GLOBALIZATION AND RACIAL COMPOSITION OF PIVOTAL CLINICAL TRIALS

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Abstract

Importance: There is a paucity of data on the changes in geography and ethnicity of patients on the key trials used by the FDA for establishing dosing, safety, and efficacy.

Objective: To describe the globalization and racial composition of regulatory data from FDA approved medications.

Design, Setting, and Participants: A descriptive analysis of 171 pivotal trials from 70 FDA new molecular entities, new combinations, and biologics approved by the Unites States Food and Drug Administration which captured racial data for 126,342 participants from the years 1997, 2004, 2009 and 2012 in the clinical areas of cardiovascular disease, central nervous system, and oncology.

Main Outcome(s) and Measure(s): The number of and the specific countries that hosted a clinical investigator site that contributed participants to the pivotal clinical trial. Also, the percentage of participants from reported racial groups of White, Black, Asian, or other in these pivotal trials.

Results: The total number of unique countries was 31 in 1997, 43 in 2004, 56 in 2009, and 61 in 2012. The mean number of countries involved per trial was 3.6 in 1997, to 4.4 in 2004, 8.3 in 2009, and 15.0 in 2012.

The percentage of patients identified as Caucasians was 91.0% in 1997, 90.6% in 2004, 87.1% in 2009, and 81.1% in 2012, all at rates higher than that of the American population[11]. The yearly percentage of black participants on pivotal trials ranged from 2.9% - 6.9% over the study period. Asian participants were 0.1% of total patients in 1997, but had risen to 10.8% of patients in 2012.

A group of 29 countries mostly from North America and Western Europe represented “classic countries” and hosted investigator sites in all fours years evaluated. Countries in the regions of Asia, Eastern Europe, and South America were not well represented on pivotal trials in the early years evaluated, but have since increased in representation.

Conclusions and Relevance: This analysis shows a doubling of the number of countries involved in pivotal trials and a quadrupling of the number of countries per individual trial over a 15-year period. This substantiates the notion that pivotal trial programs have become more global.

Despite an increase in globalization, the vast majority (>80%) of patients on pivotal clinical trials are white. These patients are now enrolled in Eastern Europe and South America in addition to the longstanding contributors from North America and Western Europe. This allows for greater confidence in the ability to determine efficacy and detect risk in white populations, but do not provide the same level of ascertainment in non-white groups.

Introduction

The development of safe and effective medication has been a vital tool in improving the quality and length of human lives across the globe. Indeed, access to medication is recognized as a human right by the World Health Organization[1]. In the United States the use of prescription drugs is widespread, with 47.9% of the population using at least one prescription drug in the past month[2].

The FDA Center for Drug Evaluation and Research (CDER) is charged with ensuring the safety and efficacy of drugs for use among the entire US citizenry. This includes the diversity of populations within the USA and moreover, CDER's scope has expanded as other regulatory bodies use FDA decisions as part of their own domestic policy.[3] The FDA's position as a global regulatory agency is relevant as biopharmaceutical clinical trials are being conducted in many regions of the globe,[4] including Eastern Europe, Latin America, and Asia[5]. Data from 300 clinical trials published in three major medical journals reveal that the number of countries hosting clinical trials has more than doubled between 1995 and 2005; with at least one third of major industry sponsored phase III trials having been conducted completely outside of the United States[6]. However, there is a paucity of data on the changes in the geography and ethnicity of patients on the key trials used by the FDA for establishing dosing, safety, and efficacy.

When assessing data from across the world, regulatory bodies consider intrinsic and extrinsic factors that may influence foreign clinical data and the ability of regulatory agencies to extrapolate the data to domestic populations. Intrinsic ethnic factors are genetic and physiologic in nature, such as race and genetic polymorphisms, while extrinsic ethic factors are associated with environment and culture[5,7,8]. Both intrinsic and extrinsic ethnic factors contribute to the decision to require a "bridging study" to allow extrapolation of the data to different regions[7].

Additionally, because of the documented differences in drug response across geographical regions[9], it is of value to assess where the pivotal trials we use to guide drug approvals and ultimately drug utilization are being conducted.

A key part of the safety and efficacy assessment are the "Pivotal Trials." These are typically large randomized controlled phase III trials from which is derived the basis for the labeled indication and approved dosages, as well as the adverse drug reaction profile. Due to their importance in the regulatory decision, these pivotal trials represent a major focus of FDA medical review and are subject to a significant degree of scrutiny. Additionally, payers use the data generated from these trials in determining initial coverage decisions and medical associations also use these data to generate clinical practice guidelines.

To answer the questions about the globalization and ethnic composition of regulatory data, a review of the pivotal trials was conducted in FDA approvals from the years 1997, 2004, 2009 and 2012 in the clinical areas of cardiovascular disease, central nervous system, and oncology. The focus is on identifying the changes in the countries that are a part of the pivotal trial landscape and on the ethnic composition of the patients in the trials.

Methods

Source of data

The lists of approvals by year and within specific clinical areas were obtained via CenterWatch.org. The identified approvals within the clinical areas and associated time period were then confirmed through the FDA registry's Drugs@FDA month-by-month approvals.

