（倫理面の配慮）

本研究はヒトを対象とするものではないため、該当しない。

C. 研究結果

1）英国の現地調査

ロンドン・聖バーソロミュー病院において、Prof. Tucker を訪問し、インタビューを行った。Prof. Tucker は、医師であり、循環器領域の医療機器の研究者であり、また、自ら医療機器開発に関するコンサルト等も行っている。さらに、聖バーソロミュー病院の倫理委員会の委員長であり、NHS の倫理コンサルタントも務めている。

Prof. Tucker によれば、英国の医療機器規制では、医療機器企業が当該機器の CE マーク取得を目的として臨床試験を実施する場合は事前に規制当局へ届出が必要とされている。一方、大学等のアカデミアにおいて医学的、生理学的な目的で行われる臨床試験の場合、使用される医療機器の CE マーク取得の有無にかかわらず、規制当局への届出は不要で、NHS または大学の倫理委員会の承認が取得されれば臨床試験を実施することができる。また、CE マークを取得した医療機器を使用する臨床試験では、スポンサーが医療機器企業であっても、規制当局への届出は不要で、NHS または大学の倫理委員会の承認のみで実施可能である。つまり、CE マーク未取得の医療機器を用いた臨床試験を行う場合、試験の目的によって、規制当局への届出の要不要が異なってくることになる。

例えばアカデミアにおいて、ある医療機器（CE マーク未取得）を用いた場合の人間の生理学的反応を検討するという目的で，規制当局に届出をせずに臨床試験を計画、実施し、後にその研究で得られたデータを当該医療機器の製造・販売企業が譲渡して、CE マークを取得するというようなことも法的には可能であり、実際に行われることがあるということであった。なお、彼の挙げた実例は、低侵襲の治療機器であった。植え込みタイプの高侵襲医療機器の場合でも同じ状況にあるかどうかは、確認できていない。

この規制状況（の矛盾）について、MHRA の担当者もこの事実に気づいており、「医療機器の国内規制については、見直すべき点がある」と認めていた。

なお、MHRA で確認されたことだが、EU 圏内では”clinical trial”という用語は、法的に医薬品を用いる臨床試験のみを示し、医療機器を用いる臨床試験は”clinical study”あるいは”clinical investigation”等と呼んでおり、”clinical trial”と区別して使用しているとのことであった。

2）モバイルメディカルアプリを含む医療用ソフトウェアの規制

多くの医療機器がコンピュータを搭載し、医用ソフトウェアでその機能を発揮するようになっている。米国 FDA は 1989 年には”FDA Policy for the Regulation of Computer Products”を発表してソフトウェアに関する規制方針を示してきた。しかし、昨今のソフトウェアの種類の多様化に伴い、2005 年に一旦この Policy を撤回し、ソフトウェアを分類し、

それぞれに対してより適切な規制を行う方針とした。その一連の行動の中で、2011年7月にFDAは”Mobile Medical Applications Draft Guidance”を発表した（http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf）。この中で、スマートフォンやタブレット型コンピューター等に搭載されるモバイルアプリのうち、一部を「モバイルメディカルアプリ」と規定して、規制の対象とされている。「モバイルメディカルアプリ」に該当する例として、「血糖値計に無線接続し、結果の表示、計算、傾向分析、変換、PDAへのダウンロードを行うアプリ」や「患者の体表面積に基づいて必要な化学療法の量を計算するアプリ」などが挙げられている。クラス分類については、「モバイルメディカルアプリ」に均一な分類はなく、その使用目的や機能に応じたクラス分類が適用されるようである。

日本国内での状況はどうか。実は、医療用ソフトウェアの規制の段階で、現状では海外とハーモナイゼーションできていない。国内では、医療機器に組み込まれたソフトウェアのみが医療機器として規制されている状況で、医療機器に組み込まれていないスタンドアローン型の医療用ソフトウェアは欧米では規制されているのに対して、日本では規制の対象外である。しかし、米国の「メディカルモバイルアプリ」規制方針の発表を受けて、2012年10月より経済産業省において、医療用ソフトウェアに関する研究会が開催され、これらの規制について検討が始まり、2013年3月には中間報告書が公表された（http://www.meti.go.jp/committee/kenkyukai/shoujo/iryou_software/pdf/report_001_02.pdf）。この報告書では、現行の薬事法で医療機器規制の枠外であるスタンドアローン型医療ソフトウェアについては、ガイドラインによる自主規制を導入する方向性を示すとともに、ガイドライン策定における基本的考え方を提示している。今後は、この報告書を元にして、ガイドラインが策定されるものと思われる。

