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Is there evidence for the racialization of pharmaceutical regulation? Systematic comparison of new drugs approved over five years in the USA and the EU

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ABSTRACT

Recent decades have seen much interest in racial and ethnic differences in drug response. The most emblematic example is the heart drug BiDil, approved by the US Food and Drug Administration in 2005 for "self-identified blacks." Previous social science research has explored this "racialization of pharmaceutical regulation" in the USA, and discussed its implications for the "pharmaceuticalization of race" in terms of reinforcing certain taxonomic schemes and conceptualizations. Yet, little is known about the racialization of pharmaceutical regulation in the USA after BiDil, and how it compares with the situation in the EU, where political and regulatory commitment to race and ethnicity in pharmaceutical medicine is weak. We have addressed these gaps by investigating 397 product labels of all novel drugs approved in the USA ($n = 213$) and the EU ($n = 184$) between 2014 and 2018. Our analysis considered statements in labeling and the racial/ethnic categories used. Overall, it revealed that many labels report race/ethnicity demographics and subgroup analyses, but that there are important differences between the USA and the EU. Significantly more US labels specified race/ethnicity demographics, as expected given the USA's greater commitment to race and ethnicity in pharmaceutical medicine. Moreover, we found evidence that reporting of race/ethnicity demographics in EU labels was driven, in part, by statements in US labels, suggesting the spillover of US regulatory standards to the EU. Unexpectedly, significantly more EU labels reported differences in drug response, although no drug was restricted to a racial/ethnic population in a manner similar to BiDil. Our analysis also noted variability and inconsistency in the racial/ethnic taxonomy used in labels. We discuss implications for the racialization of pharmaceutical regulation and the pharmaceuticalization of race in the USA and EU.

1. Background

The use of racial and ethnic categories in medicine is contentious, especially in countries with a history of scientific racism. In 2005, the US Food and Drug Administration (FDA)—the world's leading drug regulator—approved a race-specific drug, BiDil, for "self-identified blacks" with heart failure, predictably sparking major debate (Dorr and Jones, 2008). The principal trial of BiDil had tested the drug only in African American population, although the FDA also referred to exploratory analyses from two previous trials that "*hinted* at a substantial effect" in black but not white patients (Temple and Stockbridge, 2007: 57; emphasis added). Supporters, including not only FDA scientists and the drug's manufacturer, but also many minority health advocates, portrayed the decision as a breakthrough for medicine and health rights (Temple and Stockbridge, 2007; Rusert and Royal, 2011). Critics, however, accused the FDA of reifying tenuous ideas about race as a biological category based on weak and preliminary evidence (Duster, 2005).

BiDil and the accompanying debate triggered extensive social science research on race/ethnicity and pharmaceutical regulation in the USA (Lee, 2005; Duster, 2006; Epstein, 2007; Lee and Skrentny, 2010; Rusert and Royal, 2011; Roberts, 2011; Kahn, 2012; Pollock, 2012; Inda, 2016). Broadly, this scholarship analyzes two mutually reinforcing processes that together support racial/ethnic prescribing and profiling

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of patients: what we call the "racialization of pharmaceutical regulation" and the "pharmaceuticalization of race" (Fig. 1). Omi and Winant (1986: 111) utilize the term racialization "to signify the extension of racial meaning", including to institutional practices. By "racialization of pharmaceutical regulation" we thus refer to how race and ethnicity become important to drug testing and evaluation, as exemplified by the approval and marketing of BiDil as a race-specific drug (Kahn, 2012). Correspondingly, "pharmaceuticalization" has been defined by Williams et al. (2011: 711) as "the translation or transformation of human conditions, capabilities and capacities into opportunities for pharmaceutical intervention." By "pharmaceuticalization of race" we thus refer to how race and ethnicity become seen as biologically and therapeutically relevant. For example, BiDil's approval was accused of reinforcing US centered taxonomic schemes and geneticized conceptualizations among scientists and prescribers—in this way normalizing ideas that race and ethnicity are integral to the proper pharmaceutical management of patients (Kahn, 2012). Social science scholarship concurs that both processes have been gaining strength, at least in the USA, although scholars disagree on why and how this is happening, and with what consequences (e.g., Kahn, 2012; Pollock, 2012; Inda, 2016).

Whereas a large body of research considers race/ethnicity and pharmaceutical regulation in the USA, comparable research on Europe is scant, and to our knowledge, there is no systematic USA–EU comparison in this area. This gap needs addressing, first, because both the racialization of pharmaceutical regulation and the pharmaceuticalization of race may present differently in Europe. Indeed, much empirical and theoretical work has focused on BiDil, but the European Medicines Agency (EMA) never approved this drug. Second, international comparison may shed more light on these processes, even in the USA, consistent with how sociologists have researched pharmaceutical regulation more generally (Davis and Abraham, 2013).

We therefore sought to investigate the racialization of pharmaceutical regulation, alongside its implications for the pharmaceuticalization of race, using an international comparative methodology. We did this through systematically comparing regulator-approved statements about race and ethnicity for all new drugs over a five-year period. Specifically, we analyzed each drug's US and EU labels for statements about race and ethnicity. The label is an obligatory regulatory document whose stated purpose is to convey clear, structured, and relevant drug information to healthcare professionals. In the EU, the label is known as the Summary of Product Characteristics, but we use the term "label" for consistency between the EU and the USA. The label is initially drafted by the drug's manufacturer based on the results of studies performed to support marketing authorization, and is then reviewed by the regulators as part of the product assessment process (Mulinari and Davis, 2020). Crucially, in selecting a comprehensive and comparative drug sample to study race/ethnicity and pharmaceutical regulation, we deviated from typical social science research on this topic, which has centered on selected drug cases, predominantly from the USA.