In order to identify the pivotal trials, section 14 (Clinical Studies) of the original FDA Approval Label for each drug was used. The studies in this section provide the primary support of efficacy[10]. The pivotal trials were confirmed in the publicly available FDA medical reviews available online at Drugs@FDA, and revised when the FDA Medical Review explicitly identified specific trials as pivotal (for inclusion) or supportive (for omission). After these trials were confirmed, the medical reviews served as the initial sources of data on the countries of clinical investigator sites and on the racial demographics of the trial participants. Once collected, these data were supplemented by the primary published literature on the relevant trial, which were obtained through PubMed searches. The results were compiled into a Microsoft Excel® database for descriptive analysis. The investigators chose to focus on the clinical areas of cardiovascular, central nervous system (CNS), and oncology, as they represent diverse disease conditions, have a large volume of patients, and have multiple drug approvals in each of the years under assessment.

Inclusion

All approvals that were granted by the FDA within the years of interest in the clinical areas of CNS, CV, and oncology were included in this study. The FDA classifies their New Drug Applications (NDAs) by chemical type and, for the purposes of this study, we included chemical

types 1 (New Molecular Entity) and 4 (New combination) as well as Biologic Applications (BLAs). These approvals are more likely to rely on a more rigorous pivotal trial as compared to other chemical types for a new active ingredient (type 2), new dosage form (type 3), etc. There were from 17 approvals (5 CNS, 6 CV, and 6 oncology) and 65 pivotal trials in 1997, 17 approvals (6 CNS, 4 CV, and 7 oncology) with 44 trials in 2004, 17 (3 CNS, 9 CV, and 5 oncology) approvals with 38 trials in 2009, and 2012 included 19 total approvals (3 CNS, 4 CV, and 12 oncology) with 24 trials. Ethnic data was not available for two approvals (one approval with two trials in 1997 and one approval with one trial in 2004) as so approvals are not represented in Table 1. Ethnic data was not available for twelve trials in 1997, nine trials from 2004, and one trial from 2009. Country data was not available for two trials from 1997.

Definitions of Race and How Data Were Collected

The FDA follows the DHHS Office of Management and Budget recommendation for standard ethnicity categories. However, to account for expected variability in racial reporting, all information was collected as it was presented in its most detailed form. This resulted in the utilization of the following racial categories: Caucasian, Black, Asian, Hispanic/Latino, Native American, Pacific Islander, and other. In some cases, these data were presented as Caucasian/white or non-Caucasian/non-white. Hence, a new category called “Non-white unspecified” was created. If racial data had been reported as unknown, it was recorded as such. The reporting of Hispanic/Latino in medical reviews and primary publications was the least standardized because this term is largely an American construct. The difficulty of applying the Hispanic/Latino label outside of the USA prohibits its applicability globally and thus Hispanic/Latino data was combined with the Caucasian/white group.

A World Map (Figure 3) provides a snapshot of the global involvement in pivotal trials. The regional breakdown used is modified from the regional groups of the United Nations General Assembly (http://www.un.int/wcm/webdav/site/gmun/shared/documents/GA_regionalgrps_Web.pdf).

Reporting of Race

Racial information was obtained through the above methods for 87.1% of all 171 pivotal trials evaluated including 81.5% of the pivotal trials in 1997, 79.5% in 2004, 97.4% in 2009, and 100% in 2012. Within clinical areas obtainment rates were at 97.9%, 80.9%, and 87.5% for CNS, CV, and oncology respectively. Racial data was less consistently reported for oncology in 1997 with only data for 9 of 18 pivotal trials being obtained through the primary literature and FDA medical review.

A survey of the reporting of racial information from the pivotal trials on FDA approved labeling was also conducted to assess the extent to which this information has been disseminated to the general public.

Results

Number of patients

The assessment included a total of 70 FDA approvals (68 with racial data) and provided racial data on a total of 126,342 participants from 171 pivotal trials (149 with racial data) across the four years and three clinical areas (Table 1). Trials in the cardiovascular disease area enrolled the most patients, representing 70.7% of all participants evaluated. The majority of evaluated years were included over 30,000 participants with the exception of 2004, which, despite having an equivalent number of approvals, included only 14,980 patients on pivotal trials.

Global Participation

One of the major aims of this study is to provide an assessment of trends in the globalization of pivotal trials. To that point the total number of unique countries who hosted an investigator site that recruited patients for a pivotal trial in any of the three clinical areas increased across the time period from 31 in 1997, to 43 in 2004, 56 in 2009, and finally 61 countries in 2012 (Figure 1). The mean number of countries involved per trial accordingly increased from 3.6 in 1997, to 4.4 in 2004, 8.3 in 2009, and then 15.0 in 2012 (Figure 2). The mean number of countries per approval was from 9.1 in 1997, 9.0 in 2004, 14.4 in 2009, and 17.3 in 2012.

In the CNS area, the total number of unique countries hosting investigator sites across the time period was 23 in 1997, 28 in 2004, 17 in 2009, and 46 countries in 2012 (Figure 2). The mean number of countries involved per trial was 3.2 in 1997, 3.0 in 2004, 3.7 in 2009, and 15.3 in 2012 (Figure 2). The mean number of countries involved per approval was 9.6 in 1997, 7.2 in 2004, 7.0 in 2009, and 22.8 per approval in 2012 (Figure 2).

In the CV area, the total number of unique countries hosting investigator sites across the time period was 19 in 1997, 30 in 2004, 53 in 2009, and 40 in 2012 (Figure 2). The mean number of countries involved per trial was 3.5 in 1997, 4.9 in 2004, 10.1 in 2009, and 12.4 countries per trial in 2012 (Figure 2). The mean number of countries involved per approval was 9.7 in 1997, 14.0 in 2004, 18.2 in 2009, and 16.4 in 2012 (Figure 2).