D. 考察

英国における実地調査では、医療機器の臨床開発の運用状況の国内外の差が非常に大きいという実態が判明した。日本では一様に「臨床試験」と訳されるが、EU域内では”clinical trial”，“clinical study/investigation”を法的に異なる用語として使い分けているということも、今回初めて分かったことである。医療機器の臨床開発を取り巻く状況は、医薬品の世界からは想像できないほど国毎に様々であることが判明した。

医療用ソフトウェアの規制については、以前から国内外で大きな違いがあり、一部では問題となっていた。しかし、2011年のFDAの動きを受けて、日本でもようやく研究会が発足し、国内外のギャップを埋める方向性が示されたことは評価できると考える。特にモバイルアプリを含むソフトウェアの世界は、医療機器本体の物理的制限がないために「国境」がなく、規制環境のギャップは即国際競争力の低下につながるため、より積極的なハーモナイゼーションが望まれる。

E. 結論

医療機器の開発を取り巻く環境は、医薬品からは想像もつかないほど国内外の差が大きい。これらの差についての知識は、デバイス・ラグの本質を理解するとともに対処法を検討する上で不可欠である。また、医療機器の技術革新は非常なスピードで進むため、各国の規制状況も変化が速い。常に海外の医療機器規制の変化をキャッチアップして、積極的なハーモナイズを行うことが、主に国際競争力の観点から望まれる。

F. 健康危険情報

特になし。

G. 研究発表

1. 論文発表

なし

2. 学会発表

なし

H. 知的財産権の出願・登録状況

（予定を含む）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金（地球規模保健課題推進研究事業）
平成24年度分担研究報告書

デバイス・ラグ解消に向けた海外規制の実態とその対策に係る調査研究

添付文書安全性記載の国際比較

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研究要旨：
【背景】医薬品・医療機器の承認審査・市販後規制の内外差に影響を与える因子として、医療者と患者及び一般市民とのコミュニケーションの問題がある。添付文書はそのコミュニケーションのための基本資料である。
【目的】国内外の医薬品添付文書記載内容を比較することによって、規制の内外差を検討する。
【方法】2001年4月から2011年7月の間に日本で承認された新有効成分医薬品のうち、米英両国でも承認されている189品目について、添付文書の安全性記載分量の比率、及び日米両国については、警告欄（米国の場合にはBoxed warning）を持つ添付文書の比率 (PwB)並びに警告欄の有無の一致率を、効能効果別に比較検討した。
【結果】添付文書全体分量に対する安全性記載分量の比率(PSI)は、心血管系医薬品では日本が米英に比べて有意に低く、抗がん剤・免疫系医薬品では逆に日本が高かった。精神・神経系医薬品では、米国のPSIが日英より有意に高かった。禁忌記載部分の比率(PCI)は、抗がん剤・免疫系医薬品以外では、PSIと対照的な結果を示した。PwBは血液系で米国が高く、抗がん剤・免疫系では日本が高かった。警告品目は、特に血液疾患と生殖・尿路系疾患で、日米間での不一致が多かった。
【考察と結論】規制の国際調和が行われ、国際共同治験が一般的になった現在でも、添付文書の安全性記載には、効能効果により三極間で明らかな差がある。三極で共通した臨床試験データを審査しているにもかかわらず、このような差が見られるのは、臨床試験データ以外の要素が考慮されているためと考えられる。今後は、このような三極差が生じる原因を明らかにする研究、さらには、医療機器でも同様な差を検討する研究が必要である。