1.1. Policy background and literature review

One key insight from the social science scholarship referred to above is that the racialization of pharmaceutical regulation should be understood in relation to the particularities of identity and government politics in the USA. More specifically, Epstein (2007) showed how mobilization concerning minority health rights (and women's health rights) has paved the way for an "inclusion-and-difference paradigm" in US biomedicine since the 1990s. In US pharmaceutical regulation, this paradigm is evidenced by the comprehensive guidance developed over the last 30 years pertaining to race and ethnicity. A key example is the FDA's (2005) guidance "Collection of Race and Ethnicity Data in Clinical Trials," updated in 2016, which specifies the usage of US race and ethnicity census categories. The FDA's commitment in this area is further demonstrated by the Administration's internal structure (e.g., the Office of Minority Health and Health Equity), operating procedures, and research seeking to ensure that consideration of inclusion and difference permeates the Administration's work (e.g., Huang and Temple, 2008: Ramamoorthy et al., 2015). The latest strong political pressure on the FDA in this area came in 2012 when Congress passed the FDA Safety and Innovation Act (FDASIA), in which Section 907 required that the FDA assess the extent of clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups, including race and ethnicity. Congress also directed the FDA to develop an Action Plan for enhancing the collection and availability of demographic subgroup data. Among other things, this Action Plan identified potential methods for consistently communicating meaningful demographic subgroup information, including using a "standard set of concise statements" in product labeling (FDA, 2014: 15).

Contrastingly, the EMA has not established any equivalent Agency documents and structures, nor has it signaled strong commitment to race and ethnicity through publications and commentary. The EMA refers to the ICH-E5 document, "Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data" (EMA, 1998). ICH-E5 was developed by regulators and industry in the EU, the USA, and Japan, and was adopted by the respective regulators in 1998 as part of an effort to harmonize requirements for drug development and regulation under the auspices of the International Conference on Harmonization (ICH). The purpose of ICH-E5 was to reduce barriers to registration of drugs in the different jurisdictions "by recommending a framework for evaluating the impact of ethnic factors upon a medicine's effect" (EMA, 1998: 3). However, Kuo (2008: 500) described ICH-E5 as "one of the most troublesome points of contention in the history of the ICH" due to clashes between the country representatives' divergent concepts of race and ethnicity. The EU did not want to "overemphasize diversity" between races; the USA wanted to consider race a potentially important variable, but "hoped [that] the US [racial and ethnic] standards would be accepted as universal"; and Japan emphasized that the uniqueness of its population meant that the Japanese could not be subsumed under a diverse "Asian race," as the US standards would have it, meaning that drugs should be tested separately on Japanese (Kuo, 2008: 502). Despite the reported little EU interest and opposition from Japan, the final ICH-E5 document suggested that difference could be gauged at the level of three "major racial groups," i.e., Asians, Blacks, and Caucasians (EMA, 1998: 14).

The connection to the pharmaceuticalization of race is obvious because emphasis on using a set of standard categories, i.e., Asians, Blacks, and Caucasians, produces fertile ground for promoting certain race and ethnicity classifications and conceptualizations in medicine, and even beyond. Indeed, Kahn (2008: 737), citing the example of BiDil, argued that race considerations within pharmaceutical medicine have the "power to promote a regeneticization of racial categories in society at large." Similarly, Duster (2005: 1051) warned that, as part of a new

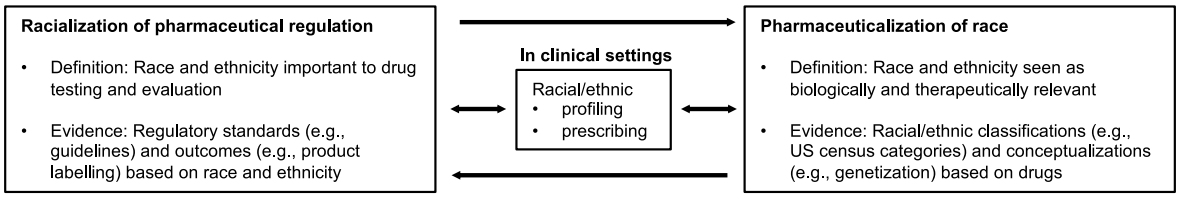

Fig. 1. "Racialization of pharmaceutical regulation" and "Pharmaceuticalization of race": definitions, outcomes and reciprocal relations.

arsenal of race-based medical technologies, BiDil is "poised to exert a cascading effect—reinscribing taxonomies of race across a broad range of scientific practices and fields." However, Rose (2007: 167) maintained that the re-inscription of race as biological—including in the case of BiDil—has little to do with the racial science of the past; rather, contemporary biology of race is probabilistic, as opposed to deterministic, and "does not seek to legitimate racial inequalities but to intervene upon its consequences."

Much of this debate hinges on the example of BiDil, because the drug offers the most vivid case of the re-inscription of race as biological (Friese, 2015). This is not to say that other cases have not been brought up: Duster (2006) refers to Iressa, Kahn (2009) to Bystolic and Warfarin, and Roberts (2011) to Travatan and Crestor—all of which fall into the regulatory category of "ethnically sensitive" drugs (EMA, 1998), though it is unclear how representative those cases are of drugs in general. This recalls the point made by Fisher et al. (2015) regarding the selection biases that haunt much case-study-based sociological research on drugs.

However, Fisher et al. (2015) also highlighted a separate stream of policy-oriented scholarship that does examine broader trends using larger drug samples, and from which sociologists can draw methodological and empirical insights. In the context of race and ethnicity, such policy-oriented research has mainly been conducted by the regulators themselves (Evelyn et al., 2001; Huang and Temple, 2008; Ramamoorthy et al., 2015; Maliepaard et al., 2019). Crucially, like the present study, those studies have examined racial/ethnic drug labeling, albeit not for recently approved drugs. They have shown that many drugs were approved with information on race and ethnicity in their labels, but that few labels contained recommendations or warnings based on race and ethnicity. Yet again, most of this research pertains to the USA, with little research on Europe (Maliepaard et al., 2019); moreover, as far as we know, no systematic US–EU comparison has been conducted.