In the oncology area, the total number of countries hosting investigator sites across the time period was 28 unique countries in 1997, 33 in 2004, 34 in 2009, and 56 in 2012 (Figure 1). This growth in the globalization of oncology trials is consistent with the trend in mean number of countries involved per trial, which corresponds to 4.0 countries in 1997, 7.1 countries in 2004, 8.9 countries in 2009, and 15.8 countries per trial in 2012 (Figure 2). The mean number of countries involved per approval was 8.2 in 1997, 7.7 in 2004, 12.0 in 2009, and 16.4 in 2012 (Figure 2).

Patient Ethnicity/Race

The percentage of patients who were identified as Caucasians was 91.0% in 1997, 90.6% in 2004, 87.1% in 2009, and 81.1% in 2012 (Table 2). Additionally, the range of Caucasian percentage in the clinical trials was 20.7% - 100% in 1997, 75.4% - 100% in 2004, 35.1% - 100% in 2009, and 47.9% - 98.1% in 2012. The percentage of pivotal clinical trial participants that were Caucasians was higher than that of the American population[11] in each of the evaluated years.

The yearly percentage of black participants on pivotal trials was 2.9% - 6.9% over the study period, consistent with the lower participations rates that have been previously reported[12,13].

Asian participants have seen an increase in representation. Over the study period Asian participants were 0.1% of total patients in 1997, but had risen to represent 10.8% of patients in 2012.

World Maps

A group of 29 countries, representing the "classic countries" involved in the landscape of pivotal trials, hosted investigator sites in all four of the years evaluated. Western Europe and all of the North American weigh prominently within this group. Seventeen of the nineteen Western European countries that hosted an investigator site in any of our four years of interest are a part of this group and eight of them (Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, and the UK) were in the top ten most represented countries in at least two of the four years. Three other "classic countries" were in the top ten in two or more years and those were Australia (2004 and 2012), Canada (all four years), and the United States (all four years). Outside of Western Europe and North America, the "classic countries" are made up of Croatia, Czech Republic, Poland, and Russia from Eastern Europe, Australia and New Zealand, South Africa from Africa and Argentina from South America. No Asian countries hosted investigator sites in all four time periods

Eastern Europe can also be classified as an emerging region. There are five "classic countries" (Croatia, Czech Republic, Hungary, Poland, and Russia) from Eastern Europe that participated in a trial in each year evaluated. However, Croatia contributed to less than 5% of the total pivotal trials in each year. Eastern European involvement grew from seven countries on trials in 1997, to eight in 2004, thirteen in 2009, and to sixteen in 2012.

Asia was not well represented on pivotal trials in 1997. In 2004, India, Malaysia, Singapore, and Thailand hosted investigator sites for pivotal trials along with Hong Kong* and Taiwan*, for a

total of six countries/territories. In 2009, the number increased to eleven with the addition of mainland China, Japan, Pakistan, and South Korea and eleven again in 2012 with the addition of Saudi Arabia and the loss of Pakistan. Also notable within the Asian region is the rapid rise to prominence of China, India, and South Korea, each of which were present on over 25% of trials in 2012.

Like Asia, South America was not well represented in 1997. Argentina, the only "classic county" from the region was the only country to contribute patients to a pivotal trial in 1997. Brazil, Chile, Peru, and Venezuela joined in 2004 to bring the total to five countries. In 2009, Ecuador hosted a site to bring the total to six countries, finally in 2012, Colombia, Costa Rica, and Guatemala hosted sites while Venezuela did not, which increased the total number of participating countries to eight. Argentina, Brazil, and Chile were present in greater than one third of trials in 2012.

Separate Clinical Areas Ethnicity/Race

The racial composition of the CNS approvals had a similar trend to what was seen in the overall results. The data (Table 2) show an excess of Caucasians, fewer blacks, and growth in Asian patient participation with the exception of 2009. In 2009, two of the three CNS approvals had over 30% black participants in the trials.

The vast majority of CV pivotal trial patients were Caucasian, although there was a decline in participation from 91.9% in 1997 to 80.6% in 2012. Overall, the percentage of black participants on trials in the CV area does not appear to have changed by a large degree over this time span from 3.1% in 1997, 4.1% in 2004, 4.9% in 2009, to 4.2% in 2012. However, there were trials in which black participants were a 46.7-79.3% of the population.

Of oncology approvals, 1997 represented the year that included the lowest percentage of Caucasian participants at 79.4%, while 18.7% of the non-Caucasian data was reported as simply not Caucasian. After 1997, the percentage of Caucasians peaked in 2009 at 87.2% while recent 2012 data reports Caucasians at 80.6%. The enrollment of black participants remained low across the timeframe while the increase of Asian participation in oncology trials increased from 0.4% in 1997 to 11.4% in 2012 (Table 2).

Discussion

This analysis shows a doubling of the number of countries involved in pivotal trials and a quadrupling of the number of countries per individual trial over a 15-year period. This substantiates the notion that pivotal trial programs have become more global. The globalization of pivotal trials supports the FDA's position as a global regulatory agency with the capability and responsibility to collect and analyze data from diverse populations across various countries. One influence of this trend toward globalization is the increased standardization of clinical trial protocols, clinical site quality, data collection and data submission, so as to meet the requirements for inclusion in FDA evaluated pivotal trial data. As pivotal trials have become more globalized, the FDA and other regulatory partners can now assess the efficacy and safety of medications holistically for final approval, and also use the data to support the efficacy and safety within specific countries or regions.

