非選択試験ではマーカーに関してだけ影響を与える可能性があるが，強化試験では，これはマーカーに関する推論に加えて，全体の完全性と試験の結果を危うくするかもしれない．

マーカーベースデザインは，特定の状況で利点がある．2値分類を具体化できる2値マーカー又は多重マーカーの識別特性において，より小さなサンプルサイズと高いイベント発生率あるいは群間でイベント発生率のより大きな差は，非選択デザインに比べて，マーカー・治療相互作用デザインで可能性が高い．マーカーベース戦略デザインは，潜在的な不利―マーカーベース群と非マーカーベース群の両方で同じレジメンで治療を受ける患者の重複―がある．注意点は，癌治療薬分野での経験がほとんどで，他分野での適用性は検証されていないことである．

後向き検証は可能か？（検証）

新たな前向きデザインの試験が様々な理由で実行できない場合，これまでに適切に実施された治療法を比較するRCTのデータを利用して，マーカーの予測能力を検討する可能性を特定の状況で考慮できる（後向き検証）．どの後向き検証にとっても，1つ以上の適切に実施された前向きRCTのデータ，そして多数の被験者からGBM状態を入手できるなどの決定的要素が，選択バイアスを避けるために重要である．更に，検証する仮説と解析計画は，後向き評価の開始前に文書化する必要がある．前述のように後向き検証では，1つ以上の独立したデータソース又はRCTの使用により必要なエビデンスの提供ができる．後向き検証に含まれる試験のデザインは，前向きの検証試験に類似する可能性が高いが，GBMに関しては非選択デザインが圧倒的多数の可能性が高い．2つの方法の違いの1つは，既に完了したRCTの後向き解析では，試験組み入れの適格性がマーカーの状態に基づかない，つまり非選択デザインの可能性があり，これはマーカーの検証の助けになるかもしれない．転移性直腸結腸癌の野生型KRASとパニツムマブ投与後の無増悪生存期間（PFS）の改善との関係を確認する研究は，後向き検証の一例である[25]．この事例では，野生型と変異型KRASの保有者間でのパニツムマブの効果の差が，GBMの事後解析により示され，セツキシマブの臨床試験から得られた関連性の生物学的合理性ともに，欧州での条件付き承認の基となっている．承認は，前向きに作られる更なるデータを条件として要求していた．GBMの状態の情報が，被験者の大部分から得られる必要があるとの考慮事項は，20020408試験で満たされていた．この1つのRCTから得られた実証データで，解析が事前に定義され，選択バイアスを回避して被験者の大部分のGBM状態が，決定可能であった．

それに比べて，又は対照的に，ゲフィチニブでのEGFR FISHと/又はEGFR変異状態間の相互作用は，いくつかの試験で評価されていたが，非小細胞肺癌患者での探索が目的であった．これらの試験には，多様な患者集団（アジア人でのISEL試験），希望者全員対象のINTEREST試験（コーカサス人種が圧倒的多数），及び混合集団でのIPASS試験が含まれている．これらの試験は前向きであったが，INTEREST試験のみEGFR FISH陽性に基づく違いを，共同主目的［co-primary objective］として事後（後向き）解析を効果的にしていた．これらの試験で示されている応答率の差は，民族性，他の臨床的特徴あるいは前治療の違いによって影響されているかもしれない．マーカーの状態が既知/同定された被験者数の違いが，それぞれのバイオマーカー（EGFR FISHの状態，EGFR変異状態，EGFR蛋白の発現）において，役割を持っていた可能性もある．全く異なる結果にもかかわらず，様々な比較間での方向性の一致と，EGFR変異状態とゲフィチニブへの応答の間で再現された相互作用のために，統合解析は，EGFR変異陽性腫瘍の場合のみゲフィチニブ治療のベネフィットを示した．特に，これら複数の試験と統合解析の結果に基づいて，CHMPと専門家助言集団の双方が，非小細胞肺癌でのゲフィチニブの広範な効能に同意せず，ゲフィチニブへの応答がEGFR変異状態に影響されている，制限された効能を承認すると判断した．ゲフィチニブ開発プログラムへの批判の1つは，様々な試験での全被験者でのバイオマーカーに関する情報が欠如していることで，これはより良く設計，計画することができるものだった．この例はGBMの後向き評価の2つの重要な側面―第1に様々な試験や集団におけるGBM・薬物応答の相互作用の再現と，第2に解析において全被験者からのGBM状態の情報を最大にする必要性―を強調している．

以上から，次の点が満たされていれば，規制上/科学的な観点で，後向き検証や後向きデータの受け入れが可能かもしれない．実施されたRCTからのデータ；RCTにおける被験者の大多数のマーカー状態の情報が利用可能；仮説と解析計画が事前定義されていること；多重検定で調整された統計的に説得力のある関連性；そして最終的に1つ以上の独立したサンプルでの結果の再現，で

25) Vectibix EPAR-2007. http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000741/WC500047707.pdf.

ある．

5. マーカーの診断性能

GBMあるいはバイオマーカーの診断性能の特性を明らかにし，この性能が疾患の特徴，他の治療的介入の効果，GBM発現の性別や民族による疫学的な違いにより影響を受けることを説明するのは重要である．例えば，HLA- B* 1502と抗てんかん剤曝露によるスティーブンジョンソン症候群の関係は，民族的多様性を示し，広い非選択集団で使用する場合，性能に影響する可能性がある．

診断性能の基準は，適格性評価とバリデーションの一般的な基準に適合する必要がある．反復性，再現性と精度推定等の特定の側面を評価する必要がある[26]．診断性能は感度と特異度の評価に基本的に関係している．

GBM又は他の従来のマーカーの値は，大抵検査される集団に特有であり，実用性は臨床使用を反映した集団で実証される必要がある．他の集団へのどの外挿も，安全性GBMのリスクの推定基準を含めて，検査・外挿された集団で実証された表現型，GBMの出現率を考慮し，適切に正当性が証明される必要がある．

以下で取り上げた事項は，一般にマーカーと一部の検査の事例の双方に適用可能であるが，診断薬の詳細な議論は本文書の範囲を超える．

5.1. 感度，特異度，NPV（陰性適中率），PPV（陽性適中率）

探索で使用する試験の種類に関係なく，予測可能性と臨床的妥当性に関するバイオマーカー性能の情報収集は重要である．マーカーの臨床的妥当性とは，検査/マーカーの感度と特異度とゲノムの異常又は変異の浸透率の複雑な相互作用である．開発的な研究は仮説生成に加えて，GBMの更なる評価が実行可能で価値があることを示すことを目指すべきである．この点は第II相臨床試験と同等の役割だが，コホート又は単一群試験における探索的データセットの限界により影響を受ける可能性が高い．これらの試験で得られたデータの検証が何らかの形で得られることが期待され，GBM自体の出現に使用していないデータで実行される必要がある．そのプロセスはGBMの予測性能に係る情報を収集すべきで，これは検証段階で更に評価される正負の予測値を含める必要がある．

PPV及びNPVは，マーカー出現率と対象の集団での表現型発現に依存する可能性がある．探索的研究で高い正負の予測値を伴うGBMは特に関心を持たれるだろうが，適用される厳密性の水準が，特に規制の観点では不明であり正確に規定できない．95%の特異度さえ許容できない場合があり，国立がん研究所は，有病率の低い卵巣癌のスクリーニングを例にしている[27]．マーカーの最終的な評価は，特に他のマーカーや特性が利用可能である場合は大抵多変量解析である．多重マーカーのパネル又は識別特性が利用されている場合，多変量解析の結果は，一定の制限—GBMで採用したカットオフ値，連続あるいは分類か，他の既存のマーカーがすべて適切にコード化されているか，変数がどのようにモデル化されたか—に依存する．尤度比，一致指数あるいは一致指数の変化に基づく代替方法が提案されており，状況によっては適切かもしれない．Yangらは，尤度比を，疾患を有する患者が実際の検査結果を有する確率と定義して用い，疾患のない患者が同じ結果を有する確率と比較した[17]．一致指数はランダムに選択された2患者のうち，より予後が悪い者が，実際により悪い予後を予測される確率である[28]．一致指数は，受信者動作特性（ROC）曲線下面積と類似している．

0と1又は確定したカットオフ値の上下のような値をもつ2値モデルでは，ROC曲線が，階層分布とは独立した最適なモデルを選択する手段を与える．ROC曲線は，マーカーの数値が関連する連続データセット内の別のカットポイントの使用も可能にし，任意の点における傾きから尤度比を計算する機能を提供し，曲線の曲線下面積が検査の正確度の尺度になる．予測コンソーシアムで評価された腎損傷マーカーでは，いくつかのマーカー（KIM-1，アルブミン，シスタチン-Cなど）で，この利用に成功しているが[29]，規制上の観点からは，GBMのこの申請成功例はほとんどない．

6. GBM評価のための機器/診断キット

GBM及び他の疾患や状況でGBMの検出に関連した分析は，市場で入手できる場合があるが，この場合の検査の検証は，既に利用可能かもしれない許容できる分析や方法として評価段階にある疾患と治療に限定される

26) Biomarker qualification-renal biomarkers. http://www.ema.europa.eu/pdfs/human/biomarkers/28329810en.pdf.

27) http://www.cancer.gov/cancertopics/understandingcancer/moleculardiagnostics/page34.

28) Kattan MW.: *Clin Cancer Res*.10: 822-824. 2004.