Another key insight from regulators' studies is that if a label does not address race and ethnicity, this does not mean that such data have not been collected or analyzed but that, for whatever reason, it was deemed insufficiently meaningful to be included, or that the subgroup sample sizes were too small. Notably, the matter of small subgroup samples are particularly common for rare disease drugs (so-called orphan drugs) as regulators often permit smaller clinical studies for such drugs (FDA, 2013). The proportion of orphan drug approvals has been steadily increasing (Darrow et al., 2020), following the more general "neoliberal" regulatory trend toward the approval of some new drugs based on significantly less clinical trial evidence to boost commercial innovation (Davis and Abraham, 2013), which is likely to work against meaningful racial/ethnic subset analyses. This point is important as it suggests a need to consider trends in drug development and regulation other than those directly related to race/ethnicity to understand the racialization of pharmaceutical regulation and the pharmaceuticalization of race. Specifically, for our purposes, it suggests that other trends can, unintentionally, work "for" or "against" racial/ethnic drug labeling.

1.2. Hypotheses

We will test four hypotheses informed by review of the existing scholarship.

Hypothesis 1. We expect US labels to more often include information on race and ethnicity than do EU labels because of the FDA's long-standing commitment to the "inclusion-and-difference" paradigm. However, because of globalization and the harmonization of drug testing and regulation (e.g., ICH), we also expect some degree of concordance between US and EU labels.

Hypothesis 2. Regarding possible mechanisms of concordance, we speculate that statements in EU labels may be modeled on statements in US labels in the absence of strong EMA commitment to race and ethnicity. Should this be the case, we anticipate a higher rate of race and ethnicity statements in EU labels of drugs already approved by the FDA with such labeling, but not the opposite, because the FDA will impose its own standards irrespective of what the EMA said before.

Hypothesis 3. In terms of explaining possible absences of race and ethnicity statements in labels, we expect labels of orphan drugs to be less likely to contain such statements because of the generally smaller clinical trials of such drugs, and hence smaller subgroup samples, impeding relevant comparison between subgroups.

Hypothesis 4. We expect the US race and ethnicity census standard to be used consistently in both US and EU labeling, because of the FDA clinical trial data collection guidelines and the absence of competing EMA guidelines.

2. Methods

2.1. Approach to testing the hypotheses

Another insight from regulators' policy-oriented research is the importance of distinguishing *different kinds of labeling statements about race and ethnicity*. First, there are two distinct study types reported in two separate label sections. (1) Efficacy and safety studies assessing *clinical endpoints*—often in many patients at late stages in drugs' development program. (2) Clinical pharmacology studies assessing *pharmacological endpoints* (i.e., drug absorption, metabolism, distribution and excretion, and pharmacogenetics)—often in fewer patients earlier in drugs' development program. Second, for each of these two types, there can be statements about: (A) study demographics, (B) subgroup analyses, (C) subgroup differences, and (D) treatment recommendations (e.g., changed doses).

Such distinctions have important methodological implications for this study. First, they permit a better understanding of precisely what kinds of statements about race and ethnicity are made (e.g., differences in safety or drug metabolism), how often they are made, and what taxonomies are used. Second, such distinctions are important because they allow us to refine the formulation and testing of our hypotheses. For Hypothesis 1, we test, for example, whether the FDA is more likely to emphasize race and ethnicity study demographics *and* differences between subgroups, and whether the pattern is the same for the efficacy and safety *and* clinical pharmacology sections.

2.2. Sample and coding

We selected all "novel drugs" approved by the FDA and EMA over the five-year period, 2014–2018, subsequent to the most recent FDA analysis (Ramamoorthy et al., 2015). The definition of "novel drug" differs between the FDA and EMA. The FDA definition encompasses all "new molecular entities" (i.e., new single-ingredient or combination drugs) and "therapeutic biologics applications" (e.g., antibodies, enzymes, and cytokines), but excludes vaccines and cellular and gene therapy products ($n = 213$). The EMA definition encompasses all drugs classified as "new active substances" ($n = 184$), which also includes vaccines and cellular and gene therapy products. Overall, 124 drugs were designated as "novel" by both the FDA and EMA in 2014–2018. We considered all "novel" drugs as well as the subset approved by both regulators for the direct comparisons between the USA and EU.

For each "novel drug," we checked its orphan designation at the time of approval in the USA and the EU. We also checked the dates of FDA approval and of EMA Committee for Medicinal Products for Human Use (CHMP) recommendation to see which agency first approved or recommended the drug. We used the date of the CHMP recommendation rather than of European Commission (EC) approval because the EC approval is a formality. Drugs' original labels were downloaded from the FDA and EMA websites and imported into NVivo. We coded the (1) efficacy/safety and (2) clinical pharmacology sections separately for the presence and absence of statements about racial/ethnic (A)

demographics, (B) subgroup analyses, (C) subgroup differences, and (D) treatment recommendations. We also coded both sections for racial/ethnic categories (e.g., White and Asian).

2.3. Statistical analysis

We tested Hypothesis 1 in two ways. First, we compared the frequency of different kinds of statements (i.e., A–D) in US and EU labels' efficacy/safety and clinical pharmacology sections by calculating relative risks (RRs) and their 95% confidence intervals (95% CIs). Second, we assessed the categorical agreement (i.e., including or not including the different kinds of statements) between US and EU labels for the same drug using Cohen's kappa, often used to calculate inter-rater reliability. A Cohen's kappa of 1 represents perfect inter-rater reliability, meaning that the US and EU labels always agree on the inclusion or not of race/ethnicity statements, although the statements did not have to be similar.

We tested Hypothesis 2 by comparing the frequency of the different kinds of race/ethnicity statements for drugs with FDA approval first versus drugs with CHMP recommendation first. We tested Hypothesis 3 by comparing the frequency of the different kinds of race/ethnicity labeling statements for drugs with and without orphan status. For both analyses, we did not separately analyze the efficacy/safety and clinical pharmacology sections, but instead combined the sections, because some groups would be very small otherwise. To assess the magnitude of differences, we calculated RRs and their 95% CIs.

We tested Hypothesis 4 by separately assessing the frequency of the different kinds of race/ethnicity categories in the efficacy/safety and clinical pharmacology sections. For this analysis, we included all drugs (US = 213, EU = 184), rather than only the 124 approved by both regulators over the study period, because we did not make direct US–EU comparisons due to the few observations for most race/ethnicity categories.