Despite an increase in globalization, the vast majority (>80%) of patients on pivotal clinical trials are white. These patients are now enrolled in Eastern Europe and South America in addition to the longstanding contributors from North America and Western Europe. This allows for greater confidence in the ability to determine efficacy and detect risk in white populations, but do not provide the same level of ascertainment in non-white groups. As non-white patients make up 22.1% of USA population and, according to the US Census Bureau Population Projections are expected to increase to 26.3% by 2035, and 31.1% by 2060, there is a need for more inclusive clinical trial planning to assure drug safety across patients of all ethnicities.

Insufficient data does not guarantee harm but do provide a basis for the delayed detection and dissemination of risk in underrepresented populations. Serious but uncommon risks are detected through post-marketing pharmacovigilance programs, such the FDA's MedWatch

program, as soon as the medication is used by a large enough population for such risks to emerge. With increased representation of previously underrepresented populations on future pivotal trials, these risks are more likely to be detected before the medication is approved for use in the general population. This should result in more accurate and targeted warnings and precautions, which improves safety and efficacy.

Aligned with the importance of the influence of race on drug efficacy and safety, the reporting of the demographic composition of the trials to the public is a robust way to disseminate this information. Regular reporting allows health care providers and patients to assess if the population studied matches the individual for which the drug may be prescribed. However, the use of the OMB categories is not sufficient for the global environment. The increased reporting of the racial data is reflective of the increased influence of its growing relevance in the public discourse. Racial data for approvals in the oncology and CV areas have been well-reported in the more recent time frame and it is important that this upward trend continues along with an increased assessment on differences in efficacy and safety between groups.

Future Directions

Because of the significant time gap between regulatory approval and pivotal study recruitment, even the 2012 data reflects trials that began in the previous decade. An “advanced search” of ClinicalTrials.gov for all open, interventional, phase III, industry sponsored trials reveals that North America is a host for 51.4% of the 2,331 total ongoing studies. This may mean that in the future trials will become even more globalized and that the United States will serve as a host for fewer pivotal trials. In order to be equipped to handle for the current and growing globalization tools for ethnobridging should be further refined and utilized.

Furthermore, in order to optimally approve medications for an increasingly diverse American and global population, pivotal trials should be altered. Ideally, pivotal trials will be populated well-enough to allow regulators to make definitive safety and efficacy decisions for people in all possible racial groups and ethnicities. This would, in turn, impact who is recruited in pivotal trials and where these trials occur. Additionally, improvements to the trial evaluation methods should be implemented. One such tool is the use of ethnobridging to allow regulators to make assessments to shorten risk signal detection time and to more quickly disseminate safety information in underrepresented trial participants.

Summary

As the drug development enterprise becomes a more global institution, the role of the United States Food and Drug Administration is expanding outside of the borders of the United States as it becomes a global regulatory agency. The number of countries hosting investigator sites has nearly doubled over the course of fifteen years between 1997 and 2012 while the number of countries per approval has also doubled and the number of countries per pivotal trial has quadrupled. The population which was previously dominated by Caucasians from North America and Western Europe has expanded into Asia, Eastern Europe, and South America but has still remained predominantly Caucasian. The new picture of the pivotal trial landscape underscores the importance of the development and utilization of ethnobridging tools to improve risk detection. These tools can also serve to improve the efficacy and safety of medicine for or an ethnically diverse global population.

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Figures and Tables

Table 1. Total Number of Patients and Pivotal Trials Assessed by Racial Demographics

	1997		2004		2009		2012		TOTAL	
	Participants	Trials	Participants	Trials	Participants	Trials	Participants	Trials	Participants	Trials
CNS	6,929	19	6,847	22	5,189	9	3,810	6	**22,775**	**56**
CV	28,031	25	5,360	6	35,811	21	20,066	5	**89,268**	**57**
Oncology	3,316	9	2,773	7	1,310	7	6,883	13	**14,282**	**36**
TOTAL	**38,293**	**53**	**14,980**	**35**	**42,310**	**37**	**30,759**	**24**	**126,342**	**149**