A.研究目的

医療者と患者・一般市民が医薬品・医療機器に関してコミュニケーションを行う際に、添付文書は、重要な基礎資料となる [1]。近年、国際共同治験が一般的になり、The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)において規制の国際調和が行われるようになった現在でも、安全性に関する規制の三極差は、厳然と存在する[2][3]。

これは、医薬品・医療機器の承認審査や規制が科学的データのみに依拠するのではなく、当該地域の国や地域の社会的・文化的背景を踏まえて医薬品・医療機器が使用されることを前提としているからと考えられる。

添付文書についても、そのガイドラインも、三極でそれぞれ独自のものが規定されており、米国と英国のように、たとえ同一の言語を用いる国・地域間でも、その書きぶりは異なる。しかし、どのような品目で、どの程度異なるのかは、これまで、系統的な研究が全くない。

本研究の目的は、特に患者・医療者間のリスクコミュニケーションに重要な影響を与える添付文書の安全性記載に注目し、その三極差を定量的手法で明らかにすることにある。

なお、本研究の成果は、Shimazawa R, Ikeda M. Safety information in drug labeling: a comparison of the United States, the United Kingdom, and Japan. Pharmacoepidemiol Drug Saf 2013;22:306-18 にて発表済みである。

B.研究方法

１．比較対象国：米国、および欧州の中では、米国と言語が共通し、国民皆保険制度を持ち、ICH で承認審査制度の国際調和も行われている英国とした。

２．対象品目：2001 年 4 月から 2011 年 7 月の間に日本で承認された新有効成分医薬品（非治療目的のワクチンや画像診断薬等を除く）のうち、米英両国でも承認されている（すなわち三極いずれでも承認されている）189 品目

３．評価項目

１）承認情報：日米英における各品目の一般名、商品名、効能効果、申請年月日、承認年月日

２）添付文書：添付文書全体の記述量に対する下記の安全性部分記述量の比

PSI (proportion of total safety information)：安全性記述部分の総和

PCI (proportion of contraindication)：禁忌記述部分

PwB (proportion of the number of labels with a boxed warning)：警告欄がある添付文書の比率（日本と米国のみ。英国の添付文書には禁忌欄のみで警告欄はなし）。警告欄の有無はハンドサーチで判断した。

それぞれの比率は、英語の場合には語数、日本語の場合には文字数により算出した。また、警告欄の有無の日米間での一致率（[日米でともに警告欄が有る＋日米でともに警告欄が無い]/[日本で有り・米国で無し＋日本で無し・米国で有り]）も算出した。

効能効果は Anatomical Therapeutic Chemical(ATC) system
http://www.whocc.no/atc_ddd_index/
に依拠した。

４．対象資料：下記の URL から閲覧可能な公開文書

日本の承認情報
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html

米国の承認情報
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

米国の添付文書情報
http://dailymed.nlm.nih.gov/dailymed/about.cfm

欧州の承認情報
European public assessment reports.
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125

英国の添付文書情報
The Electronic Medicines Compendium
http://www.medicines.org.uk/emc/

なお、本研究は、個人情報を含まない公開文書を用いた横断的研究であり、ヒトあるいはヒト試料を対象とした研究ではない。

C.研究結果

表 1 に効能効果別 (ATC code)に PSI を日米英間で比較した結果を示す。全体の平均では PSI は日米英ともに 47%前後で一致し、差は見られないが、特定の分野では統計学的に有意な差が見られた。すなわち、循環器系(code C)では、日本の添付文書で PSI が 40%と米英の 52%, 51%に比べて有意に低かった。抗がん剤・免疫系(code L)では、日本の PSI が米英よりも高かった。精神・神経系(code N)では、米国の PSI が日英に比して有意に高かった。

表 2 に効能効果別 (ATC code)に PCI を日米英間で比較した結果を示す。全体の平均では米国の PCI が日英に比較して低かった。消化管系(code A)、生殖・泌尿器・性ホルモン系(code G)、抗がん剤・免疫系(code L)のいずれでも、日本の PCI は米英に比して高かった。