2.4. Analysis of regulatory documents

We analyzed two kinds of documents to investigate possible reasons for discordances between the FDA and EMA regarding race/ethnicity labeling. First, we reviewed FDA and EMA labeling guidelines pertaining to the efficacy/safety and clinical pharmacology sections, focusing on instructions regarding race and ethnicity (FDA, 2006, 2016; European Commission, 2006). Second, we analyzed FDA reviews and European Public Assessment Reports (EPARs) for drugs whose US and/or EU labels had statements about differences between racial and ethnic groups (n = 20). FDA reviews and EPARs are publicly available and provide more detailed information about the drug and the regulatory assessment process. We used this information together with the labeling to generate, inductively, possible explanations for the observed differences in labeling.

3. Results

3.1. Race and ethnicity labeling guidelines

We begin by describing labeling guidelines regarding race and ethnicity, as they constitute the most proximate regulatory instructions relevant to the data presented below, and they differ slightly between the FDA and EMA.

For the main efficacy/safety section, both regulators recommend that manufacturers report study demographics, but only the FDA is explicit that this refers to, among other things, race/ethnicity. Regarding subgroup analyses, the EMA says that they should only be included in the labeling in those "exceptional cases" in which they are clinically relevant. Still, the EMA's accompanying instruction material offers an example of such an "exceptional case": "Subgroup analysis revealed a difference in treatment success where 27% of non-white women and 39% of white women showed a marked or better improvement," clearly showing that it considers race/ethnicity subgroup analyses relevant.

The FDA guideline sets a lower threshold as it recommends reporting subgroup analyses if they "had a reasonable ability to detect subgroup difference." Alternatively, the FDA recommends that it should be noted "when analyses were not useful because of inadequate sample size," for example, by including the statement: "There were too few African-American subjects to adequately assess differences in effects in that population."

For the clinical pharmacology section, the FDA requires a heading on effects in "Specific Populations," which "should include results of studies or analyses that evaluate the potential for PK [i.e., pharmacokinetic] differences in subpopulations defined by age, sex, race/ethnicity, renal function, hepatic function, and pregnancy." The FDA also recommends a specific "Racial or Ethnic Groups" subheading, if such studies have been conducted, which should contain "descriptions and results of studies and analyses conducted to identify differences in PK among race/ethnicity groups."

The EMA also asks for information on the pharmacokinetic "characteristics in specific groups of subjects." Strikingly, however, the EMA refrains from mentioning race/ethnicity in the list of relevant variables: "age, weight, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic disease, including degree of impairment." Still, in its accompanying instruction material, the EMA offers this example of an appropriate subheading and statement: "*Race* There was a slight decrease (16%) in the AUC [area under the plasma concentration time curve] and C_{max} [peak plasma concentration] of active substance X in Black subjects relative to Caucasian subjects. However, the safety profile of active substance X between the Black and Caucasian subjects was similar."

Overall, the FDA is explicit about including race and ethnicity information in the label. The EMA refrains from making explicit recommendations, though they are implicit because of the examples provided. Nonetheless, the lack of explicit EMA recommendations on reporting race/ethnicity data and subgroup analyses, together with the statement that subgroup analyses of safety and efficacy should only be provided in *exceptional* cases, is consistent with the idea that US labels should more often include race and ethnicity information, i.e., Hypothesis 1.

3.2. Hypothesis 1: regarding differences in race/ethnicity labeling for novel drugs

The FDA approved 213 novel drugs between 2014 and 2018, of which 89.2% (190) had one or more race/ethnicity labeling statement, versus in 75.5% (139) of EU labels for 184 novel drugs (RR = 1.18, 95% CI 1.07–1.30) (Table 1). The difference between US and EU labels was explained by about 80% more US labels mentioning race/ethnicity demographics in their efficacy and safety section (RR = 1.81, 95% CI 1.52–2.16).

Although significantly more US than EU labels contained statements on race/ethnicity demographics, this did not translate into more US labels reporting race/ethnicity subgroup analyses. Actually, a slightly higher proportion of EU labels reported race/ethnicity subgroup analyses (EU: 62.5% vs. US: 59.6%), usually pertaining to drugs' clinical pharmacological properties (EU: 57.6% vs. US: 55.9%), albeit typically stating that race or ethnicity had no significant or meaningful effect (EU: 48.3% vs. US: 49.8%). None of these differences between EU and US labels was statistically significant. What was clear, however, was that EU labels—unexpectedly—were almost twice as likely to report *differences* between racial/ethnic groups (RR = 1.98, 95% CI 1.06–3.72). Overall, the EMA and FDA approved ten and two labels, respectively, with statements about racial/ethnic differences in safety, one and zero about differences in efficacy, and 16 and 13 about differences in clinical pharmacology. However, no drug label had a treatment recommendation based on race or ethnicity.

The results were similar for the 124 drugs approved in both regions over the study period (Table 1). Thus, 83.1% (103) of US labels and

Table 1
Race/ethnicity statements in labels of novel drugs approved by the FDA and EMA, 2014–2018.