Figure 1. Total Number of Countries Hosting Investigator Sites per Year

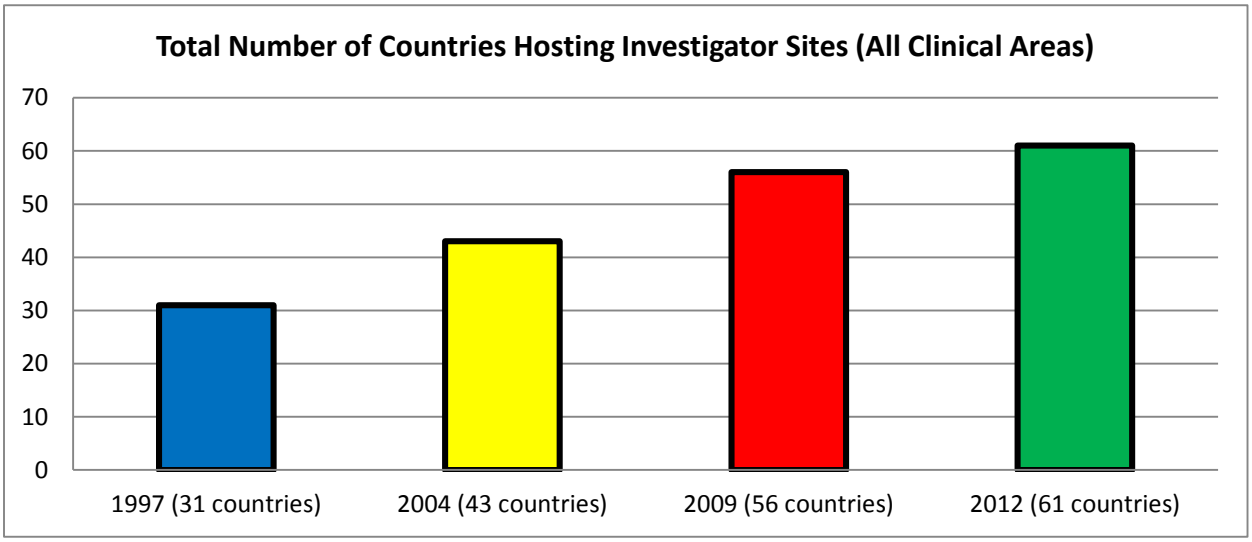


Figure 1a. All Clinical Areas

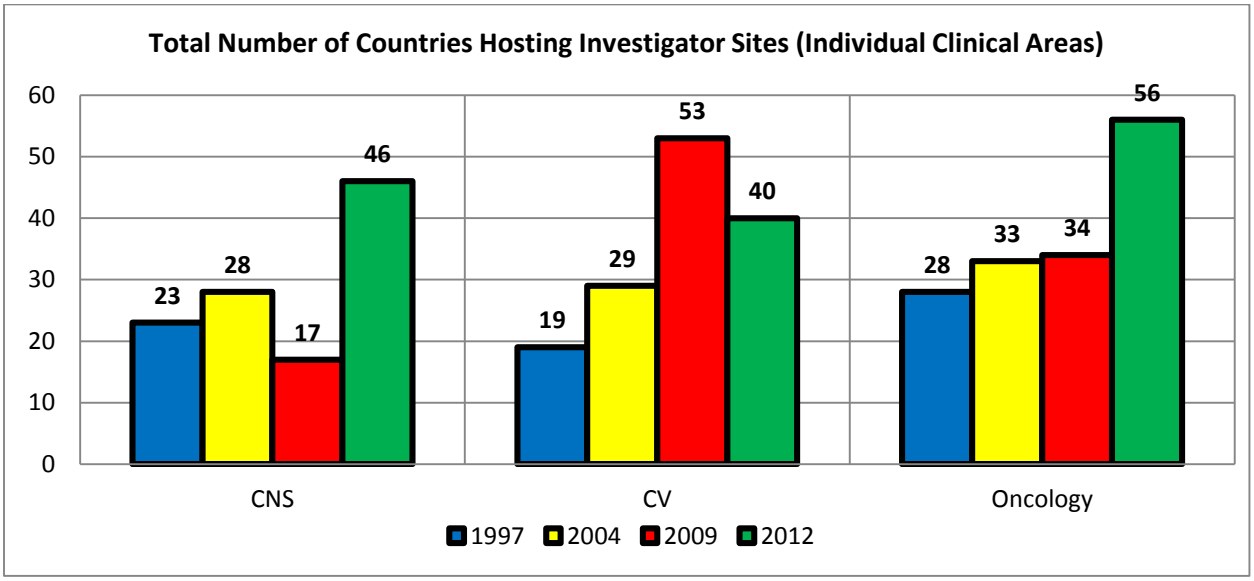


Figure 1b. Separate Clinical Areas