29) Nephrotoxicity BMs. Final conclusions of EMA/FDA VXDS experience. EMEA/679719/2008 Rev.1

(例えばHLA対立遺伝子)．新たに同定された又は特定のGBMは，医薬品開発と併行して，特定の分析/キットの開発が必要かもしれない．ほとんどは薬剤と「コンパニオン診断薬」の共同開発であり，市販検査の分析特異度と感度に関する問題を考慮する必要がある．同様の考察は，GBM検出に利用できる他の分析又は検査（一般的に「自家製の検査」と呼ばれるものなど）に適用される．本文書の目的は，主にGBMに関連する方法論的側面を議論することにあり，市販検査やキットの性能ではない．しかし，以下のような見解がある．

・医薬品開発の観点から，開発プログラム内にコンパニオン診断薬が含められる可能性がある．特定の診断キットや方法論をピボタル試験で採用し，その検査がGBMの同定/定量に特有である場合，その特定の検査方法とGBMの値を関連づける必要があるかもしれない．免疫組織化学（IHC）又はFISH検査を利用したHER2過剰発現の同定と定量はその一例である．この例では，医薬品のラベルが，この追加情報を結果の記述の一部として提供する．他にもこのような例が存在する（Dako社製検査とセツキシマブ，Monogram社trofile検査とマラビロク）．

・GBM同定に使用する検査がより包括的性質，すなわち特別に開発したGBMではない場合（例えば，CYP2D6遺伝子多型の同定），コンパニオン診断用検査の特性に関する議論が，医薬品ラベルに含まれる可能性は低い．特定の診断キットの提供も期待されない．

・臨床試験で使用した分析/検査が利用できず，新しい又は別の検査に代える可能性がある．この場合，GBMマーカーの状態を測定する臨床試験の分析と市販の検査が同等であることが期待される．同様の他の市販検査間の同等性も重要な検討事項であるが，これらの議論は本文書の現在の範囲を超えている．

7. GBM評価に関する潜在的な外部からの影響

マーカーと治療効果の関係は，表現型と関連し，問題となっている薬剤への個々の応答を決定している他のゲノム，又は非ゲノムの要因によっても影響される可能性があることを認識すべきである．これは検討している標的疾患あるいは健康状態とは独立しているかもしれない．例えば，パロキセチンとタモキシフェンの同時投与や併用のようなCYP450基質又は阻害剤の使用は，ピボタル試験で制御されていない場合，ER陽性乳癌の治療結果に影響するとの議論がある．これはタモキシフェンの代謝（CYP2D6基質）に影響を与える特定のCYP2D6遺伝子多型による効果と似ている．

同様に，薬物受容体に関わる多型は，基礎疾患あるいは疾患とは独立に，1つ以上の薬物への応答に影響を与える可能性がある．薬剤への応答は，他の代謝酵素の遺伝子多型によっても影響を受ける可能性がある．例えば，ワルファリンに対する応答でのCYP2C9遺伝子多型の相互作用は，同時にVKORC1遺伝子多型の遺伝的形質によって影響される．したがって全体的な効果は，2つの影響の複合であり，評価中には相対的な寄与に関して明確にすることを要求すべきである．

初期研究におけるゲノム薬理学GBM評価の詳細な議論は，別文書（EMA/CHMP/37646/2009-下記参照）が利用可能である．

8. 他の側面

本考察書は，以下のガイダンスと併せて読まれるべきである．

・Position paper on terminology in Pharmacogenetics (EMEA/CPMP/3070/01)
(薬理遺伝学の専門用語に関する方針説明)
・Reflection paper on pharmacogenomic samples and data handling (EMEA/CHMP /201914)（ゲノム薬理学のサンプル及びデータ処理に関する考察書）
・ICH Topic E 15：Establish definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories (CHMP/ICH/437986/2006)
(ICHトピックE 15：ゲノムバイオマーカー，ゲノム薬理学，薬理遺伝学，ゲノムデータとサンプルコード化分類の定義の確立)
・Reflection paper on the use of pharmacogenetic in the pharmacokinetic evaluation of medicinal products (EMA/641698/2008)（医薬品の薬物動力学的評価における薬理遺伝学の利用に関する考察書）
・EMEA/CHMP/SAWP/72894/2008 Corr1. Qualification of Novel methodologies for Drug Development: Guidance to Applicants.（医薬品開発のための新しい方法論の適格性：申請者向けガイダンス）
・EMA/CHMP/ICH/380636/2009; Genomic biomarkers related to drug response: context, structure and format of qualification submissions.（薬剤応答に関連するゲノムバイオマーカー：適格性に関する提出の背景，構成と形式）
・EMA/CHMP/37646/2009; Guideline on the use of

pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products.（医薬品の薬物動態学的評価における薬理遺伝学的手法の利用に関するガイドライン）

9. 用語集

Accuracy：正確度

測定値とその真の値への近さの示す尺度

Analytical Validity：分析的妥当性

ゲノムバイオマーカーにおける分析的妥当性とは，対象の遺伝子型（マーカー）を正確に（確実に）測定する特定の検査能力を説明するもの．これは，検査の性能を評価する．

Biomarker：バイオマーカー

通常の生物学的プロセス，発病過程又は治療的介入への薬理学的応答の指標として，測定や評価される特性．

Classifier：分類指標

分類指標は，バイオマーカーの値を一連の予後分類に変換する数学的な関数であり，患者分類を可能にするマーカーとして定義することもできる．

Clinical Utility：臨床的有用性

マーカー又は検査が役立つことの臨床的有用性とは，検査（マーカー）が介入の転帰の改善につながる可能性のことである．言い換えると，マーカー(GBM) が，他の標準的な臨床的特徴に加えて，マーカーで定義された集団の薬物反応や予後評価の予測を提供してくれる価値のこと．

Clinical Validity：臨床的妥当性

検査が臨床疾患や表現型の存在（又は不在）を予測する正確度を指す．

Genomic biomarker：ゲノムバイオマーカー

通常の生物学的プロセス，発病過程又は治療的介入への薬理学的応答の指標として，測定可能なDNA及び/又はRNA特性．

(Biomarker) Qualification：(バイオマーカー) 適格性確認

適格性確認とは，提案されたバイオマーカーの用法の範囲内において，当該バイオマーカーが生物学的過程，反応あるいは事象を適切に反映し得ると判断され，医薬品又はバイオ技術開発におけるその使用が支持されるというバイオマーカーに関する評価結果を踏まえた結論．

Reproducibility：再現性

独立した従事者/研究者/研究室によって，正確に再現又は反復される検査又は実験の能力を指す．

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Pharmacogenetics

Approval gap of pharmacogenomic biomarkers and *in vitro* companion diagnostics between the United States and Japan

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SUMMARY

What is known and objectives: ***In vitro*** **companion diagnostic devices (CDx) provide information on pharmacogenomic biomarkers (PGBMs) to enable the safe and effective use of targeted agents for personalized therapy. These devices require specific regulations that strike a balance between scientific evidence and financial burden. The aims were to compare approval of PGBMs and CDx in the USA and Japan and to help inform current discussions on personalized medicine.**

Methods: **We analysed published documentation from the USA and Japan for CDx and PGBMs, listed by the US Food and Drug Administration (FDA). Aspects evaluated were aim, approval state and therapeutic area. Coverage by the National Health Insurance in Japan was also investigated.**

Results and discussion: **Thirty-eight PGBMs were listed in the FDA table as of March 2013. In the USA, the aim was efficacy in 55% (21/38). The largest therapeutic area was oncology (39%, 15/38). Fifty-three per cent (20/38) of the PGBMs had a corresponding CDx approved. Of the 38 PGBMs in the FDA table, six had no approved drug in Japan; in 16 of the remaining 32 PGBMs, the aim was efficacy. The largest therapeutic area was oncology (34%, 11/32). Of the 32 PGBMs, 15 were associated with an approved and/or covered CDx, with only 11 having an approved CDx. Four PGBMs had a covered CDx without prior approval in Japan.**

What is new and conclusion: **Our study confirms that there is still a substantial gap in the approval of PGBMs and CDx between Japan and the USA. Complementary coverage of unapproved CDx by the National Health Insurance, however, is raising access to a similar level in both countries. Because the number of expensive personalized medicines and CDx is increasing, patient access will continue to be an important challenge to healthcare systems in all countries.**

WHAT IS KNOWN AND OBJECTIVE

For many years, healthcare professionals have used diagnostic tests to select appropriate treatments for patients or to optimize dosing regimens. Pharmacogenomic biomarkers (PGBMs) can help inform therapeutic decisions in personalized medicine.[1–3] More than 100 drug labels are included in the table of PGBMs published by the US Food and Drug Administration (FDA).[4] *In vitro* companion diagnostics (CDx) provide information essential for the safe and effective use of targeted therapeutic products.[5] Ethical implementation of personalized medicine, however, requires balancing scientific evidence and financial burden.[6]

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical companies in the USA, Europe and Japan to discuss scientific and technical aspects of drug registration. Harmonization in the development and regulation of PGBMs and CDx, however, remains to be implemented. In July 2011, the FDA issued draft guidance on CDx,[5] whereas the European Medicines Agency (EMA) issued a draft reflection paper[7] focusing on the use of PGBMs in the clinical development of CDx and patient selection. In contrast, the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese counterpart of the FDA and EMA, has not yet issued any document on the development of CDx. Although the FDA and EMA desire co-development of drugs and diagnostics, most approved CDx were not developed concurrently with the drugs concerned.[8]

In addition to approval by a regulatory authority, general use of a CDx requires coverage and reimbursement by health insurers. Coverage decisions are critical factors in patient access to personalized medicine. Policy makers and payers have to make decisions about the financial sustainability of healthcare delivery, whereas regulatory authorities have to optimize access to safe and effective medications.[9] In the USA, FDA approval is not a guarantee of coverage.[8,10] Lack of evidence for the clinical use of many CDx has led payers to deny or restrict reimbursements.[6,11] For example, the CMS does not routinely cover genotyping for CYP 2C9 and VKORC1[12] in patients being prescribed warfarin. It requires evidence that such testing will deliver improved clinical outcomes.