	All drugs			Subset approved by both FDA and EMA		
	US (n = 213)	EU (n = 184)	RR (95% CI)	US (n = 124)	EU (n = 124)	RR (95% CI)
Any statement in label	190 (89.2%)	139 (75.5)	**1.18 (1.07–1.30)**	114 (91.9)	105 (84.7)	1.09 (0.99–1.19)
Demographics	171 (80.3)	87 (47.3)	**1.70 (1.44–2.00)**	104 (83.9)	64 (51.6)	**1.63 (1.34–1.96)**
Subgroup analyses	127 (59.6)	115 (62.5)	0.95 (0.82–1.12)	84 (67.7)	93 (75.0)	0.90 (0.77–1.06)
Difference reported	14 (6.6)	24 (13.0)	**0.50 (0.27–0.94)**	8 (6.5)	18 (14.5)	**0.44 (0.20–0.98)**
Treatment recommendation	0	0	N/A	0	0	N/A
Any efficacy and safety	175 (82.2)	96 (52.2)	**1.57 (1.36–1.83)**	106 (85.5)	72 (58.1)	**1.47 (1.25–1.74)**
Demographics	170 (79.8)	81 (44.0)	**1.81 (1.52–2.16)**	103 (83.1)	59 (47.6)	**1.75 (1.42–2.13)**
Subgroup analyses	26 (12.2)	34 (18.5)	0.66 (0.41–1.06)	20 (16.1)	29 (23.4)	0.69 (0.41–1.15)
Difference reported	2 (0.9)	10 (5.4)	**0.17 (0.04–0.78)**	2 (1.6)	7 (5.6)	0.29 (0.06–1.35)
Any clinical pharmacology	131 (61.5)	116 (63.0)	0.98 (0.84–1.14)	84 (67.7)	90 (72.6)	0.93 (0.79–1.10)
Demographics	11 (5.2)	9 (4.9)	1.06 (0.45–2.49)	6 (4.8)	6 (4.8)	1.00 (0.33–3.02)
Subgroup analyses	119 (55.9)	106 (57.6)	0.97 (0.82–1.15)	79 (63.7)	85 (68.5)	0.93 (0.78–1.11)
Difference reported	13 (6.1)	16 (8.7)	0.70 (0.35–1.42)	7 (5.6)	13 (10.5)	0.54 (0.22–1.30)

Statistically significant difference in bold.

47.6% (59) of EU labels mentioned race/ethnicity demographics in their safety and efficacy section (RR = 1.75, 95% CI 1.42–2.13). Furthermore, more EU than US labels reported race/ethnicity subgroup analyses, though the differences were not statistically significant (EU: 75.0% vs. US: 67.7%). Finally, more EU than US labels reported differences between racial/ethnic groups (EU: 14.5% vs. US: 6.5%; RR = 2.25, 95% CI 1.02–4.98). Overall, for the 124 drugs, the EMA and FDA approved seven and two labels, respectively, reporting differences in safety, none in efficacy, and 13 and seven in clinical pharmacology.

Among the 124 novel drugs approved by both regulators there were many discordant pairs, i.e., for which US and EU labels for the same drug diverged regarding the inclusion of information on race/ethnicity (Table 2). Discordances were highest for the inclusion of race/ethnicity study demographics (e.g., κ = 0.28, 95% CI 0.16–0.40, for safety and efficacy). However, there were also many discordant pairs for race/ethnicity subgroup analyses (e.g., κ = 0.46, 95% CI 0.30–0.62, for clinical pharmacology).

There were seven cases (involving six drugs) in which a drug's EU *and* US labels reported racial/ethnic differences, and there were 15 cases (involving 14 drugs) in which EU and US labels diverged in this respect. Details of these concordances and discordances are provided in Supplementary Tables 1 and 2.

We identified three possible, non-mutually exclusive reasons that increase the likelihood of EU labels reporting differences compared with US labels.

Table 2
Concordance and discordance in the inclusion of information on race/ethnicity in US and EU drug labels, 2014–2018.

	Concordant		Discordant		κ (95% CI)
	Included in both US and EU labels	Absent from both US and EU labels	Included only in US label	Included only in EU label	
Efficacy and safety					
Demographics	58	20	45	1	0.28 (0.16–0.40)
Subgroup comparison	13	88	7	16	0.42 (0.23–0.61)
Difference reported	2	117	0	5	0.43 (0.03–0.83)
Clinical pharmacology					
Demographics	0	112	6	6	−0.05 (−0.08 to −0.02)
Subgroup comparison	67	27	12	18	0.46 (0.30–0.62)
Difference reported	5	109	2	8	0.46 (0.18–0.74)

1. *The EMA is more willing to include claims of differences considered clinically non-meaningful.* This happened with six of the 12 drugs that had differences included only in EU labels. For example, the letermovir label in the EU states: "Based on popPK [population pharmacokinetic] analyses, letermovir AUC is estimated to be 33.2% higher in Asians compared to Whites. *This change is not clinically relevant* (emphasis added)." Moreover, EU labels for empagliflozin, daclatasvir, ixazomib, palbociclib, and nintedanib reported differences that both the FDA and EMA agreed were uncertain or unlikely to be clinically relevant. However, the opposite happened for isavuconazole, for which the FDA included a statement about differences acknowledged by both regulators as unlikely to be clinically relevant. Furthermore, some statements about racial/ethnic differences found in both US and EU labels for the same drug were acknowledged to be clinically non-meaningful, specifically for naloxegol and vorapaxar (see Supplementary Table 1).
2. *The FDA sometimes rejects company claims about the impact of race/ethnicity.* This happened with two of 12 drugs: nintedanib and ixazomib. For nintedanib, the FDA rejected the company's argument because, first, the company had varyingly classified Asian Indians as "Caucasians" and "Asians" and, second, because of unexplained large differences between Asian patients from different countries. The EMA, contrastingly, included the company's claims of differences in the label, although noting that the differences were not clinically relevant (see Supplementary Table 2).
3. *The FDA tends to approve drugs earlier, which means it has fewer data and is therefore less able to assess differences* (see more below). For most drugs, we identified the same or very similar analyses in FDA reviews and EPARs. For one drug, tedizolid, the EMA referred to a study not submitted to the FDA, likely because it was unavailable when the FDA reviewed the marketing application.

3.3. Hypothesis 2: regarding effect of jurisdiction of first approval on race/ethnicity labeling

Of the 124 drugs approved in both regions over the study period, 65% (80) were approved by the FDA before a positive CHMP recommendation (median = 139 days before, interquartile range [IQR] = 230, min = 1, max = 1557). Conversely, 35% (44) had a positive CHMP recommendation before FDA approval (median = 59 days before, IQR = 137, min = 1, max = 1120). Drugs approved by the FDA first were more likely to have race/ethnicity statements in their US and EU labels, but the only conclusive difference was seen for the inclusion of demographic information in EU labels (RR = 1.80, 95% CI 1.15–2.81) (Table 3). Strongly supporting the idea that demographics statements in EU labels are sometimes modeled on statements in US labels, we found that among the 58 drugs for which there were safety and efficacy trial demographic information in both their US and EU labels (see Table 2), 31.0% (18) had

Table 3
Race/ethnicity statements in labels of novel drugs approved in both the USA and EU, 2014–2018, by initial jurisdiction of approval.