Figure 2. **Number of Countries Hosting Investigator Sites per Pivotal Trial**

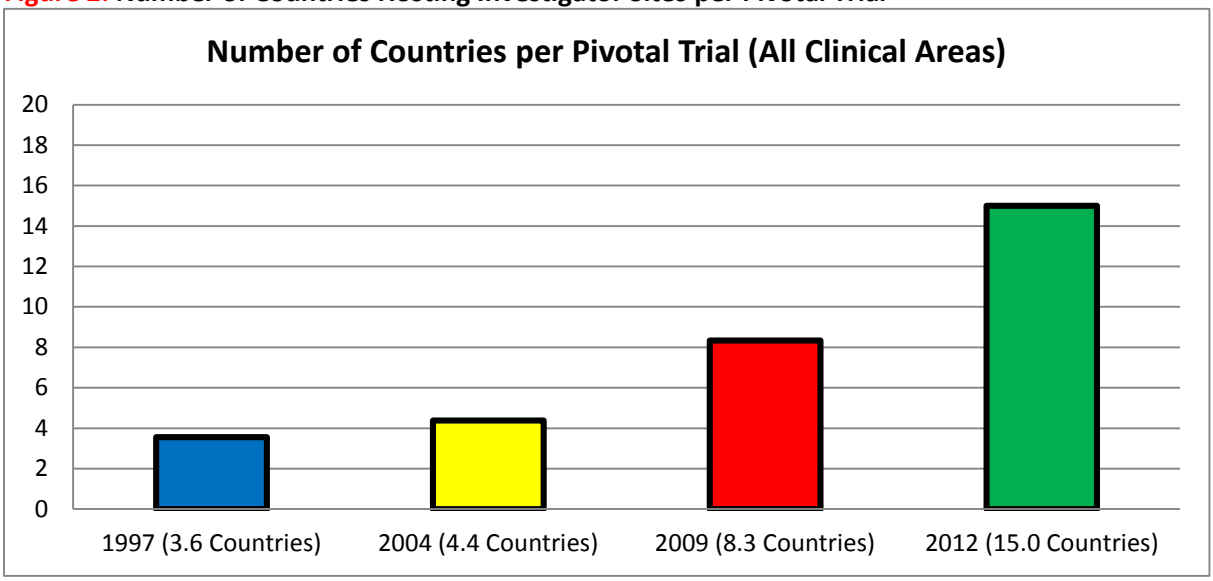


Figure 2a. **All Clinical Areas**

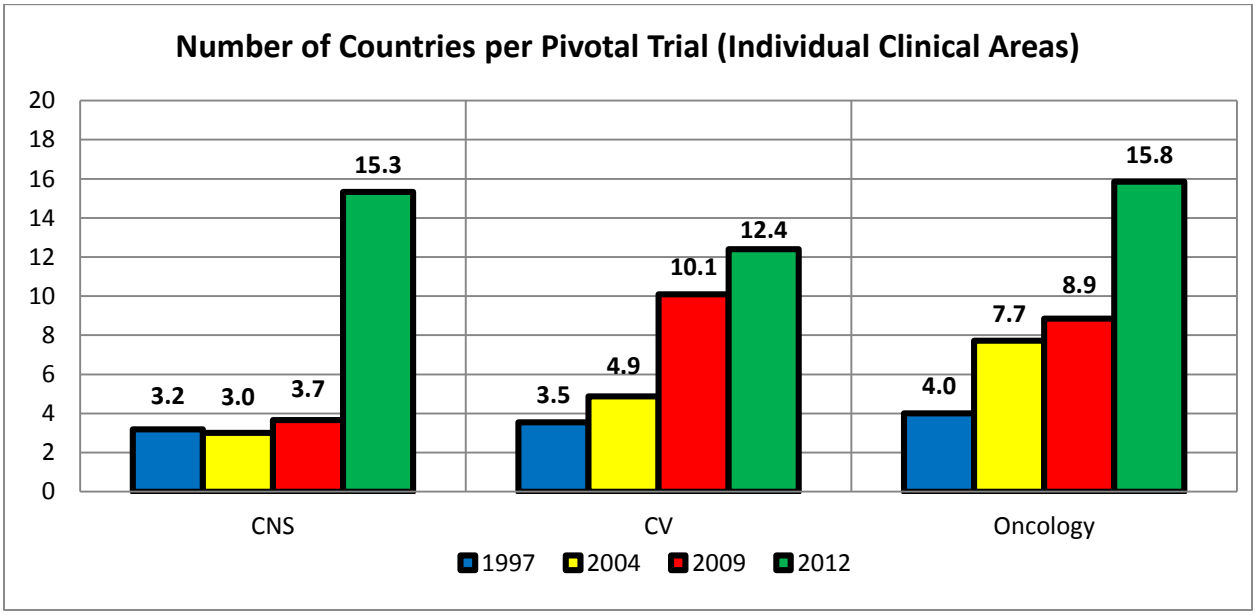
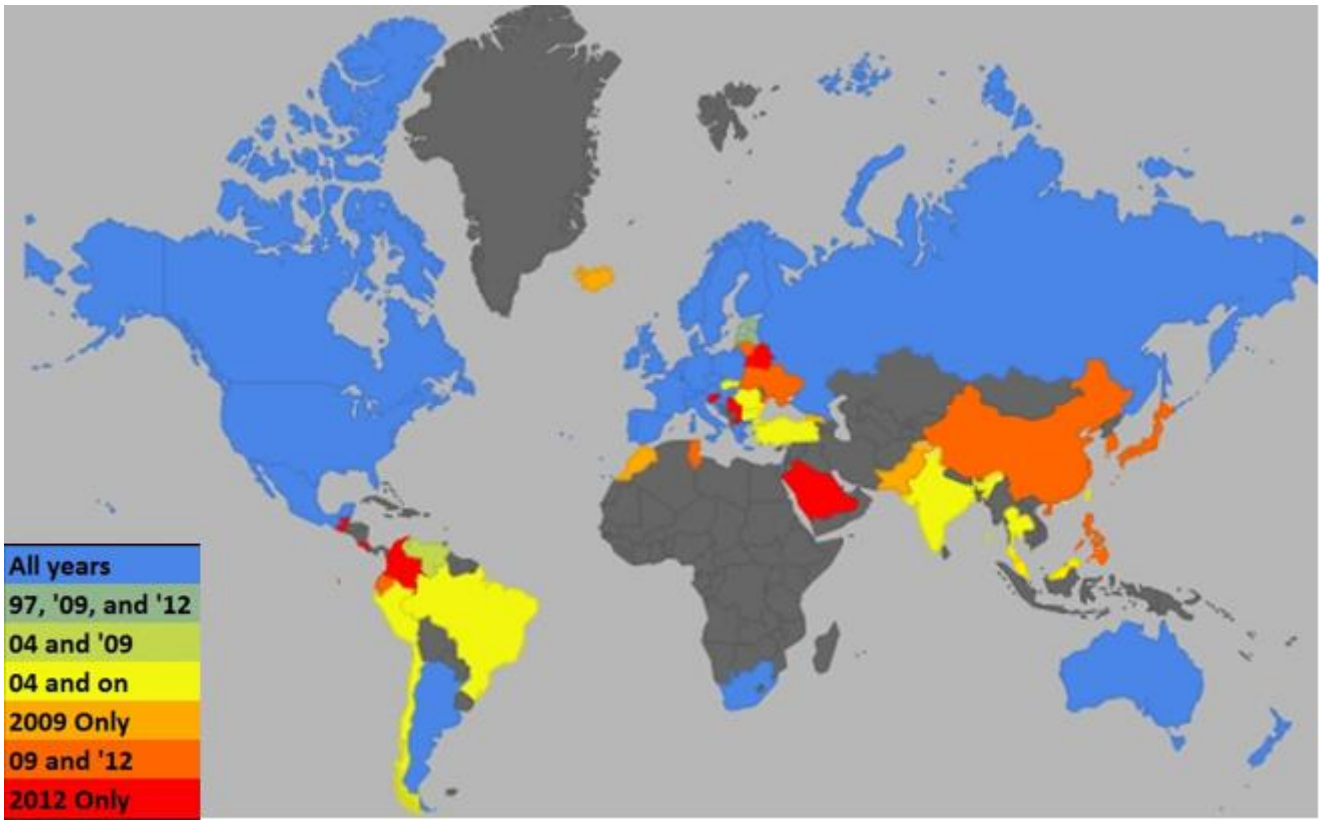