Assessment of health outcome measures[13] has shown that Japan holds a favourable position in the development of personalized medicine through its industrial, regulatory and reimbursement processes. The National Health Insurance (NHI) in Japan[14] covers virtually all medications and diagnostics approved by the PMDA. Sometimes payers even reimburse for off-label medications and unapproved devices,[15] depending on clinical necessity. Surging healthcare costs, however, are challenging the system. For example, Japanese physicians are struggling with reimbursement for genetic testing.[16]

The objectives of this study were to investigate the differences in approval of PGBMs and CDx in the USA and Japan and to help

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inform current discussion on barriers to personalized medicine in both countries. We also evaluated coverage of CDx by the NHI in Japan.

METHODS

Study design

This was a cross-sectional study of documents published on the FDA's and PMDA's websites as of March 2013. PGBMs approved only in Japan, for example HLA-A*3101[17] and CCR4,[18] were not included in this study because we used the FDA table[4] as the reference.

Data sources

PGBMs were listed in the Table of Pharmacogenomic Biomarkers in Drug Labels on the FDA's website.[4] We also obtained US CDx data from the FDA's database of 510(k) Premarket Notification[19] and Premarket Approval.[20] Japanese CDx data were obtained

Table 1. Approval in the USA and Japan of pharmacogenomic biomarkers and corresponding *in vitro* companion diagnostics

Biomarker	Aim	Therapeutic area	US CDx approval	JPN drug approval	JPN CDx approval	JPN CDx coverage
ALK	Efficacy	Oncology	A	A	A	C
Antithrombin III deficiency (SERPINC1)	Safety	Haematology	A	A	A	C
Apoprotein E2	Efficacy	Metabolic and endocrinology	U	A	U	NC
BRAF	Efficacy	Oncology	A	U	U	NC
C-Kit	Efficacy	Oncology	A	A	U	C
CCR5	Efficacy	Antivirals	U	A	U	NC
CD20 antigen	Efficacy	Oncology	A	U	A	C
CD25	Efficacy	Oncology	U	U	U	NC
CD30	Efficacy	Oncology	A	U	U	NC
CFTR (G551D)	Efficacy	Pulmonary	A	U	U	NC
Chromosome 5q	Efficacy	Haematology	U	A	U	C
CYP1A2	Monitoring	Gastroenterology	U	U	U	NC
CYP2C19	Monitoring	Two or more areas	A	A	A	NC
CYP2C9	Monitoring	Two or more areas	A	A	U	NC
CYP2D6	Monitoring	Two or more areas	A	A	A	NC
DPD	Safety	Two or more areas	U	A	U	NC
EGFR	Efficacy	Oncology	A	A	A	C
ERBB2 (HER2)	Efficacy	Oncology	A	A	A	C
Estrogen receptor	Efficacy	Oncology	A	A	A	C
Estrogen/progesterone receptor	Efficacy	Oncology	A	A	A	C
Factor V Leiden	Safety	Two or more areas	A	A	U	NC
FIP1L1-PDGFRα	Efficacy	Oncology	U	A	U	C
G6PD	Safety	Two or more areas	A	A	U	NC
HGPRT	Safety	Transplantation	U	A	U	NC
HLA-B*1502	Safety	Neurology	U	A	U	NC
HLA-B*5701	Safety	Antivirals	U	A	U	NC
IL28B	Efficacy	Antivirals	U	A	U	NC
KRAS	Efficacy	Oncology	A	A	A	C
LDL receptor	Efficacy	Metabolic and endocrinology	U	A	U	NC
NAT1; NAT2	Safety	Two or more areas	U	A	U	NC
PDGFR	Efficacy	Oncology	U	A	U	NC
Ph1/BCR-ABL	Efficacy	Oncology	U	A	A	C
PML/RARα translocation	Efficacy	Two or more areas	U	A	U	C
Prothrombin F2 mutation	Safety	Oncology	A	A	U	NC
TPMT	Safety	Two or more areas	U	A	U	NC
UCD	Safety	Two or more areas	U	A	U	NC
UGT1A1	Safety	Two or more areas	A	A	A	C
VKORC1	Monitoring	Haematology	A	A	U	NC

CDx, *in vitro* companion diagnostics; JPN, Japanese; ALK, anaplastic lymphoma kinase; A, approved; C, covered; SERPINC1, serpin peptidase inhibitor, clade C (antithrombin), member 1; U, unapproved; NC, not covered; BRAF, v-raf murine sarcoma viral oncogene homolog B1; C-Kit, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog; CCR5, chemokine receptor type 5; CD, cluster of differentiation; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ERBB2 (Her2), v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2 (human epidermal growth factor receptor 2); FIP1L1-PDGFRα, FIP1-like 1-platelet-derived growth factor receptor alpha fusion gene; G6PD, glucose-6-phosphate dehydrogenase; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; HLA, human leucocyte antigen; IL, interleukin; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; LDL, low-density lipoprotein; NAT, N-acetyltransferase; PDGFR, platelet-derived growth factor receptor; Ph1/BCR-ABL, Philadelphia chromosome/breakpoint cluster region-Abelson tyrosine kinase; PML/RARα, promyelocytic leukaemia/retinoic acid receptor alpha; TPMP, thiopurine S-methyltransferase; UCD, urea cycle disorders; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; VKORC1, vitamin K epoxide reductase complex, subunit 1.

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from the PMDA label data of *in vitro* diagnostics.[21] We obtained US drug approval data of these drugs from Drugs@FDA[22] and Japanese drug approval data from the PMDA website's section on new drug approval.[23] We obtained Japanese coverage data of CDx from the NHI database.[24]

Evaluation and analysis

The aim of each PGBM was evaluated according to the FDA guidance[5] as follows. Efficacy is to identify patients who are most likely to benefit from a particular therapeutic product; safety is to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with a particular therapeutic product; monitoring is to monitor responses to treatment for the purpose of adjusting treatment (e.g. schedule, dose and discontinuation) to improve safety or effectiveness. We used Fisher's exact test to determine the relationship between the aim (efficacy/safety and monitoring) and therapeutic area (oncology/non-oncology) on the approval status of the CDx. A P value <0·05 was regarded as statistically significant.

RESULTS AND DISCUSSION

Characteristics of PGBMs

Detailed information on the PBGMs and corresponding CDx in Tables S1 (online only). Table 1 shows the 38 PGBMs listed in the FDA table as of March 2013.[4] The aims of the PGBMs included 21 (55%) for efficacy, 12 (32%) for safety and five (13%) for monitoring. Therapeutic areas with PGBMs included antivirals (3; 8%), gastroenterology (1; 3%), haematology (3; 8%), metabolic and endocrinology (2; 5%), neurology (1; 3%), oncology (15; 39%), pulmonary (1; 3%), transplantation (1; 3%) and two or more areas (11; 29%).

Of the 38 PGBMs in the FDA table, six did not have related approved drugs in Japan (Table 1). These included BRAF (vemurafenib), CD20 antigen (tositumomab), CD25 (denileukin diftitox), CD30 (brentuximab vedotin), CFTR (ivacaftor) and CYP1A2 (dexlansoprazole). Both biological and non-biological factors can affect regulatory decisions. For example, a much lower incidence of cystic fibrosis and melanoma in Japan compared with the West could discourage the makers of ivacaftor and vemurafenib to file an application to the PMDA.[3] Denileukin diftitox and tositumomab, which were approved for lymphoma by the FDA in 1999 and 2003, respectively, remain unavailable both in the EU and Japan probably because better treatment modalities are available now.

Of the remaining 32 PGBMs in Japan, the aims were efficacy in 50% (16/32), safety in 38% (12/32) and monitoring in 12% (4/32) (Table 2). The therapeutic areas were antivirals in 9% (3/32), haematology in 9% (3/32), metabolic and endocrinology in 6% (2/32), neurology in 3% (1/32), oncology in 34% (11/32), transplantation in 3% (1/32) and two or more areas in 34% (11/32) (Table 3).

Approval gap of CDx between the USA and Japan

Twenty of the PGBMs (53%) had a corresponding CDx approved in the USA. Of the 20 PGBMs with an approved CDx in the USA, only three [ALK, ERBB2 (HER2) and BRAF] showed successful drug diagnostic co-development.[25] In the other 17 PGBMs, the drug and its CDx were approved separately. Table 2 shows the aim of each PGBM and whether a CDx was approved. Approval was not associated with whether the aim of the PGBM was efficacy, safety or monitoring (P = 0·64). Table 3 shows the therapeutic area of each PGBM and whether a CDx was approved. The percentage of oncology PGBMs with an available CDx (73%, 11/15) was significantly higher than that of non-oncology PGBMs with an available CDx (39%, 9/23, P = 0·041).