	FDA first (n = 80)	CHMP first (n = 44)	RR (95% CI)
US labels			
Any demographics	71 (88.8%)	33 (75.0)	1.18 (0.98–1.43)
Any subgroup comparison	56 (70.0)	28 (63.6)	1.10 (0.84–1.43)
Any difference	7 (8.8)	1 (2.3)	3.85 (0.49–30.3)
EU labels			
Any demographics	49 (61.3)	15 (34.1)	**1.80 (1.15–2.81)**
Any subgroup comparison	63 (78.8)	30 (68.2)	1.16 (0.92–1.46)
Any difference	13 (16.3)	5 (11.4)	1.43 (0.55–3.75)

Statistically significant difference in bold.

identical or very similar statements about trial demographics and 88.8% (16) of those drugs were approved by the FDA first.

3.4. Hypothesis 3: Regarding effect of orphan designation on race/ethnicity labeling

Of the 124 drugs approved in both regions over the study period, 43.5% (54) had orphan designation in the USA and 28.2% (35) in the EU at their time of approval. In both the USA and the EU, orphan drugs were significantly less likely to have statements about race/ethnicity subgroup analyses (Table 4). Nevertheless, there was no apparent association between orphan status and inclusion of race/ethnicity demographics statements in the label. The results were the same regardless of whether the US or EU orphan designation was used to group labels.

3.5. Hypothesis 4: regarding racial and ethnic taxonomy in drug labels

We assessed the use of race/ethnicity categories in all US (n = 213) and EU (n = 184) labels. We identified 72 different categories that we grouped into six higher-level classes (Table 5). White categories (e.g., Caucasian) were by far the most common, followed by Asian (e.g., Japanese) and Black (e.g., African American).

Supplementary Table 3 provides the detailed breakdown of the 72 racial/ethnic categories used. The most common categories in both US and EU labels were, in descending order, White, Asian, Caucasian, Black, Black/African American, and Other. Together, those six categories accounted for the great majority of coded cases in US and EU labels, suggesting a high level of standardization of terminology based on US census categories. However, many other categories were used infrequently, showing substantial room for non-standard taxonomy. Forty-one of 72 categories occurred only once and eight categories only twice across all US and EU labels. The majority (25 of 49) of rare categories belonged to the class "other or multiple or unknown." The Asian and Black classes also contained numerous rare categories. For the Black class, the rare categories mainly represented different ways of describing Blacks; however, for the Asian class, they represented subgroups defined by geography or descent, for example, non-Japanese Asian.

Regarding the White class, we found evidence that White and Caucasian were sometimes used interchangeably. Thus, 20 drug labels used both categories when referring to safety and efficacy trials, typically when describing populations of two or more trials, and there were three cases in which White/Caucasian was used. There were also striking differences in the use of White and Caucasian. We observed a tendency to prefer White when describing the clinical trials for efficacy and safety (EU: White 25.0%, n = 46 vs. Caucasian 15.8%, n = 29, RR = 1.59, 95% CI 1.04–2.41; US: White 52.1%, n = 111 vs. Caucasian 30.5%, n = 65, RR = 1.71, 95% CI 1.34–2.17). In contrast, more labels used Caucasian than White in their clinical pharmacology sections, though the differences were not statistically significant. This suggests that White is preferred over Caucasian for describing the racial composition of safety and efficacy trials, but not for clinical pharmacology comparisons in which both terms are used to a relatively similar degree.

Interestingly, categories in the Asian class were common in clinical pharmacology sections. Indeed, some labels described comparisons between Asian populations, but no label described comparisons within other "races." For example, the US label for apalutamide states "No clinically significant differences in the pharmacokinetics of apalutamide or N-desmethyl apalutamide were observed based on … race (Black, non-Japanese Asian, Japanese)." Yet, contradictorily, Japanese were also frequently treated as representatives of the Asian race. For example, the EU label for olaparib states: "In population-based PK analyses … race (including White and Japanese patients) were not significant covariates." However, in other instances, Japanese (and other Asian subgroups) were grouped into an East Asian racial group. For example, the US label for avatrombopag states: "race [Whites, African Americans, and East Asians (i.e., Japanese, Chinese, and Koreans)] … did not have clinically meaningful effects on the pharmacokinetics of avatrombopag."

Finally, the Other/Multiple/Unknown class was also frequent in clinical pharmacology sections. This seems to reflect analyses wherein several categories are combined in a non-standard way, possibly to get a sufficient sample size, for example, non-Asian to compare with Asian.

4. Discussion

4.1. Implications for the racialization of drug regulation

So far, the racialization of drug regulation has been mainly explored through case studies of drugs or policy analysis, primarily in the USA. Here, we have shown how racialization is taking place across a greater range of drugs, and in Europe, too. Nevertheless, we also found striking differences between the USA and the EU, suggesting that the racialization of pharmaceutical regulation differs between the two regions.

We found that US and EU drug labels almost always contain racial and ethnic demographic information and/or statements about subgroup analyses, but that, in line with Hypothesis 1, race/ethnicity labeling was

Table 4
Race/ethnicity statements in labels of new drugs approved in both the USA and EU, 2014–2018, by US and EU orphan designation.