表 3 に効能効果別 (ATC code)に PwB を日米間で比較した結果を示す。PwB は、全体の平均では米国で 38%、日本で 42%とほぼ同様だったが、血液系(code B)では米国で 70%に対し日本で 40%、抗がん剤・免疫系(code L)では米国 58%に対し日本では 95%など、効能効果によって大きな差がある分野があった。警告欄の有無の一致率についても、全体では 71%であり、消化管系(code A)で 85%、感染症系(code J)で 87%、感覚器系(code S)で 86%と高かったのに対し、血液系(code B)で 50%、抗がん剤・免疫系(code L)

で63%と低かった。

D.考察

今回の検討により、添付文書の安全性記述輌は、日米英間で、明確に異なることが示された。その相違は、3種類の安全性記述の指標により、また効能効果により、それぞれ異なった差異のパターンを示した。

いわゆるドラッグ・ラグ（諸外国に比して日本で新薬の承認が遅れること）[4]の原因として、日本の規制当局が過度に安全性を懸念するためという指摘が時に見受けられるが、こと医薬品添付文書の安全性記述を定量的に見る限りでは、そのような主張の根拠は得られなかった。

今回の検討は横断研究であり、結果の原因考察には限界がある。今後さらに研究を進め、医療機器においても医薬品と同様の差異があるのかを検証し、あるとすれば、その差異の背景・原因を明らかにするとともに、質的研究によって、その差の内容をも明らかにする必要がある。

E.結論

効能効果により、日米英間には、医薬品添付文書の安全性記述量に明確な差が存在する。原則として品目の科学的データには明確な差異がないのだから、添付文書の安全性記述量の差は、たとえば、医療保険制度のような、科学的データ以外の地域特有の要素に基づくものと思われる。

より適切な添付文書のあり方を明らかにするためには、本研究で示された安全性記述量の内外差の原因を解明する、更なる研究が必要である。

F.健康危険情報

なし

G.研究発表

1.論文発表

Shimazawa R, Ikeda M. Safety information in drug labeling: a comparison of the United States, the United Kingdom, and Japan. Pharmacoepidemiol Drug Saf 2013;22:306-18

2.学会発表

今年度は、なし

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表 1. Proportion of total safety information to all information on the label classified according to ATC code

ATC Code	A (n=20)	B (n=10)	C (n=10)	D (n=3)	G (n=10)	H (n=5)	J (n=30)	L (n=40)	M (n=5)	N (n=32)	P (n=1)	R (n=10)	S (n=7)	V (n=6)	All (n=189)
US	41 [7]	47 [8]	52 [5]	56 [11]	45 [7]	36 [11]	42 [12]	52 [7]	47 [10]	58 [11]§	63	44 [7]	51 [13]	49 [11]	48 [10]
UK	41 [9]	43 [12]	51 [6]	54 [8]	50 [8]	42 [5]	47 [12]	47 [9]	43 [8]	50 [11]	60	39 [8]	48 [10]	51 [13]	47 [10]
Japan	44 [11]	46 [7]	40 [7]*	41 [9]	47 [13]	42 [7]	42 [11]	56 [9]‡	47 [12]	45 [8]	46	36 [8]	41 [8]	50 [8]	46 [11]
P value	0.52	0.66	<.001	0.18	0.58	0.34	0.04†	<.001	0.74	<.001		0.05	0.26	0.97	0.09

Abbreviations: ATC, Anatomical Therapeutic Chemical; A, Alimentary tract and metabolism; B, Blood and blood forming organs; C, Cardiovascular system; D, Dermatologicals; G, Genitourinary system and sex hormones; H, Systemic hormonal preparations, excluding sex hormones; J, General anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculo-skeletal system; N, Nervous system; P, Antiparasitic products; R, Respiratory system; S, Sensory organs; V, Various.

Values are means (%) [SD].

* Smaller than the US and the UK.

† ANOVA indicates *P* value= .04, but a Scheffe's *post-hoc* test does not show significant differences between the means.

‡ Larger than the UK.

§ Larger than the UK and Japan.