Figure 2b. **Individual Clinical Areas**

Table 2. Racial Composition of Pivotal Trials

Year	White		Black		Asian		Other (or unspecified)	
COMBINED								
	% Total	Range	% Total	Range	% Total	Range	% Total	Range
1997	91.0	20.7 – 100	2.9	0 – 70.3	0.1	0 – 4.5	5.9	n/a
2004	90.6	75.4 – 100	5.4	0 – 20.0	1.5	0 – 12.4	2.5	n/a
2009	87.1	35.1 – 100	6.9	0 – 50.4	4.2	0 – 23.5	1.8	n/a
2012	81.1	47.9 – 99.0	3.8	0 – 46.7	10.8	0 – 34.6	2.3	n/a
CNS								
	% Total	Range	% Total	Range	% Total	Range	% Total	Range
1997	93.3	74.8 – 100	2.9	0 – 22.2	0.3	0 – 2.1	3.5	n/a
2004	92.1	75.4 – 100	6.3	0 – 20.0	0.6	0 – 4.6	0.9	n/a
2009	69.2	35.1 – 100	22.1	3.2 – 50.4	4.6	0.6 – 21.7	4.1	n/a
2012	84.5	65.0 – 100	1.7	0 – 7.0	11.9	0 – 34.6	1.9	n/a
CV								
	% Total	Range	% Total	Range	% Total	Range	% Total	Range
1997	91.9	20.7 – 100	3.1	0 – 79.3	0.1	1.0 – 4.5	5.0	n/a
2004	90.3	79.9 – 100	4.1	0 – 13.6	0.8	0 – 2.1	4.8	n/a
2009	89.7	71.6 – 100	4.9	0 – 17.1	4.0	0 – 23.5	1.5	n/a
2012	80.6	47.8 – 100	4.2	0 – 46.7	10.4	0 – 11.1	1.8	n/a
ONCOLOGY								
	% Total	Range	% Total	Range	% Total	Range	% Total	Range
1997	79.4	70.1 – 100	1.1	0 – 16.9	0.2	0 – 3.2	19.3	n/a
2004	87.3	77.6 – 100	5.6	0.2 – 12.2	5.2	0 – 12.4	2.0	n/a
2009	87.9	77.5 – 100	3.1	0 – 21.1	7.2	0 – 13.6	1.8	n/a
2012	80.6	59.4 – 100	4.0	0 – 23.5	11.4	0 – 32.3	3.9	n/a

Figure 3. **World Map of Pivotal Trial Distribution**



Country	Region	1997	2004	2009	2012	Categorization
Morocco	Africa	0.00	0.00	2.63	0.00	2009 only
South Africa	Africa	7.94	9.09	15.79	33.33	All years
Tunisia	Africa	0.00	0.00	5.26	4.17	2009 and 2012
China	Asia	0.00	0.00	5.26	25.00	2009 and 2012
Hong Kong*	Asia	0.00	4.55	7.89	12.50	2004 and on
India	Asia	0.00	2.27	18.42	37.50	2004 and on
Japan	Asia	0.00	0.00	2.63	16.67	2009 and 2012
Malaysia	Asia	0.00	2.27	5.26	8.33	2004 and on
Pakistan	Asia	0.00	2.27	2.63	0.00	2009 only
Philippines	Asia	0.00	0.00	7.89	16.67	2009 and 2012
Saudi Arabia	Asia	0.00	0.00	0.00	4.17	2012 only
Singapore	Asia	0.00	4.55	2.63	20.83	2004 and on
South Korea	Asia	0.00	0.00	10.53	33.33	2009 and 2012
Taiwan*	Asia	0.00	4.55	2.63	16.67	2004 and on
Thailand	Asia	0.00	2.27	5.26	12.50	2004 and on
Australia	Australia	7.94	15.91	21.05	45.83	All years