	US non-orph. (n = 70)	US orph. (n = 54)	RR (95% CI)	EU non-orph. (n = 89)	EU orph. (n = 35)	RR (95% CI)
US labels						
Any demographics	56 (80.0%)	48 (88.9)	0.90 (0.77–1.05)	75 (84.3)	29 (82.9)	1.02 (0.85–1.21)
Any subgroup comparison	55 (78.6)	29 (53.7)	**1.46 (1.11–1.93)**	67 (75.3)	17 (48.6)	**1.55 (1.08–2.22)**
Any difference	7 (10)	1 (1.9)	5.40 (0.68–42.6)	7 (7.9)	1 (2.9)	2.75 (0.35–21.57)
EU labels						
Any demographics	31 (44.3)	33 (61.1)	0.72 (0.52–1.02)	47 (52.8)	17 (48.6)	1.09 (0.73–1.61)
Any subgroup comparison	59 (84.3)	34 (63.0)	**1.34 (1.07–1.68)**	73 (82.0)	20 (57.1)	**1.44 (1.06–1.94)**
Any difference	12 (17.1)	6 (11.1)	1.54 (0.62–3.85)	15 (16.9)	3 (2.9)	1.97 (0.61–6.38)

Statistically significant difference in bold.

Table 5
Higher-level racial/ethnic classes in US and EU labels for new drugs, 2014–2018.

Racial/ethnic classes	*n* categories	Example	US labels ($n = 213$)		EU labels ($n = 184$)	
			Eff./saft.	Clin. pharm.	Eff./saft.	Clin. pharm.
Asian	14	Japanese	80 (37.6%)	31 (14.6)	42 (22.8)	28 (15.2)
Black	11	African American	81 (38.0)	25 (11.7)	37 (20.1)	14 (7.6)
Latino	4	Hispanic	33 (15.5)	5 (2.3)	14 (7.6)	3 (1.6)
Native American	2	American Indian/Alaska Native	7 (3.3)	0	1 (0.5)	0
Other/multiple/unknown	30	non-Black	35 (16.4)	19 (8.9)	25 (13.6)	24 (13.0)
White	11	Caucasian	163 (76.5)	47 (22.1)	75 (40.8)	33 (17.9)

much more common in the USA. This difference was explained by about 60% more US labels having race/ethnicity demographic information regarding safety and efficacy trials. Furthermore, compared with comparable studies of earlier periods, we found a greater proportion of US labels with race/ethnicity demographic information, suggesting that the emphasis on including such information has increased over time in the USA. For example, in 2004–2007, 46% (37/81) of US labels contained race/ethnicity demographic information (Huang and Temple, 2008), versus 80% (171/213) in our 2014–2018 sample.

Although most US labels had safety and efficacy trial race/ethnicity demographics, few reported subgroup analyses for these trials. Here, it is important to recall that subgroup analyses have likely been submitted by manufacturers and assessed by regulators even though they are not reported in labels (FDA, 2013). However, without information on subgroup analyses, the reported trial demographics are not particularly informative to prescribers. Therefore, much of the race/ethnicity labeling seems to primarily reflect the policy emphasis on the *inclusion* of racial/ethnic groups in the trials. Importantly, the issue of racial/ethnic diversity in clinical trials is paid high-level political and scientific attention in the USA in a manner and with an intensity not seen in Europe, as shown, for example, when Congress passed FDASIA in 2012. Therefore, the frequent and increasing reporting of race/ethnicity demographics in US labels is unsurprising.

However—and for all the same reasons—it seems odd at first that very few US labels (only about 5%) reported race/ethnicity demographics in their clinical pharmacology sections, especially considering that this section is where subgroup analyses are most often reported (about 55% of labels). However, as Fisher and Kalbaugh (2011) noted, the debate about inclusion has almost exclusively focused on safety and efficacy trials. The debate has largely ignored earlier-stage trials in which much of the clinical pharmacology analyses are conducted (and in which minorities might actually be overrepresented). Consistent with this interpretation, FDASIA directed the FDA to consider the inclusion and reporting of *safety and effectiveness* data, but not clinical pharmacology data, by subgroup (FDA, 2013).

Still, however, almost half of EU labels contained racial/ethnic demographic information *without* US-style political pressure being applied on the EMA and without strong Agency commitments to this issue. We suggest that one mechanism that can explain the reporting of race/ethnicity information on EU labels is via the transposition of US reporting standards (Hypothesis 2). Consistent with this hypothesis, we found that the probability of reporting race/ethnicity demographic information on EU labels was 80% higher for drugs already approved in the USA. Furthermore, we found that statements about racial/ethnic demographics in drugs' EU labels are sometimes modeled on statements in their US labels. This is important, demonstrating how regulatory developments in the USA potentially spill over to other regions.

All this still cannot explain why numerically more EU labels referred to subgroup analyses and, importantly, why significantly more EU labels reported racial/ethnic differences. It seems that although the FDA puts greater emphasis on showcasing *inclusion* than does the EMA, it is less keen on reporting *differences*. This finding was unexpected given the government-imposed racial and ethnic census standard promulgated by the FDA (2005), strongly contrasting to the political and cultural "ban" on race or ethnicity within official statistical apparatuses in many European countries (Simon, 2012) and to the lack of strong EMA guidance on, and commitment to, race and ethnic data collection and analysis. Why the EMA seems more open to communicating differences is not entirely clear, but Mulinari and Davis's (2017) research on institutionalized regulatory review practices suggested that, at least in the past, the FDA conducted more penetrating product reviews and was more concerned about the statistical perils of subgroup analyses than European regulators—false positives due to multiple comparisons. Supporting this interpretation, we also found evidence of the FDA sometimes challenging companies' assertions about racial/ethnic differences. However, discordances between the FDA and EMA can also be expected simply due to time-dependent differences in data availability or maturity (Kashoki et al., 2020), specifically, that the FDA more often approves drugs before the EMA. Yet, our analyses of FDA reviews and EPARs did not highlight this as a likely explanation for most of the discordances considered. Instead, many discordances appeared to reflect the FDA being more careful about promulgating ideas about differences without a clear therapeutic rationale for doing so. We hypothesize that the FDA's higher threshold for including statements about differences—which may appear paradoxical in light of the Administration's greater emphasis on race and ethnicity—is because the FDA considers that such statements can and should influence prescriber behavior.