表 2. Proportion of contraindications to all information on the label classified according to ATC code

ATC Code	A (n=20)	B (n=10)	C (n=10)	D (n=3)	G (n=10)	H (n=5)	J (n=30)	L (n=40)	M (n=5)	N (n=32)	P (n=1)	R (n=10)	S (n=7)	V (n=6)	All (n=189)
US	0.3 [0.2]	0.6 [0.6]	1.8 [1.5]	1.3 [1.2]	1.3 [0.8]	0.7 [0.5]	0.8 [0.9]	0.5 [0.5]	0.4 [0.2]	0.8 [0.9]	1.4	0.5 [0.4]	1.0 [0.4]	0.6 [0.7]	0.7‡ [0.9]
UK	0.4 [0.3]	0.8 [0.8]	1.5 [0.9]	1.1 [1.4]	2.8 [1.3]	1.4 [1.0]	1.0 [0.9]	0.6 [0.5]	0.9 [1.1]	1.7 [1.7]	3.9	0.8 [0.7]	0.8 [0.4]	1.2 [1.0]	1.1 [1.1]
Japan	0.8* [0.5]	1.4 [1.2]	1.9 [1.1]	0.9 [0.4]	3.9* [2.2]	1.6 [1.6]	1.2 [1.2]	0.9* [0.6]	1.8 [1.4]	1.6 [1.8]	3.0	0.7 [0.6]	1.0 [0.6]	1.0 [0.5]	1.3 [1.4]
P value	<.001	0.104	0.713	0.870	0.004	0.450	0.211	0.014	0.146	0.038†		0.461	0.774	0.46	<.001

Abbreviation: ATC, Anatomical Therapeutic Chemical; A, Alimentary tract and metabolism; B, Blood and blood forming organs; C, Cardiovascular system; D, Dermatologicals; G, Genitourinary system and sex hormones; H, Systemic hormonal preparations, excluding sex hormones; J, General anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculo-skeletal system; N, Nervous system; P, Antiparasitic products; R, Respiratory system; S, Sensory organs; V, Various. Values are Mean (%) [SD].

* Larger than the US and the UK.

† ANOVA indicates *P* value=0.04, but a Scheffe's *post hoc* test does not show significant differences between the means.

‡ Smaller than the UK and Japan

表 3. Proportion of the number of labels with a boxed warning to that of all labels classified according to ATC code

ATC Code	A (n=20)	B (n=10)	C (n=10)	D (n=3)	G (n=10)	H (n=5)	J (n=30)	L (n=40)	M (n=5)	N (n=32)	P (n=1)	R (n=10)	S (n=7)	V (n=6)	All (n=189)
US	20 (4)	70 (7)	50 (5)	0	20 (2)	20 (1)	33 (10)	58 (23)	20 (1)	41 (13)	0	30 (3)	0	50 (3)	38 (72)
Japan	25 (5)	40 (4)	20 (2)	0	40 (4)	0	33 (10)	95 (38)	60 (3)	25 (8)	100 (1)	0	14 (1)	50 (3)	42 (79)
US+/Japan+	15 (3)	30 (3)	20 (2)	0	0	0	27 (8)	58 (23)	20 (1)	16 (5)	0	0	0	50 (3)	25 (48)
US+/Japan-	5 (1)	40 (4)	30 (3)	0	20 (2)	20 (1)	7 (2)	0	0	25 (8)	0	30 (3)	0	0	13 (24)
US-/Japan+	10 (2)	10 (1)	0	0	40 (4)	0	7 (2)	38 (15)	40 (2)	9 (3)	100 (1)	0	14 (1)	0	16 (31)
US-/Japan-	70 (14)	20 (2)	50 (5)	100 (3)	40 (4)	80 (4)	60 (18)	5 (2)	40 (2)	50 (16)	0	70 (7)	86 (6)	50 (3)	46 (86)
Concordance *	85 (17)	50 (5)	70 (7)	100 (3)	40 (4)	80 (4)	87 (26)	63 (25)	60 (3)	66 (21)	0	70 (7)	86 (6)	100 (6)	71 (134)

Abbreviation: ATC, Anatomical Therapeutic Chemical; A, Alimentary tract and metabolism; B, Blood and blood forming organs; C, Cardiovascular system; D, Dermatologicals; G, Genitourinary system and sex hormones; H, Systemic hormonal preparations, excluding sex hormones; J, General anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculo-skeletal system; N, Nervous system; P, Antiparasitic products; R, Respiratory system; S, Sensory organs; V, Various. Values are % (No.).