New Zealand	**Australia**	4.76	9.09	10.53	4.17	All years
Belarus	**Eastern Europe**	0.00	0.00	0.00	8.33	2012 only
Bulgaria	**Eastern Europe**	0.00	2.27	7.89	12.50	2004 and on
Croatia	**Eastern Europe**	1.59	2.27	2.63	4.17	All years
Czech Republic	**Eastern Europe**	3.17	4.55	21.05	25.00	All years
Estonia	**Eastern Europe**	1.59	0.00	5.26	16.67	All but 2004
Georgia	**Eastern Europe**	0.00	0.00	2.63	0.00	2009 only
Hungary	**Eastern Europe**	6.35	4.55	15.79	25.00	All years
Latvia	**Eastern Europe**	1.59	0.00	5.26	8.33	All but 2004
Lithuania	**Eastern Europe**	0.00	0.00	7.89	8.33	2009 and 2012
Macedonia	**Eastern Europe**	0.00	0.00	0.00	4.17	2012 only
Poland	**Eastern Europe**	1.59	13.64	34.21	54.17	All years
Romania	**Eastern Europe**	0.00	2.27	7.89	25.00	2004 and on
Russia	**Eastern Europe**	3.17	4.55	31.58	45.83	All years
Serbia	**Eastern Europe**	0.00	0.00	0.00	4.17	2012 only
Slovakia	**Eastern Europe**	0.00	4.55	7.89	8.33	2004 and on
Slovenia	**Eastern Europe**	0.00	0.00	0.00	4.17	2012 only
Ukraine	**Eastern Europe**	0.00	0.00	10.53	25.00	2009 and 2012
Austria	**Western Europe**	12.70	11.36	13.16	37.50	All years
Belgium	**Western Europe**	20.63	18.18	23.68	33.33	All years
Denmark	**Western Europe**	6.35	6.82	26.32	16.67	All years
Finland	**Western Europe**	7.94	6.82	15.79	25.00	All years
France	**Western Europe**	20.63	18.18	26.32	62.50	All years
Germany	**Western Europe**	23.81	20.45	39.47	75.00	All years
Greece	**Western Europe**	1.59	4.55	5.26	20.83	All years
Iceland	**Western Europe**	0.00	0.00	2.63	0.00	2009 only
Ireland	**Western Europe**	7.94	4.55	5.26	4.17	All years
Israel	**Western Europe**	4.76	9.09	15.79	16.67	All years
Italy	**Western Europe**	12.70	13.64	34.21	70.83	All years
Netherlands	**Western Europe**	22.22	15.91	28.95	41.67	All years
Norway	**Western Europe**	3.17	6.82	18.42	16.67	All years
Portugal	**Western Europe**	3.17	4.55	7.89	16.67	All years
Spain	**Western Europe**	9.52	15.91	28.95	50.00	All years
Sweden	**Western Europe**	15.87	18.18	26.32	37.50	All years
Switzerland	**Western Europe**	7.94	13.64	7.89	12.50	All years
Turkey	**Western Europe**	0.00	6.82	7.89	20.83	2004 and on
UK	**Western Europe**	28.57	22.73	44.74	58.33	All years
Canada[l]	**North America**	30.16	18.18	36.84	54.17	All years

Mexico[@]	**North America**	1.59	4.55	5.26	20.83	All years
USA[$]	**North America**	71.43	77.27	73.68	91.67	All years
Argentina	**South America**	1.59	4.55	18.42	33.33	All years
Brazil	**South America**	0.00	9.09	10.53	41.67	2004 and on
Chile	**South America**	0.00	4.55	7.89	37.50	2004 and on
Colombia	**South America**	0.00	0.00	0.00	8.33	2012 only
Costa Rica	**South America**	0.00	0.00	0.00	4.17	2012 only
Ecuador	**South America**	0.00	0.00	2.63	4.17	2009 and 2012
Guatemala	**South America**	0.00	0.00	0.00	4.17	2012 only
Peru	**South America**	0.00	2.27	2.63	12.50	2004 and on
Venezuela	**South America**	0.00	2.27	2.63	0.00	2004 and 2009

Figure Legend

- **Table 1.**
  - **Title** - Total Number of Patients and Pivotal Trials Assessed by Racial Demographics
  - **Caption -** Number of participants from pivotal trials with available racial data that were included within the corresponding category.

- **Figure 1.**
  - **Title -** Number of Countries Hosting Investigator Sites per Pivotal Trial
  - **Caption -** a) All clinical areas b) Individual clinical areas

- **Figure 2.**
  - **Title -** Number of Countries Hosting Investigator Sites per Pivotal Trial
  - **Caption -** a) All clinical areas b) Individual clinical areas

- **Table 2.**
  - **Title -** Racial Composition of Pivotal Trials
  - **Caption -** Percentage of total patients from all included pivotal trials within year and clinical area that were White, Black, Asian, or Other (or unspecified). And range of percentage of racial composition within year and clinical area.

- **Figure 3.**
  - **Title -** World Map of Pivotal Trial Distribution
  - **Caption** – World map detailing changes in global pivotal trial distribution over 15-year period. Numbers are the percentage of pivotal trials within the given year that included a clinical investigator site in country.
  - **Footnotes** :
    - * Hong Kong and Taiwan - grouped separate from China if reported as such in original data
    - $^{!}$ Canada – considered in the “Western Europe and Other state” per UN
    - $^{@}$ Mexico – considered “Latin American and Caribbean state” per UN
    - $^{\$}$ USA – not a member of any UN regional group