Another key finding is that orphan drugs' labels had a significantly lower probability of including subgroup analyses in both the USA and the EU. This was predicted (Hypothesis 3) because many orphan drugs are approved based on small studies, which may impede making racial/ethnic comparisons (FDA, 2013). From the sociological perspective, this finding is critical because it suggests the opposing effects on racialization of two parallel regulatory reform programs—each underpinned by its own social, political, and organizational processes—namely, the "neoliberal reform" of drug regulation to boost commercial innovation, including by loosening evidential requirements for certain classes of drugs (Davis and Abraham, 2013), and the "inclusion-and-difference" paradigm seeking to ensure that racial/ethnic diversity is given high priority in the testing and regulation of drugs (Epstein, 2007).

4.2. Implications for the pharmaceuticalization of race

The pharmaceuticalization of race implies that drugs have important consequences for understandings and practices related to race and ethnicity in medicine, and even in society at large. Our data, together with previous analyses of drug labeling (e.g., Ramamoorthy et al., 2015), shed further light on this process. First, from a pharmaceuticalization of race perspective, it matters whether most drugs are approved with claims of population differences that are interpreted as biologically or therapeutically meaningful, versus whether such claims are rare. In particular, if they are very rare, it would provide less evidence of either a "molecular re-inscription" (Duster, 2006), "regenetication" (Kahn, 2008), or "molecularization" (Rose, 2007) of race. The truth of the matter is that while race and ethnicity data are routinely collected and analyzed, over the last two decades, very few drugs have been approved with recommendations of differential treatment due to race/ethnicity, and no drug has been restricted to a racial/ethnic population in a

manner similar to BiDil. Therefore, the pharmaceuticalization of race might have been overstated. In particular, predictions of a growing number of race-based products (Kahn, 2016) or differential results by race (Bliss, 2012) are not supported.

Of course, the pharmaceuticalization of race cannot be reduced to the number drugs that are approved with race-based recommendations or claims of population differences. Specifically, the routine report of race/ethnicity demographics and analyses may prime prescribers to believe that race and ethnicity are biologically and therapeutically meaningful *even* when labels suggest no differences and particularly when they assert minor or ambiguous differences. Furthermore, studies conducted once a drug is on the market might reveal racial/ethnic differences that are interpreted as biologically and therapeutically meaningful. However, quantitative evidence suggests that such cases are relatively rare. Thus, a recent study of 928 Cochrane reviews of medical interventions showed that only one reported race and ethnicity subgroup analyses, and that study was about the effect of diet and physical activity in diabetics, not a pharmaceutical intervention (Liu et al., 2020).

Second—and perhaps counterbalancing the previous argument—our data suggest that the pharmaceuticalization of race is also happening in the EU, which underscores the importance of broadening the research on race/ethnicity and pharmaceutical regulation to encompass Europe as well. In fact, more EU than US labels contained statements about racial and ethnic differences, which suggests that, all things being equal, the room for pharmaceuticalization of race is greater in the EU. It seems pertinent, therefore, to follow how racial/ethnic drug labeling is interpreted and operationalized in various European countries given their highly disparate conceptions and practices related to race and ethnicity and their histories of scientific racism (Simon, 2012).

Third, our data can help moderate claims of the hegemony of US census categories in drug research and regulation. Previous research emphasized the conceptual power of the FDA—as opposed to, for example, the ICH—in forcing or incentivizing companies and researchers to adopt US racial and ethnic standards nationally and globally (Epstein, 2007). Furthermore, it was argued that, consequently, biological and therapeutic conclusions are being drawn from socially defined US categories acknowledged by regulators to have questionable applicability elsewhere (Bliss, 2012; Kahn, 2012). However, we found that categories used to describe and gauge differences are less standardized than might be expected, especially in the clinical pharmacology section of labels, and even in the USA. This implies that although the US census categories dominate, consistent with Hypothesis 4—especially in describing safety and efficacy trials—there is still room for eschewing the hegemony of the US taxonomy. This may produce more variable conceptions and classifications of race and ethnicity than previously assumed, corresponding to the variabilities and inconsistencies in taxonomy and classifications seen in epidemiology (Bradby, 2003) and genetics (Bliss, 2012). Further, research has shown that the US census categories can be transformed at the national level in Europe, introducing further variabilities and inconsistencies in pharmaceutical medicine (Smart and Weiner, 2018).

Fourth, our data show that the concept of the Asian "race" is treated differently from other "races" in drug testing and regulation. While Asians were often treated as an undifferentiated group when describing clinical trials for safety and efficacy, clinical pharmacology analyses seemed to assume potentially important differences *between* Asian groups. Contradictorily, Asian sub-categories such as Japanese were also frequently treated as representatives of the Asian race, but in other instances, Japanese (and other Asian sub-groups) were grouped into a separate East Asian racial group. This special—and inconsistent—treatment of the Asian "race" likely reflected commercial considerations and regulatory requirements related to the large Asian drug market, including Asian regulators' demand for ethnicity-based subgroup analyses (Kuo, 2008), rather than any "objective" assessments of the nature of population differences, for example, that differences between Japanese and Chinese are more relevant than between, for instance, African Americans and sub-Saharan migrants in Europe (Huddart et al., 2019). This highlights the impact of broader international trends in drug development and regulation on race and ethnicity drug labeling—even in the USA.

5. Conclusion

The racialization of pharmaceutical regulation is an internationally extended yet variable process. Thus, systematic comparison of the labels of hundreds of novel drugs revealed broad similarities between the USA and the EU, but also some expected and unexpected differences. It seems that although the FDA puts greater emphasis on showcasing the *inclusion* of racial and ethnic subgroups in trials than does the EMA, it is less keen on reporting *differences*—despite political pressure being applied on the FDA and its longstanding commitments to this issue. Our study helps moderate several assertions and assumptions in the social science literature, including regarding the growing number of race-based products or differential results by race, and regarding the dominance of US census categories in pharmaceutical medicine. Overall, this underscores the importance of systematic international comparisons to study the intersection between race/ethnicity and medicine.

Credit author statement

Conceptualization; SM, AB; Data curation; SM, AV, PO; Formal analysis; SM; Funding acquisition: SM, AB; Investigation; SM, AV; Methodology: SM: Roles/Writing - original draft: SM. Writing - review & editing: SM, AV, PO, AB.

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Appendix A. Supplementary data

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