidelines and completion of human genome project. Some of the examples are enlisted in the following tables.

Table lists examples of currently marketed drugs with labeling that includes specific race or genetic information intended to facilitate the optimal use of medications in various population groups. Some of the observed racial differences may be explained by the genetic differences listed in labeling (e.g., warfarin and carbamazepine). Possible mechanisms for others either have not yet been included in labeling (e.g., rosuvastatin and tacrolimus) or are as yet unknown (e.g., isosorbide dinitrate– hydralazine, which is effective in heart failure in black patients) [12].

Table 4: Examples of recent FDA drug product labeling that included ethnicity or genetic information [12]

Therapeutic area	Drug products: generic (brand) names	Ethnicity information	Genetics information
Cardiorenal	Isosorbide dinitrate hydralazine (BiDil)	Indicated for self-identified blacks	-
	Angiotensin II antagonists and ACE inhibitors	Smaller effects in blacks	-
Metabolic	Rosuvastatin(Crestor)	Lower dose for Asians	-
Transplant	Azathioprine (Imuran)	-	Dose adjustments for TPMT variants

	Tacrolimus (Protopic)	Higher dose for blacks	-
Oncology	Trastuzumab (Herceptin)	-	Indicated for HER2 overexpression
	Irinotecan (Camptosar)	-	Dose reduction for *UGT1A1*28*
	6-Mercaptopurine (Purinethol)	-	Dose adjustments for TPMT variants
	Erlotinib (Tarceva)	-	Different survival and tumor response in EGFR positive and - negative patients reported
	Maraviroc (Selzentry)	-	Indicated for CCR5-positive patients
Antiviral	Oseltamivir (Tamiflu)	Neuropsychiatric events mostly reported in Japan	-
	Abacavir (Ziagen)	-	Boxed warning for HLA-B*5701 allele
Pain	Codeine	-	Warnings for nursing mothers that CYP2D6 UM metabolized codeine to morphine more rapidly and completely[b]
Hematology	Warfarin (Coumadin)	Lower dose for Asians	Lower initial dose for CYP2C9- and VKORC1-sensitive variant
	Thioridazine (Mellaril)	-	Contraindication for CYP2D6 PM
Psychopharmacological	Atomoxetine (Strattera)	-	Dosage adjustments for CYP2D6 PM; no drug interactions with strong CYP2D6 inhibitors expected for PM
Neuropharmacological	Carbamazepine (Tegretol)	Box warning for Asians with variant alleles of *HLA-B*1502*	Box warning for Asians with variant alleles of *HLA-B*1502*

ACE, angiotensin-converting enzyme; CCR5, chemokine (C-C motif) receptor 5; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; PM, poor metabolizer; TPMT, thiopurine methyl transferase; UGT, uridine diphosphate glucuronosyl transferase; UM, ultra-rapid metabolizer; VKORC, vitamin K reductase complex.

Impact on the drug regulatory authorities

Impact of ICH E5 guidelines was observed across the ICH regions (Japan, USA & EU) as well as non-ICH regions such as Taiwan. Taiwan one of the few countries which are embracing the ICH E5 in a big way by bringing the guidelines to determine the need for bridging studies during the drug approval process. The flowchart to determining ethnic sensitivity and waiver for clinical trial as follows [13].

Table 5: Announcements for waiving clinical trials in Taiwan [13]

Verification of ethnic insensitivity not required	Verification of ethnic insensitivity required
Drugs for AIDS treatment	Anticancer drugs
Drugs for organ transplantation	Drugs with breakthrough efficacy
Topical agents	Drugs of single use
Nutrition supplements	Drugs with different salt of an approved active ingredient but the route of administration is the same
Cathartics prior to surgery	Drugs for chronic psychiatric or immunological diseases with difficulty in conducting domestic clinical trails
Radiolabelled diagnostic pharmaceuticals	A new combination drug with each component approved for the same indication previously
The drug is the only choice of treatment for a given severe disease	Drugs with the mechanism, route of administration, efficacy and adverse effect, similar to the approved drugs
Drugs for life-threatening disease have demonstrated a breakthrough efficacy	New combination composed of compounds approved for the same indication
Drug with lacking adequate trial subjects and used for rare disease	Active immunity vaccines
Vaccines with lacking adequate trial subjects or for preventing emergent and severe infectious disease or complication	

Impact on the drug approval

Clinical development periods for drugs by use of a bridging strategy were shorter by about 24 months (median) than the periods for drugs not subject to this bridging strategy. However, this result implies that a bridging strategy can shorten the time for clinical development in a new region. It should be noted that, for most of the 26 NDAs using a bridging strategy (Table 6), full clinical development including phase 1 studies in Japan was originally planned because the ICH E5 guideline was not established at that time. After the guideline was established, clinical development plans for these drugs were changed to incorporate a bridging strategy. It is believe that the time for clinical development can be reduced substantially if a bridging strategy is planned from the beginning as a clinical development approach in a new region. If a bridging strategy is successful, costs for drug development in the new region can also be saved, because another large phase 3 trial and longterm study in a new region, which are very expensive, can be skipped or minimized. It was concluded that a bridging strategy helps accelerate drug development and minimize duplicative work in each region.