Of the 32 PGBMs approved in Japan, 15 (47%) were associated with an approved and/or covered CDx, with only 11 having an approved CDx. The four PGBMs with an unapproved but covered CDx in Japan are c-kit, chromosome 5q, FIP1L1-PDGFRα and PML/RARα translocation. The four PGBMs for which a CDx is covered in Japan, but not approved in the USA, were chromosome 5q, FIP1L1-PDGFRα, Ph1/BCR-ABL and PML/RARα transloca-

Table 2. Aims of pharmacogenomic biomarkers with or without an *in vitro* companion diagnostic device available in the USA and Japan

	USA		Japan	
	CDx		CDx	
Pharmacogenomic biomarker aim	Available	Unavailable	Available	Unavailable
Efficacy	11	10	11	5
Safety	5	7	2	10
Monitoring	4	1	2	2
Total	20	18	15	17

CDx, *in vitro* companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.

Table 3. Therapeutic areas of pharmacogenomic biomarkers with or without an *in vitro* companion diagnostic device available in the USA and Japan

	USA		Japan	
	CDx		CDx	
Therapeutic area	Available	Unavailable	Available	Unavailable
Antivirals	0	3	0	3
Gastroenterology	0	1	0	0
Haematology	2	1	2	1
Metabolic and endocrinology	0	2	0	2
Neurology	0	1	0	1
Oncology	11	4	9	2
Pulmonary	1	0	0	0
Transplantation	0	1	0	1
Two or more	6	5	4	7
Total	20	18	15	17

CDx, *in vitro* companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.

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tion. CDx for CYP2C19 and CYP2D6 are approved, but not covered in Japan. A CDx for CD20 antigen is approved and covered, although the corresponding drug, tositumomab, has not been introduced in Japan, probably because rituximab, indicated for the treatment of patients with CD20-positive B-cell non-Hodgkin lymphoma, is already approved in Japan.

Table 2 shows the aim of the 32 PGBMs according to the availability of the CDx (i.e. whether it is approved and/or covered). The percentage of PGBMs aiming at efficacy and with an available CDx (69%, 11/16) was significantly higher than that of PGBMs aiming at safety or monitoring (25%, 4/16, $P = 0{\cdot}016$). Table 3 shows the therapeutic area of the 32 PGBMs according to the availability of a CDx. The percentage of oncology PGBMs with an available CDx (82%, 9/11) was significantly higher than that of non-oncology PGBMs with an available CDx (29%, 6/21, $P = 0{\cdot}006$).

Our study confirmed that there is still a substantial approval gap for PGBMs and CDx between Japan and the USA. Approval gaps between the two countries were also observed for neurological[26] and psychiatric drugs.[27] When we focused on oncology, however, there was no approval gap for CDx. The percentage of oncology PGBMs that had an approved CDx was 73% (11/15) in the USA and 82% (9/11) in Japan. This is probably because the drug lag has been markedly reduced in oncology[28] where PGBMs play an important role.

Complementary coverage by the National Health Insurance to close the approval gap

Although the percentage of PGBMs with an approved CDx was lower in Japan (34%, 11/32) than in the USA (50%, 19/38), availability (i.e. the percentage of CDx approved or covered) was similar in Japan (47%, 15/32). This is because although four PGBMs, chromosome 5q, c-kit, FIP1L1-PDGFRα and PML/RARα translocation, were associated with unapproved CDx, they were covered and reimbursed by the NHI. The reason for this is unclear although testing for these four PGBMs is specified as required in the Japanese labels of the corresponding drugs[23] and in the relevant guidelines.[29] We could not provide data on coverage or reimbursement of CDx in the USA because the healthcare reimbursement and payment system in the USA is much more complex[10,12] than that of the NHI in Japan. Coverage and reimbursement for a CDx are separate from and more multifaceted than for the corresponding drug in the USA.[6,30]

WHAT IS NEW AND CONCLUSION

Our study confirms that there is still a substantial gap in the approval of PGBMs and CDx between Japan and the USA. However, complementary coverage of an unapproved CDx by the NHI has increased availability to Japanese patients to a level similar to that of US patients. Caution should be exercised, however, because of the marked differences in the two healthcare systems. Because the number of expensive and targeted personalized medicine drugs and CDx is increasing, patient access will continue to be an important challenge to healthcare systems of all countries.

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CONFLICT OF INTEREST

The authors report no conflict of interest in this work.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Information on the pharmacogenomic biomarkers and corresponding *in vitro* companion diagnostics. It includes the type of biomarker, approved assay method, disease or molecule in focus, CDx target, and corresponding drugs.

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Differences in pharmacogenomic biomarker information in package inserts from the United States, the United Kingdom and Japan

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SUMMARY

What is known and objective: **The provision of pharmacogenomic information in drug package inserts (PIs) has become more common in recent years. The content of PIs can be tailored to meet specific requirements of the target populations. Our objective was to identify, assess and report on differences in pharmacogenomic information in PIs from the United States (USA), the United Kingdom (UK) and Japan.**

Methods: **Package inserts were obtained from the US Food and Drug Administration (FDA) Table of Pharmacogenomic Biomarkers in Drug Labels on 1 October 2012. Corresponding PIs were obtained concurrently from Japan and the UK. We compared the pharmacogenomic information included, where the information was located, the therapeutic class of the drug, the type and purpose of the biomarker and the initial US approval year.**

Results and discussion: **One hundred eighteen PIs were included in the FDA table. Of the 118 PIs, 29 provided information on drug targets, 69 on metabolizing enzymes and 20 on other aspects. Genomic biomarkers were described in 71 PIs from the UK and 44 from Japan. Consistency in labelling across the three jurisdictions was greater in the 'Indications' section of the PIs than that in the 'Precautions' section. There appears to be greater concordance across countries for the biomarker information in the 'Indications' sections (UK 65% and Japan 48% relative to the US information) than that in the 'Precautions' sections (UK 41% and Japan 17%).**

What is new and conclusion: **There are substantial differences in the pharmacogenomic information included in PIs from the USA, the UK and Japan. The differences varied according to the PI sections, and type and purpose of the biomarkers. The differences appeared to vary according to the strength of the evidence supporting use of the biomarkers. Further analyses are necessary to determine the causes of these differences.**

WHAT IS KNOWN AND OBJECTIVE

Individual differences in drug efficacy and patients' susceptibility to adverse effects are well recognized. Studying the genomic basis of these differences can help clinicians to optimize therapy and reduce adverse drug reactions.

The United States (US) Food and Drug Administration (FDA) released their 'Guidance for Industry: Pharmacogenomic Data Submissions' document in March 2005 to help drug developers understand the agency's policies and processes for accepting and using pharmacogenomics data.[1] Similarly, the FDA created a 'Genomics' web portal, providing up-to-date regulatory and background information on genomics in relation to drug efficacy, safety, pharmacokinetics, pharmacodynamics and dosage.[2] Among other regulatory activities, the FDA attempts to incorporate genomic information into drug labels by requiring the revision of existing labels on the basis of clinical findings or the inclusion of appropriate wording in drug labels of new products. A list of pharmacogenomic biomarkers identified in the context of approved drug labels can be found on the FDA's website.[3] The FDA's European counterpart, the European Medicines Agency (EMA), has similarly published a variety of scientific guidelines on pharmacogenomics.[4]

Drug package inserts (PIs) represent the most fundamental tool for providing information on approved drugs to healthcare professionals and for promoting proper use of the drugs. The contents of PIs can be tailored to meet the requirements of the target populations and take local guidance into consideration.

The availability of pharmacogenomic information presented in PIs has been investigated in recent years in the United States, Europe and Japan.[5–10] Findings showed that 121 of the 1200 PIs from the United States released over the period 1945–2005 contained pharmacogenomic information.[5] In the European Union, the PIs from approximately 20% of the 584 products reviewed by EMA as of 2011 contained genomics information to personalize their use.[10] In Japan, 32 of 199 PIs (16%) reviewed by the Pharmaceutical Medical Device Agency (PMDA) from 2002 to 2006 included pharmacogenomic information.[8] However, there have been few comparisons of the pharmacogenomic information in PIs between countries.[9] We selected the United States, the United Kingdom (UK) and Japan for our comparison because of similarities in their drug regulations, as all three are members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The UK, like Japan, has a national health service that controls drug cost reimbursement.[11]

The aim of the current study was to investigate differences in information on genomic biomarkers in PIs from the United States, the UK and Japan. The findings should provide a basis for further regulatory standardization and highlight justifiable population-specific differences in pharmacogenomic information in PIs.

METHODS

A list of pharmacogenomic biomarkers in PIs from the United States is available from the FDA website.[3] PIs from the United

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States were obtained from Drugs@FDA[12] and DailyMed,[13] whereas PIs from the UK (Summaries of Product Characteristics; SPCs) were obtained from the Electronic Medicines Compendium (eMC).[14] Japanese PIs were obtained from the PMDA website.[15] 'PI is not available' indicates that PIs were not available from the eMC in the UK or the PMDA in Japan, for yet-to-be approved or discontinued products.

Because the lists of pharmacogenomic biomarkers and PIs are updated from time to time at irregular intervals, results are subject to changes over time but were current on 1 October 2012. We chose to manually screen genomic biomarker information because it was scattered throughout different sections of PIs approved by the respective regulatory authorities.[16–19] Our screening was based on a set of selection criteria that identified descriptions of genomic biomarkers (genotype and/or phenotype) that affected drug efficacy, safety, pharmacokinetics, pharmacodynamics or dosage.