+ represents labels with a boxed warning. - represents labels without a boxed warning.

*Concordance represents the sum of labels with a boxed warning both in the US and in Japan and those without a boxed warning either in the US or in Japan.

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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.

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,

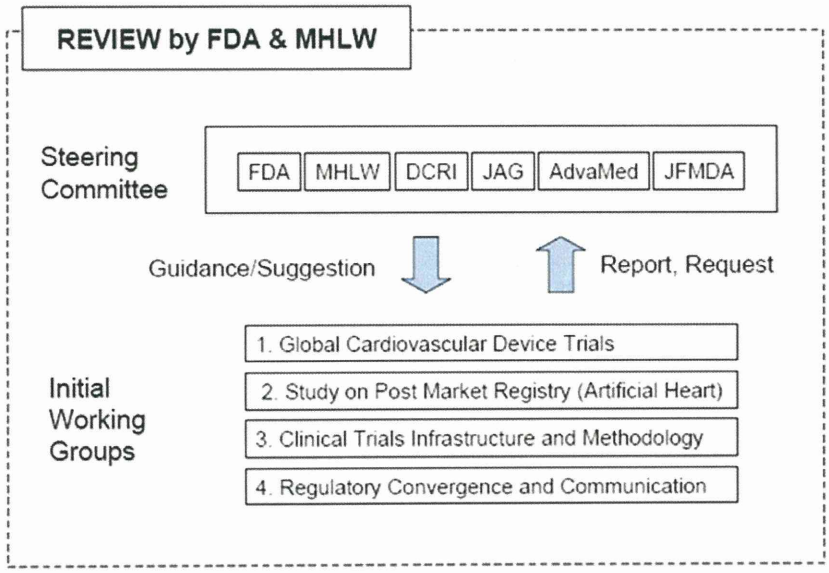

Figure. Structure of Harmonization by Doing. The Steering Committee is composed of representatives from the industry, academia, and government agencies in both the USA and Japan. AdvaMed, Advanced Medical Technology Association; DCRI, Duke Clinical Research Institute; FDA, US Food and Drug Administration; 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.

WG Key Activities

WG1: HBD-Related Clinical Studies – Endeavor Japan and SPIRIT Japan Trials

As described here, the ultimate goal of the HBD initiatives is to lead to more expeditious development and marketing in both countries for those new therapies that have been demonstrated to be reasonably safe and effective. One important step toward accomplishing this objective is the carrying out of global clinical trials enrolling patients worldwide using harmonized study protocols. In line with this HBD concept, the Endeavor Japan trial was initiated in the spring of 2005 for Medtronic's Endeavor® Zotarolimus-Eluting Coronary Stent. This Japanese study for a new DES utilized the identical study protocol that was used in the global Endeavor-II trial,[10] which was an important supporting study for US marketing approval. Following the Endeavor Japan study, a second study, the SPIRIT Japan study, to evaluate the Abbott Vascular XIENCE V Everolimus-Eluting Coronary Stent, was conducted in the USA and Japan simultaneously under a global DES development strategy.

There were several discussion points in executing these clinical trials. One was whether these trials should be separated from a larger global trial of each. It was a dilemma. Future clinical trials might not happen if these trials failed, but if the trials were separated, Japan might lose opportunities to catch up with the advanced countries. Finally, as a learning step, the separated study design with an identical study was chosen.

Experience from these studies then demonstrated that the Japanese cardiology community was in fact ready to participate fully in global DES trials. Ten Japanese sites joined a global DES trial, the PLATINUM trial, and contributed very effectively.[11]

WG2: INTERMACS and J-MACS

Referring to the INTERMACS program,[12] the J-MACS program[13] was launched in 2010 for post-marketing follow-up for the 2 left ventricular assist devices approved in Japan in 2010, EVAHEART[14] and DuraHeart.[15] HBD WG2 fully supports this program.