However, adequate planning is required for a successful bridging strategy, and drug safety should be carefully monitored after approval. When a bridging strategy is being planned, it is recommended reanalyzing all available information. An adequately planned and well-organized bridging strategy/bridging study will accelerate drug development and the time to approval in a new region. To plan an adequate bridging strategy, it will be beneficial to have discussions between the regulatory authority in a new region and the sponsor from the early stages of drug development. It is also noteworthy that the conduct of multinational/multiregional clinical trials is becoming more common in drug development. These trials allow direct comparison of results in different regions [14].

Table 6: Examples of drugs approved after doing bridging studies in Japan

S.No.	Non proprietary name	Approva	Target disease	Standard dose and administration*		
				Japan	United States	European Union
1.	Sildenafil citrate	1999	Erectile dysfunction	25-50 mg, 1hour before Sexual activity†	50 mg (minimum, 25 mg; maximum, 100 mg), 1 hour before sexual activity	50 mg (minimum, 25 mg; maximum 100 mg), 1 hour before sexual activity
2.	Oseltamivir phosphate	2000	Influenza infection	75 mg twice daily for 5days	75 mg twice daily for 5days	Switzerland‡: 75 mg twice daily for 5days
3.	Sumatriptan succinate	2001	Migraine	50 mg, may be increased to 100 mg; maximum, 200 mg/24 hour	50 mg; maximum, 200 mg/24 hour	United Kingdom‡: 50 mg, 100 mg may be necessary; maximum, 300 mg/24 hour
4.	Risedronate Sodium	2002	Osteoporosis	2.5 mg once daily†	5 mg once daily	5 mg once daily
5.	Leflunomide	2003	Rheumatoid arthritis	Starting dose, 100 mg/day for 3day; maintenance dose, 20 mg once daily; may be decreased to 10 mg once daily in some patients	Starting dose, 100 mg/d for 3 days; maintenance dose, 20 mg once daily	Starting dose, 100 mg/d for 3 days; maintenance dose, 10-20 mg once Daily

The dosing information is at the time of approval in Japan and may be different from the current status in each region. Information here is based on the information in the summaries of data submitted by applicants.
†Major differences in "Dosage and Administration."
‡Information in a country in Europe was only available in the summaries.

ETHNIC CONSIDERATION

A medicine's sensitivity to ethnic factors can be judged by pharmacokinetic, pharmacodynamic, or other characteristics which suggest the potential for clinically significant or minimal impact by intrinsic and/or extrinsic ethnic factors on safety, efficacy and dose response.

The critical properties of a medicine for assessment of sensitivity to ethnic factors have been enumerated in appendix D of the ICH E5 guideline. The critical properties of a medicine that make it less likely to be sensitive to ethnic factors include linear pharmacokinetics (PK), flat pharmacodynamic (PD) curve, wide therapeutic range, minimal metabolism, high bioavailability, low potential for protein binding, little potential for interactions, nonsystemic mode of action, and little potential for inappropriate use.

The critical properties of a medicine that make it more likely to be sensitive to ethnic factors include nonlinear pharmacokinetics (PK), steep pharmacodynamic (PD) curve, narrow therapeutic range, high metabolism, genetic polymorphism, administration as a prodrug with the potential for ethnically variable enzymatic conversion, high inter-subject variability, low bioavailability, high likelihood of use in a setting of multiple co--medications and high potential for inappropriate use [2].

CONCLUSION

Approval of drugs with or without bridging studies at various regulatory authorities in the world should be tried by appropriate institutions like WHO, NGOs', pharma companies etc., to

realize the goals of ICH E5 guideline i.e., minimizing duplication of clinical studies, cost and supplying medicines expeditiously to needy patients for their benefit.

To realise full potential of ICH E5 guideline goals, there is need to identify and register more drugs which are approved in one country but not approved in the another country.

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How to cite this article: Sudershan Goud Gokari, Dr. Vijayanarayana, Sujitha Bajjuri, Santosh Kumar Panda. A review of consideration of ethnic factors during drug approval process. Int J of Allied Med Sci and Clin Res 2018; 6(1): 203-213.

Source of Support: Nil. **Conflict of Interest:** None declared.