In the present study, a set of drugs and biomarkers was counted as one PI. For all PIs identified in this analysis, genomic biomarker information was extracted manually, according to the context in which the genomic biomarkers were included in the PIs. We divided PI sections in the three countries into five categories (Table 1). UK PI sections had no counterpart for the 'Warning' section. When genomic biomarker information was scattered throughout more than one section (e.g. 'Indications' and 'Dosage'), the upper-categorized section in Table 1 (e.g. 'Indications') was assigned priority.

In addition, we analysed associated factors, including type of biomarker, purpose of biomarker, therapeutic area and initial approval year of the drug in the United States. Biomarkers were categorized into three types (drug target, metabolizing enzyme and others), with two groups for 'purpose' (efficacy and safety). Therapeutic areas were designated according to the FDA table.[3]

RESULTS AND DISCUSSION

Characteristics of pharmacogenomic biomarkers in PIs

118 sets of drugs and genomic biomarkers in PIs (106 as drugs) were included on the FDA list as of 1 October 2012. The 39 individual genomic biomarkers on the list were tabulated by biomarker type and purpose (Table 2). Cytochrome P450 (CYP) 2D6 was the most frequent biomarker found in PIs (37 PIs, 31%). More than half of the biomarkers (69 PIs, 58%) were classified as metabolizing enzymes, and safety-related biomarkers constituted 69% (81 PIs). Numbers of PIs, stratified by therapeutic area and initial approval year in the United States, are shown in Table 3.

Table 1. Package insert section categories for analysis

	PI sections in the USA, the UK and Japan		
Section categories for analysis	USA	UK	Japan
Indications	Indications and usage	4·1 therapeutic indications	Indications Precautions for indications
Warning	Boxed warning	Not applicable	Warning
Dosage	Dosage and administration	4·2 posology and method of administration	Dosage and administration Precautions for dosage
Contraindications	Contraindications	4·3 contraindications	Contraindications
Precautions	Others	Others	Others

Table 2. Type and purpose of genomic biomarkers in the FDA list

Type (number of PIs)	Purpose	Biomarker (number of PIs)
Drug target (29)	Efficacy	ALK (1), BRAF (1), C-Kit (1), CCR5 (1), CD20 antigen (1), CD25 (1), CD30 (1), CFTR (1), EGFR (4), ER (2), ER &/PgR (2), FIP1L1-PDGFRα (1), Her2/neu (4), PDGFR (1), Ph chromosome (4), PML/RARα (2), VKORC1 (1)
Metabolizing enzyme (69)	Safety	CYP1A2 (1), CYP2C19 (14), CYP2C9 (3), CYP2D6 (37), DPD (2), G6PD (3), NAT1/NAT2 (2), TPMT (4), UGT1A1 (3)
Others (20)	Efficacy (8)	ApoE2 (1), chromosome 5q (1), IL28B (3), KRAS (2), LDLR (1)
	Safety (12)	AT III (1), factor V Leiden (2), HGPRT (1), HLA-B*1502 (2), HLA-B*5701 (1), prothrombin mutations (1), Rh genotype (1), UCD (3)

ALK, anaplastic lymphoma kinase; ApoE2, apolipoprotein E2; AT III, antithrombin III; BRAF, v-raf murine sarcoma viral oncogene homologue B1; C-Kit, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homologue; CCR5, chemokine receptor type 5; CD, cluster of differentiation; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; FDA, Food and Drug Administration; FIP1L1, FIP1 like 1; G6PD, glucose-6-phosphate dehydrogenase; Her2/neu, human epidermal growth factor receptor 2; HGPRT, hypoxanthine–guanine phosphoribosyltransferase; HLA, human leucocyte antigen; IL28B, interferon-lambda-3; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue; LDLR, low-density lipoprotein receptor; NAT, N-acetyltransferase; PDGFR, platelet-derived growth factor receptor; PDGFRα, platelet-derived growth factor receptor, alpha polypeptide; Ph, Philadelphia; PgR, progesterone receptor; PML/RARα, promyelocytic leukaemia/retinoic acid receptor alpha; TPMT, thiopurine S-methyltransferase; UCD, urea cycle disorder; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; VKORC1, vitamin K epoxide reductase complex, subunit 1.

Table 3. Package inserts stratified by therapeutic area and initial approval year in the USA

	Number of PIs (%)
Therapeutic area	
Analgesics	3 (3)
Antiarrhythmic	1 (1)
Antifungals	2 (2)
Antiinfectives	2 (2)
Antivirals	5 (4)
Cardiovascular	8 (7)
Dermatology and dental	4 (3)
Gastroenterology	8 (7)
Haematology	5 (4)
Metabolic and endocrinology	2 (2)
Musculoskeletal	1 (1)
Neurology	6 (5)
Oncology	36 (31)
Psychiatry	27 (23)
Pulmonary	2 (2)
Reproductive	1 (1)
Reproductive and urologic	2 (2)
Rheumatology	2 (2)
Transplantation	1 (1)
US initial approval date	
1940s	1 (1)
1950s	9 (8)
1960s	11 (9)
1970s	9 (8)
1980s	7 (6)
1990s	26 (22)
2000s	44 (37)
2010s	11 (9)

The largest therapeutic area was oncology, followed by psychiatry. Sixty-nine per cent of the oncology group PIs (25/36 PIs) included drug target biomarkers, whereas 96% (26/27 PIs) of the psychiatry group PIs provided metabolizing enzyme polymorphisms, notably CYP isoenzymes. 75% (27/36 PIs) of the oncology drug PIs referred to biomarkers to highlight efficacy issues. In contrast, all 27 psychiatric drug PIs provided the information to comment on the drugs' safety. For initial US drug approvals, more than two-thirds (81 PIs, 69%) of the PIs with genomic biomarker information were approved from 1990 onwards. Of the 29 PIs with drug target biomarkers, the majority (26 PIs, 90%) were initially approved in 1990 or later, whereas 59% (41/69 PIs) of metabolizing enzyme biomarkers were approved after 1990.

The cross-sectional study design we used provides results specific to a time point. For example, the information on Rh genotype was deleted from the clomiphene PI from the United States on 22 October 2012. In addition, changes in the classification of the type and purpose of biomarkers may also vary over time. For example, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS), not usually a direct target of drugs, may become so over time.[9]

Number of PIs containing pharmacogenomic biomarkers in the three countries

The numbers of PIs containing pharmacogenomic information from the United States, the UK and Japan by PI section, as categorized in Table 1, are shown in Fig. 1, along with types of biomarkers. With respect to the number of PIs that contained genomic information, those from the United States contained all 118 PIs, followed by the UK (71 PIs, 60%) and Japan (44 PIs, 37%). PIs classified as 'Precautions' were the most common PI sections cited in all three countries, followed by 'Indications' and 'Dosage'.

For the United States, information in the 'Indications' section typically comment on drug target biomarkers (25/31 PIs, 81%), whereas the 'Dosage' and 'Precautions' sections mainly included information on metabolizing enzyme biomarkers (14/15 PIs, 93% and 50/64 PIs, 78%, respectively). The genomic biomarker information in the 'Indications' section of the PIs was limited to seven therapeutic areas (antivirals, dermatology and dental, gastroenterology, haematology, metabolic and endocrinology, oncology, pulmonary), of which oncology predominated 77% (24/31 PIs). The 'Precautions' section of the PIs with genomic information included all 19 therapeutic areas, but 31% (20/64 PIs) of the PIs related to psychiatry.

For the UK and Japan, 21 (18%, 20 drugs) and 34 (29%, 32 drugs) of drugs with PIs that included genomic information in the United States were not approved or were discontinued. Of these, 18 PIs (15%, 17 drugs) were not available in either the UK or Japan. Relevant biomarkers were not described in 26 (22%) and 40 (34%) PIs from the UK and Japan, respectively, and 21 of these PIs (18%) did not mention relevant biomarkers in either the UK or Japan. As with the United States, the majority of the 'Indications' section PIs from the UK (18/23 PIs, 78%) and Japan (12/16 PIs, 75%) described drug targets. In contrast, no metabolizing enzyme biomarkers appeared in the 'Indications' section in any of the three countries. The 'Precautions' section mainly contained metabolizing enzyme information in the UK (27/38 PIs, 71%) and Japan (15/25 PIs, 60%); however, some PIs recommended or required a specific action according to the effect of the metabolizing enzyme in the 'Warning', 'Dosage' and 'Contraindication' sections. PIs from the UK had no counterpart to the 'Warning' section. The majority of the 'Indications' section PIs belonged to the area of oncology, both in the UK (19/23 PIs, 83%) and Japan (13/16 PIs, 81%), similar to those in the United States. On the other hand, only 18% (7/38 PIs) and 8% (2/25 PIs) of the 'Precautions' section PIs were in psychiatry in the UK and Japan, respectively. Most PIs of psychiatric drugs did not state relevant biomarkers or were not available in the UK (17/27 PIs, 63%) or in Japan (23/27 PIs, 85%).

Figure 1 shows that the United States was the country most likely to include pharmacogenomic information in PIs, followed by the UK and then Japan. The number of Japanese PIs that provided information on genomic biomarkers was small (44 PIs) compared with those of the United States (118 PIs) and the UK (71 PIs). The notorious 'drug lag' in Japan may have partly contributed to this.[20,21] Another reason for this discrepancy might be ethnic differences, such as differences in allele frequencies in the populations concerned. For example, factor V Leiden, which has an incidence of 5% among Caucasians in North America, is extremely rare in people of Asian descent.[22] The frequencies of CYP2D6 poor metabolizers (PMs), which was the most frequent biomarker found in PIs, are approximately 1% in Asians and approximately 5–10% in Caucasians. CYP2C19 PMs have prevalences of 15–30% in Asians and 3–6% in Caucasians.[23,24] Ethnic factors may therefore account for some of the differences seen in Japanese PIs relative to the other blocks.