WG3: Infrastructure for Clinical Studies in Japan

Through the clinical studies described here (the WGs 1- and 2-related studies), infrastructure for clinical studies in Japan was further developed. This might lead to more clinical studies from Japan such as the 2 post-market studies in cardiology, the TAXUS Japan Postmarket surveillance study[16] and, the MIRACLE-ICD outcome measured in Japanese indication (MOMIJI) study.[17]

WG4: Collaborative Consultation and Review of Pre-Marketing Applications Pilot Program and Research Papers

Led by WG4, a direct consequence of HBD is the Medical Device Collaborative Consultation and Review of Pre-marketing Applications pilot program.[18,19] This unique program involves the active engagement of the industry sponsor with both US FDA and MHLW/PMDA. A goal of the pilot program is to advance both the speed and quality of clinical/statistical consultations and the regulatory review process for potential earlier market access and improved public health benefit.

WG4 compared GCP between Japan and the USA. The outcome was published as a key accomplishment of WG4.[20] The research concluded that there were several administrative differences but no essential differences between the 2 sets of GCP.

HBD Future and Conclusions

The next HBD East Think-Tank Meeting, HBD East 2013 is currently planned for 9 and 10 July in Tokyo, Japan. As a dynamic program, HBD has recognized that it must be able to adapt as necessary to address new therapies and new scientific challenges. In addition to innovations in DES technology, such as the use of biodegradable materials, this meeting will address transcatheter aortic and mitral valve interventions. Moreover, it is envisioned that, over time and with appropriate support from its participating stakeholders, HBD could expand to include other medical devices such as orthopedic products. Finally, as the HBD program matures, other regulatory bodies in other countries could be involved.

Development of innovative medical devices is often a driver for evolution in medicine. Physicians, industry, and regulators all have an important role to play in ensuring that new medical devices provide safe and effective therapy. Physicians are primary contributors to medical device development through their participation in clinical trials. In clinical research activities for medical device development, collaboration among clinicians, the device industry, and regulators is an essential to making innovative therapy available to patients. Unlike GHTF, HBD provides physicians with an open platform on which to collaborate with industry and regulators. Contributions from each stakeholder group will be needed to ensure the future success of HBD, but with a focus on clinical and scientific challenges and new product innovation, HBD will continue to streamline the advance of new medical devices.

Disclaimer

This article represents the personal views of the authors and does not represent official FDA correspondence or guidance or official MHLW/PMDA correspondence or guidance. The HBD program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the USA and Japan.

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Disclosures

Conflict of Interest: Gary Thompson is a full-time employee of Abbott Vascular. He receives travel expenses and salary, which are unrelated to research and exceed an annual total of 50,000 yen from the company.

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The vaccine gap between Japan and the UK

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ABSTRACT

Objective: To study and compare the Japanese vaccine policy with the policy in the UK and to discuss factors that may explain the gap in vaccine availability between the two countries.
Methods: We analysed approval and immunisation programme data from Japan and the UK for 20 common vaccines, all of which were approved and available from the UK National Health Service.
Results: Of these 20 common vaccines, only four were introduced in Japan. Of the 16 unapproved vaccines, 11 were combination vaccines. Indications for the other five unapproved vaccines were the prevention of infection with meningococcus (3 vaccines) and pneumococcus (2 vaccines). Coverage of diphtheria, tetanus, pertussis, and poliomyelitis vaccines was similar between the two countries whereas that of measles and rubella was higher in Japan.
Conclusions: These results show that there is still a large gap between Japan and the UK regarding access to 20 common vaccines and immunisation programmes. The keys to closing this gap include: (1) revision of vaccine regulations, (2) amendment of vaccine-related laws to secure funding and cooperation between professionals and public health authorities, and (3) improvement in the perception of vaccines among the general public and mass media.