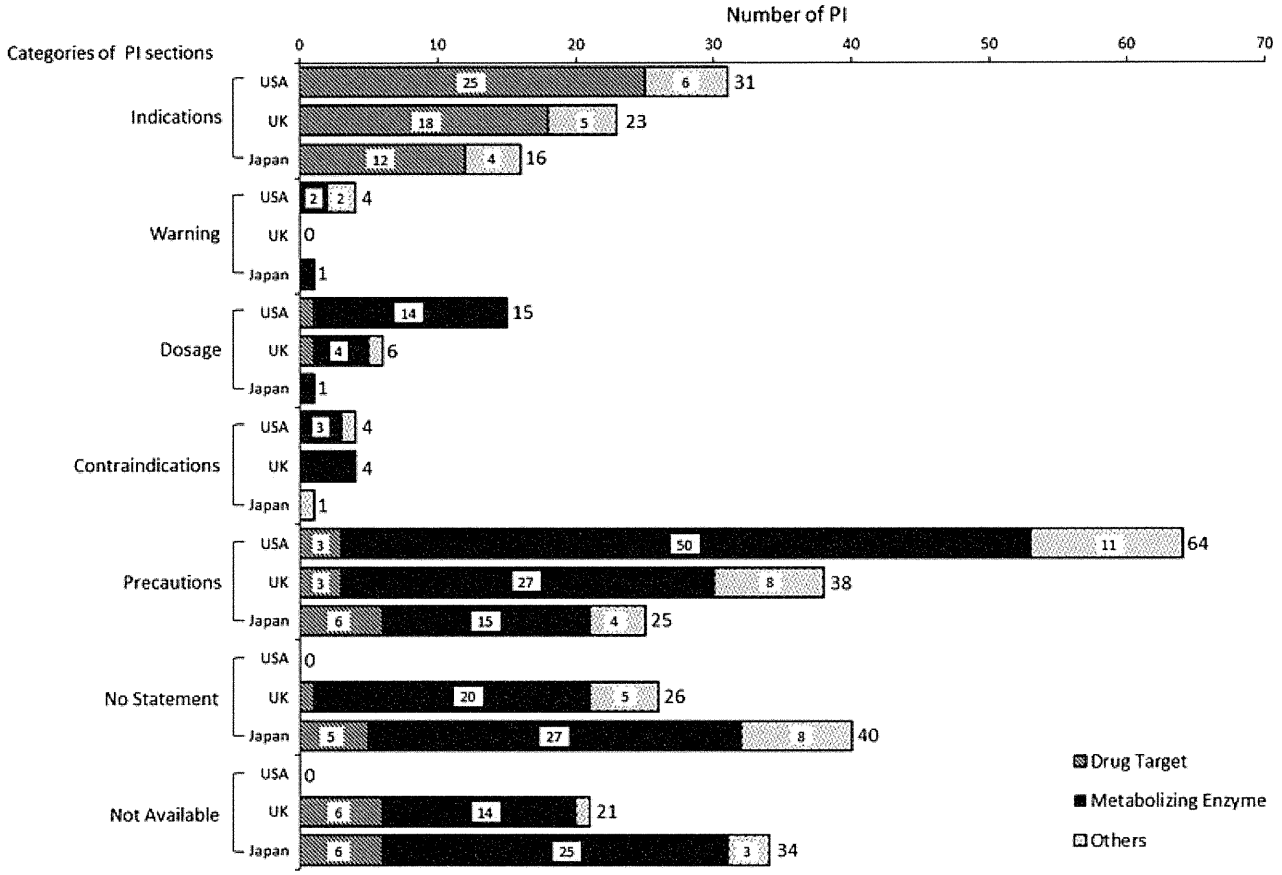

Fig. 1. Package insert sections for pharmacogenomic information in the USA, the UK and Japan.

Another reason for the difference is likely related to variations in the guidance issued by the different drug regulators for inclusion of pharmacogenomic information in PIs. The FDA and EMA provide instructions on how pharmacogenomic information should be incorporated into PIs,[17,19,25–27] whereas the Japanese regulatory guidelines have not been updated since 1997[18] and do not mention pharmacogenomics. In the United States, applicants have the option of creating a separate 'Pharmacogenomics' subsection in the Clinical Pharmacology section, if appropriate.[26] The establishment of guidelines and support from regulatory agencies would facilitate the translation of pharmacogenomic knowledge into routine clinical practice.

Comparisons of genomic biomarkers in PIs among the three countries

Details of the pharmacogenomic information in the 118 PIs from the United States, the UK and Japan are compared in Tables S1–S3 (online only), based on PI sections in the United States. Tables S1–S3 provide PI information on the 'Indications' section, 'Precautions' and sections other than 'Indications' and 'Precautions', respectively. Analyses of PI section differences between the United States and the UK, the United States and Japan, and the UK and Japan are shown in Tables 4–6, respectively. The 'not available' (NA) column was introduced to the tables between the United States and the UK or Japan (Tables 4 and 5) because 21 (18%) and 34 (29%) PIs were not available in the UK and Japan, respectively. The three tables show that there was significant disconcordance in the PI sections among the three countries, even though the regional authorities regulated the same product with considerable discussions on harmonization. We observed that the differences were stratified by PI section in the United States (Tables 4 and 5) or the UK (Table 6), type of biomarker, purpose of biomarker, therapeutic area and initial US approval period.

Stratification by PI section

The 'Indications' section showed higher concordance rates between countries (UK/USA 65%, Japan/USA 48% and Japan/UK 61%) than those of the 'Precaution' section (UK/USA 41%, Japan/USA 17% and Japan/UK 37%). As Fig. 1 demonstrates, PI section was linked to type of biomarkers, and the majority of the 'Indications' section PIs described drug targets in all three countries.

Stratification by type and purpose of biomarker

In the PIs from both the UK and Japan, the genomic information appeared more consistently in the same section relative to the US PIs for drug targets (UK 55%, Japan 41%) than that for metabolizing enzyme (UK 36%, Japan 14%). In this study, pharmacogenomic information in the PIs was classified roughly as describing the drug's pharmacological target (mainly efficacy oriented) or the drug's

Table 4. Analysis of differences in information in package inserts between the USA and the UK

Stratified factor (number of PIs)	Number of PIs		
	Differences between the USA and the UK		
	Concordant (51)	Different (46)	NA in UK[a] (21)
PI section in the USA			
Indications (31)	20	4	7
Precautions (64)	26	26	12
Others (23)	5	16	2
Type of biomarker			
Drug target (29)	16	7	6
Metabolizing enzyme (69)	25	30	14
Others (20)	10	9	1
Purpose of biomarker			
Efficacy (37)	20	11	6
Safety (81)	31	35	15
Therapeutic area			
Oncology (36)	18	13	5
Psychiatry (27)	7	13	7
Others (55)	26	20	9
Initial US approval period			
Before 1979 (30)	6	18	6
1980–1999 (33)	20	11	2
After 2000 (55)	25	17	13

[a]PI was not available in the UK.

Table 5. Analysis of differences in information in package inserts between the USA and Japan

Stratified factor (number of PIs)	Number of PIs		
	Differences between the USA and Japan		
	Concordant (29)	Different (55)	NA in Japan[a] (34)
PI section in the USA			
Indications (31)	15	8	8
Precautions (64)	11	32	21
Others (23)	3	15	5
Type of biomarker			
Drug target (29)	12	11	6
Metabolizing enzyme (69)	10	34	25
Others (20)	7	10	3
Purpose of biomarker			
Efficacy (37)	16	14	7
Safety (81)	13	41	27
Therapeutic area			
Oncology (36)	14	16	6
Psychiatry (27)	4	11	12
Others (55)	11	28	16
Initial US approval period			
Before 1979 (30)	2	20	8
1980–1999 (33)	7	18	8
After 2000 (55)	20	17	18

[a]PI was not available in Japan.

metabolizing enzymes (mainly safety oriented). A drug target can be used to stratify a disease into two or more distinct illnesses or syndromes based on their biological characteristics, and clinical trials are increasing designed with the use of genomic biomarkers for inclusion eligibility. The majority of genomic biomarkers in the 'Indications' section consisted of drug targets in all three countries examined. The four biomarkers that were not drug targets, included in the 'Indications' section, were chromosome 5q (USA, Japan), KRAS (all), low-density lipoprotein receptor (LDLR, all) and urea cycle disorder (UCD, USA and UK). Chromosome 5q, KRAS and LDLR are not direct targets of drugs but are markers of efficacy. UCD is a safety biomarker for valproic acid but an efficacy biomarker for sodium phenylbutyrate. Differences in drug target descriptions in the PIs among the three countries were mainly related to whether the relevant indication was approved.

Compared with drug target biomarkers, polymorphisms of metabolic enzymes affect drug pharmacokinetics and usually have more modest impacts on drug response. The present study shows that inclusion of information on a metabolic enzyme's genomics is more inconsistent across the three countries when with drug target information. Interindividual variability in drug pharmacokinetics is caused by several factors, including sex, age, weight, renal and hepatic function and genetics. Therefore, pharmacokinetic variability does not necessarily influence drug safety and/or efficacy significantly. The inclusion of information on genomic biomarkers in the PIs for clopidogrel, tamoxifen and warfarin illustrates this issue well. The FDA updated the clopidogrel PI to include, in the 'Warning' section, information stating that the patient's genotype for CYP2C19 could affect the antiplatelet activity of the drug.[28] The warning recommends alternative medications for CYP2C19 PMs. On the other hand, the UK and Japanese PIs provide information on CYP2C19 PM in the 'Precautions' sections (Table S3). The American College of Cardiology Foundation and the American Heart Association published a Clinical Alert that emphasized that information regarding the predictive value of genetic testing is still very limited and that current evidence is insufficient to recommend routine genetic function testing at the present time.[29] Current evidence also does not support personalized treatment with clopidogrel tailored to the CYP2C19 genotype.[30]

In contrast, although several studies of tamoxifen have addressed the association between CYP2D6 genotype and clinical outcome,[31–38] only the UK PI includes information about CYP2D6 pharmacogenomics in the 'Precautions' section. A possible reason for this discrepancy could be differences in the results of relatively small and mostly retrospective studies.[39–41]

The information on genomic biomarkers for tamoxifen was more consistent as there was no information described in only one country.

The warfarin's PI included genomic information on both drug target (VKORC1; vitamin K epoxide reductase complex, subunit 1) and metabolizing enzyme (CYP2C9). A number of retrospective studies have reported a strong association between the presence of VKORC1 and CYP2C9 variants and warfarin dosing, and polymorphisms in VKORC1 have been shown to be more important than those in CYP2C9.[42–44] However, prospective evidence for any clinically relevant benefit of VKORC1 and/or CYP2C9 testing is limited or of uncertain clinical relevance.[45–49] The US warfarin PI provided dosing schedules according to a combination of

Table 6. Analysis of differences in information in package inserts between the UK and Japan

	Number of PIs	
	Differences between the UK and Japan	
Stratified factor (number of PIs)	Concordant (68)	Different (50)
PI section in the UK		
Indications (23)	14	9
Precautions (38)	14	24
Others (10)	1	9
No statement (26)	21	5
Not available (21)	18	3
Type of biomarker		
Drug target (29)	19	10
Metabolizing enzyme (69)	38	31
Others (20)	11	9
Purpose of biomarker		
Efficacy (37)	25	12
Safety (81)	43	38
Therapeutic area		
Oncology (36)	23	13
Psychiatry (27)	16	11
Others (55)	29	26
Initial US approval period		
Before 1979 (30)	14	16
1980–1999 (33)	18	15
After 2000 (55)	36	19

VKORC1 and CYP2C9 genotypes, whereas the PI from the UK gave information only on genetic variability of VKORC1 and CYP2C9. The Japanese PI only presented information on the existence of CYP2C9 polymorphism (Table S3).

The way in which genomic information was described in the PIs depended on the strength of the available data and on the efficacy and expected safety consequences. When the biomarker is a drug target, there is preliminary evidence that the genomic biomarker was associated with drug response prior to initiating the clinical trials. Confirmatory trials were then undertaken for prospective validation of the biomarker. Differences in PIs occurred when there was a lack of strong evidence to provide clear information and recommendations to the prescriber and when the safety or efficacy consequences differed according to subpopulations considered.

Some of the differences may result from differences in health insurance provisions between the three countries. For example, the national health services of the UK and Japan do not reimburse CYP genotyping tests. In the United States, some payers have championed personalized approaches, even if reimbursement is limited.[50] This might lead to some US PIs (e.g. iloperidone, pimozide, tetrabenazine) strongly recommending CYP2D6 genotyping to individualize dosing, whereas there were no recommendations in the PIs from the UK and Japan (Table S3).

Stratification by therapeutic area

The present study showed contrasting results between oncology and psychiatry. The majority of the PIs with genomic information in the 'Indications' section were of the oncology area for all three countries (USA 77%, UK 83%, Japan 81%). In cancer treatment, diagnostic tests are available and pharmacogenomic approaches are already implemented in clinical practice in all three countries. On the other hand, molecular personalized medicine is still not common in psychiatry. Pharmacogenomic studies with concrete results in psychiatry have largely been on genes encoding metabolic enzymes because most psychiatric drugs are metabolized by CYP isoenzymes.

Stratification by initial approval year in the United States

The PIs from the UK and Japan were more likely to differ from PIs from the United States for drugs approved prior to 1980 (Tables 4 and 5). PIs with drug target biomarkers tended to be approved in the United States later than PIs with biomarkers for metabolizing enzymes.

WHAT IS NEW AND CONCLUSION

The United States was the country most likely to introduce genomic information into PIs, followed by the UK and Japan. Pharmacogenomic information in PIs differed among the three countries depending on type of biomarkers and therapeutic area. These differences appeared to vary according to the strength of the evidence supporting use of the genomic biomarkers and on the practicability of translating pharmacogenomic knowledge into PIs. Guidance by drug regulators on appropriate presentation of pharmacogenomic data in PIs should help facilitate the wider use of such information.

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CONFLICT OF INTEREST

The authors report no conflict of interests in this work.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Pharmacogenomic information in the 'Indications' section of the package inserts (PI) of products marketed in the US, UK and Japan.

Table S2 Pharmacogenomic information in the 'Precautions' section of the package inserts (PI) of products marketed in the US, UK and Japan.

Table S3 Pharmacogenetic information in sections, other than 'Indications' and 'Precautions' sections of the package inserts (PI) of products marketed in the US, UK and Japan.

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ORIGINAL ARTICLE
Cardiovascular Intervention

Global Cardiovascular Device Innovation: Japan-USA Synergies

– Harmonization by Doing (HBD) Program, a Consortium of Regulatory Agencies, Medical Device Industry, and Academic Institutions –

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on behalf of the Harmonization by Doing Program Working Group

Background: Global medical devices have become more popular, but investment money for medical device development is not easily available in the market. Worldwide health-care budget constraints mean that efficient medical device development has become essential. To achieve efficient development, globalization is a key to success. Spending large amounts of money in different regions for medical device development is no longer feasible.

Methods and Results: In order to streamline processes of global medical device development, an academic, governmental, and industrial consortium, called the Harmonization by Doing program, has been set up. The program has been operating between Japan and the USA since 2003. The program has 4 working groups: (1) Global Cardiovascular Device Trials; (2) Study on Post-Market Registry; (3) Clinical Trials; and (4) Infrastructure and Methodology Regulatory Convergence and Communication. Each working group has as its goals the achievement of speedy and efficient medical device development in Japan and the USA. The program has held multiple international meetings to deal with obstacles against efficient medical device development.

Conclusions: This kind of program is very important to deliver novel medical devices. Involvement of physicians in this type of activity is also very helpful to achieve these goals. (*Circ J* 2013; **77:** 1714–1718)

Key Words: Cardiovascular devices; Harmonization by Doing; Medical device innovation

Innovation and Safety Issues in Cardiovascular Devices

Cardiovascular devices continue to revolutionize and transform practice with unique solutions to unmet clinical needs. Coronary stents continue to become smaller, more flexible, and yet more durable. Percutaneous heart valves now deliver life-saving therapies that once required surgical implantation. Improved and smaller designs of defibrillators, pacemakers, and ventricular assist devices now allow treatment of a broader group of patients and/or disease states. As they advance, however, the design and manufacturing of these novel devices become progressively complex. Animal and bench models are limited in their ability to characterize device performance in humans, especially for novel devices, and thus, careful, well-designed and ethical clinical trials in patients continue to be the gold standard to provide data to establish a reasonable assurance of safety and effectiveness to support approval by regulatory authorities. Even after approval, widespread post-market use of breakthrough medical device technologies may produce unexpected safety concerns,[1] such as reports of very late stent thrombosis in patients treated with drug-eluting stents (DES).[2]

In addition, investment money is not easily available for medical device development in the market. The worldwide health-care budget constraint has been putting pressure on the medical device industry. Krucoff et al address such points well in the July issue of *JACC Cardiovascular Interventions*.[3] Dr Maisel also addressed regulatory challenges and opportunities in medical device development from the US Food and Drug Administration (FDA)'s standpoint in the same issue.[4]

Increasingly, development and evaluation of novel medical devices require a global approach. Although regulatory standards and processes differ across countries and regions, regulatory authorities in the USA and Japan have undertaken an

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Table. Harmonization by Doing Working Groups

Working group	Current mission
1. Global Cardiovascular Device Trials	Improve the interactions and exchange of ideas between Japan MHLW/PMDA, US FDA, academia, and industry, and to provide a forum to identify, discuss, and develop solutions to barriers to single-protocol clinical trials to be conducted in both the USA and Japan, in order to facilitate the timely and more cost-effective global introduction of new, safe, and effective device technologies.
2. Study on Post-market Registry	Facilitate multilevel discussion and collaboration between Japanese and US institutions regarding post-market global monitoring of MCSDs, including the incorporation of Japanese data with that of the USA in the INTERMACS registry and to use these data to guide future use of this technology. While the current WG2 mission is currently concentrated on MCSDs, WG2 activities should be expanded to include global post-market data collection for other cardiovascular devices, and the application of this information to guide the continued use of these device technologies, as well as to guide the evaluation of future devices.
3. Clinical Trial Infrastructure and Methodology	Facilitate the development of a robust and effective clinical trial infrastructure in the USA and Japan to support the conduct of global clinical trials to allow the timely introduction of new safe and effective medical devices into the USA and Japan.
4. Regulatory Convergence and Communication	Facilitate the timely global introduction of new medical technologies by identifying and addressing specific regulatory barriers through proof-of-concept projects, specifically, to improve administrative practices within the context of existing regulations with the goal of convergence between Japanese and US practices and improved communication between stakeholders.

FDA, Food and Drug Administration; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCSD, mechanical circulatory support device; MHLW, Ministry of Health, Labor and Welfare; PMDA, Pharmaceuticals and Medical Devices Agency.

initiative to demonstrate how cardiovascular device development and evaluation can be efficiently conducted using such a global approach, to the benefit of patients in both countries.

Device Lag in Japan and the USA Compared to Europe

Historically, new medical devices have been launched onto the market in Europe, because the regulatory standard in the European Union (EU) is the demonstration of safety and performance, which typically has been accomplished through a small or medium-sized clinical study. Additional preclinical evaluation and larger pivotal clinical trials are then performed to support marketing of these devices in the USA, and sometimes further trials in Japan lead to marketing approval and release in Japan. Despite the fact that the USA and Japan constitute the 2 most lucrative medical device markets in the world, this approach has meant that doctors and patients in Japan and the USA have had, at times, significant delays in access to new medical devices, and certain devices are never marketed in these countries at all. In Japan, this delay has been called "device lag" and the Japanese regulatory authority the Pharmaceuticals and Medical Devices Agency (PMDA), recognizes this phenomenon as an important issue. PMDA has made tremendous efforts to solve this problem since the first Mid-term Plan started in April 2004.[5,6] The current approach followed by industry, to obtain marketing approval in Europe first, and only then in the USA and Japan, not only results in time delays to access, but also to redundancy and added cost in research and development as clinical trials are independently performed in each country. Most importantly, such fragmented efforts can ultimately lead to poorer quality data overall, particularly for information related to rare but catastrophic safety problems.

Global Regulatory Collaboration

The recognition that the biology and epidemiology of cardiovascular disease is largely driven by common risk factors independent of ethnic, scientific, clinical and economic factors, has encouraged growing interest in efforts to study new devices through more efficient, high-quality global collaborations. Such efforts respect the independence of individual governmental jurisdictions of national regulatory authorities, while concomitantly encouraging the convergence of basic principles of medical device safety and performance evaluation through the best ethics, science, and methods of human clinical research. The Global Harmonization Task Force (GHTF), through its founding member nations, Japan, Canada, Australia, the EU, and the USA, has focused manufacturers and regulators on the development of consensus guidelines for such principles for more than a decade.[7] Moreover, a new consortium, the International Medical Device Regulators Forum (IMDRF) was set up in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. The IMDRF is a voluntary group of medical device regulators from Australia, Brazil, Canada, China, the EU, Japan and the USA, as well as the World Health Organization, who have come together to build on the strong foundational work of the GHTF, and to accelerate international medical device regulatory harmonization and convergence.[7] Furthermore, a more pragmatic program that includes academic clinicians along with other stakeholders, the Japan-USA Harmonization by Doing (HBD) program,[8] was initiated in 2003.

HBD Program

The HBD program provides a forum for collaboration between Japanese and US regulators, industry, and academic clinicians, where all stakeholders can engage in open discussions toward the identification and resolution of obstacles to conducting global clinical trials and harmonization of regulatory processes. The objective of HBD is to eliminate redundancies, added costs, and time delays inherent in sequential clinical trials. The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective breakthrough cardiovascular technologies to benefit patients worldwide. HBD is uniquely different from other global harmonization initiatives in that the program aims to fulfill its mission through practical experience – that is, by doing – and sharing lessons learned from these experiences. This is achieved through proof-of-concept projects, in which specific challenges are identified and potential solutions are tested. The current membership of HBD includes members of the FDA, Japan's Ministry of Health,

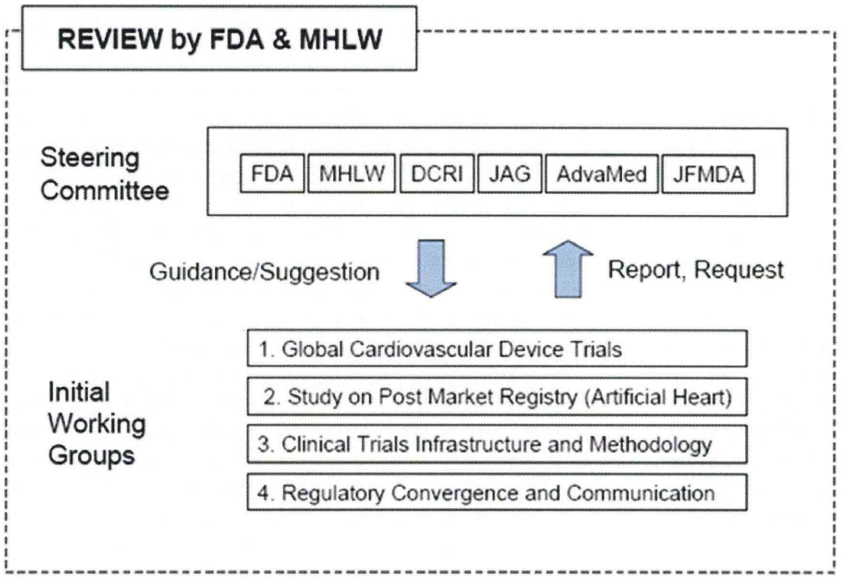

Figure. Structure of Harmonization by Doing. The Steering Committee is composed of representatives from the industry, academia, and government agencies in both the USA and Japan. AdvaMed, Advanced Medical Technology Association; DCRI, Duke Clinical Research Institute; FDA, US Food and Drug Administration; JAG, Japanese Academic Group; JFMDA, Japan Federation of Medical Devices Associations; MHLW, Ministry of Health, Labor and Welfare.

Labour and Welfare (MHLW)/PMDA, US industry (represented by the Advanced Medical Technology Association [AdvaMed] and other cardiovascular device manufacturers who are not members of AdvaMed), Japanese industry (represented by the Japan Federation of Medical Devices Associations [JFMDA]), US cardiovascular academia (represented by Duke Clinical Research Institute [DCRI]), and the Japanese academic community from cardiovascular fields. The HBD program is overseen by a steering committee, which includes members from each stakeholder group, and includes 4 working groups (WGs). **Table** outlines the 4 WGs and their current mission.

Through the activities of each of the WG, as well as the HBD steering committee, the complex array of challenges faced when designing and executing global clinical trials can be overcome in a more manageable stepwise manner. Furthermore, potential harmonization of regulatory practices and communication between US and Japanese regulatory authorities can shorten the device approval time lag through the streamlining of processes and the gaining of a common understanding of the scientific challenges, without adversely affecting current review practices or time lines. HBD's premise is that if all stakeholders share a portion of their experiences on different aspects of global trials, as well as lessons learned through the regulatory review processes required to conduct such global trials and achieve market approval for new devices where possible, all parties involved would benefit through a reduction in duplicative efforts by solving common problems. This sharing of information, however, must be carried out in a manner that protects the confidential and trade secret information of industry sponsors that are involved, and with the agreement of all stakeholders involved.

HBD History

From December 2003 to March 2004, joint meetings between FDA, MHLW-PMDA, DCRI and industry were held at FDA in Rockville, Maryland, USA to talk about the HBD concept and the HBD collaboration process. This was followed by other similar meetings at MHLW in Tokyo, Japan, and the first public announcement in a program at the annual scientific meeting of the Japan Circulation Society in March of 2004. The first in-depth HBD East Think-Tank Meeting took place in Tokyo in December 2005. Three main outcome goals were agreed on at the 2005 Think Tank meeting: (1) build a more robust clinical research infrastructure; (2) compare medical device good clinical practice (GCP) to determine if any significant differences exist that could be obstacles to the HBD process; and (3) define and clarify the rules for increased and better cooperation among all parties involved. The second HBD Think-Tank Meeting was successfully held in January 2007 in Durham, North Carolina, USA as HBD West 2007. Representatives from more than 25 academic institutions, industry organizations and companies as well as government regulators from the USA and Japan attended and engaged in discussion during this 2-day meeting. During the HBD West 2007 meeting, the HBD structure (**Figure**) and the initial 4 HBD WG missions were introduced. The third HBD Think-Tank Meeting, HBD East 2008, was convened in July of 2008 in Tokyo, Japan. This meeting provided a forum for discussion on convergence of regulatory requirements and practices through concrete experience "by doing" in the USA and Japan. To continue the discussions and review the past HBD activities, the HBD West 2009 Think-Tank Meeting was held in Silver Spring, Maryland, USA in July of 2009. Unfortunately, the HBD East 2011 Thank-Tank Meeting planned on 16 and 17 March in Tokyo was cancelled due to the earthquake in East Japan that occurred on 11 March 2011. There were several HBD sessions, however, held by each WG to share progress and accomplishment during the AdvaMed Medtech Conferences 2011 on 26 September in Washington, DC, USA, as well as the Transcatheter Cardiovascular Therapeutics (TCT) 2011 meeting on 4–7 November 2011 in San Francisco, California, USA Another global educational program titled "Japan-USA Synergies in Global Medical Device Innovation: Harmonization by Doing" was held at the TCT 2012 meeting.[9] Most recently, an HBD-related open-to-the-public meeting was held during the Kamakura Live 2012 in Kamakura, Japan.