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1. Introduction

Although many health-related indicators, such as life expectancy and the infant mortality rate show that the health situation in Japan is among the best in the world [1], there is a large gap between Japan and other developed countries in the use of vaccines to prevent serious infections [2]. For example, the 7-valent pneumococcal conjugate vaccine (PCV) was only recently approved in Japan (October 2009), more than 8 years after its approval in the UK. Many common vaccines, including those for measles, mumps, and rubella (MMR), the inactivated poliovirus vaccine, and combination vaccines, are not yet available in Japan. This vaccine gap has major implications for public health both in Japan and in other countries. From the perspective of global public health, Japan is cited as an exporter of infectious diseases to countries that have those diseases under better control through vaccination [3]. Global interconnectedness allows infectious diseases to spread greater distances than ever before.

In the case of meningococcal vaccines, the epidemiology of meningococcal meningitis, which has an incidence of around 1000 cases per year in England and Wales [4], but only around 10–20 cases per year in Japan [5], can explain the vaccine availability gap. In other cases, however, the characteristics and causes of the vaccine gap are multifactorial. A large gap between Japan and other developed countries still exists regarding access to new drugs [6,7], despite several important reforms in the Japanese drug approval system. These included the implementation of the International Conference on Harmonisation of

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Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice, the establishment of a new regulatory authority in 1997, and the implementation of Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5) guidelines in 1998 [8,9]. Apart from vaccine development and regulation, one possible cause for the gap relates to the organisation and funding of the immunisation programme [10]. In Japan, the immunisation programme is outside the national health insurance system, whereas in the UK, the immunisation programme is an important part of the NHS. Funding of the immunisation programme in Japan [11,12] has historically been determined by local governments, with the effect of subsidies being sometimes questionable [13]. The effect of public perception on vaccine use is another common problem in developed countries. This is exemplified by the low MMR vaccine coverage in the UK following negative publicity about possible links between the vaccine and autism [14]. The outbreak of pertussis in several US states was probably caused by perception-related vaccine refusal [15].

The purpose of this study was to identify factors contributing to the vaccine gap between Japan and the UK and to advocate solutions for overcoming the problem. We compared data from the vaccine approval and immunisation programmes of the two countries. We selected the UK as a comparator because Japan and the UK have the following background features in common. First, the UK, like Japan, provides a National Health Service. Second, both the UK and Japan offer a non-compulsory immunisation programme. Third, according to ICH guidelines [16], the regulation of vaccines is harmonised between Japan and the EU, of which the UK is a member state. Fourth, both the UK [14] and Japan [17] suffered the effects of negative public perception and widespread concern regarding the MMR vaccine. These similarities highlight the vaccine gap and allow us to analyse its causes.

2. Methods

2.1. Study design

Cross-sectional study of documents published on regulatory agencies' websites.

2.2. Data sources

To compare the approval status of vaccines in Japan with that in the UK, we analysed data on 20 common vaccines routinely offered to children or available from the NHS to adults in certain 'at risk' groups. The 20 common vaccines are all approved in the UK and listed in the electronic Medicines Compendium (eMC) [18] and European public assessment reports (EPAR) [19]. European legislation aims to ensure that the terms by which vaccines are authorised are harmonised across the EU. The European Medicines Agency takes responsibility for the authorisation of vaccines, working with national medicines regulatory authorities, such as the Medicines and Healthcare products Regulatory Agency in the UK.

Japanese approval data were obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) website in the new drug approval section [20], which included a review of all new molecular entities and biologics approved in Japan between June 1999 and March 2012. The UK approval (market authorisation) data were obtained from the eMC [18]. A more detailed description of the regulatory review of the vaccines is given in EPAR [19]. The Japanese immunisation data were obtained from the Infectious Disease Surveillance Center [21]. The UK immunisation data were obtained from the NHS Information Centre website [22].

2.3. Evaluation and analysis

Documents were examined for administrative information and the dates and types of regulatory approval were recorded. Approval delay was defined as the difference between the date of approval in Japan and that of first authorisation in the UK. Review time was defined as the time between the date of application for approval and the actual date of approval. Because of the limited number of vaccines analysed, results are presented in a descriptive manner without statistical interpretation.

3. Results

Table 1 shows approval status data for 20 common vaccines. Four vaccines, i.e., *Haemophilus influenzae* type b (Hib), bivalent and quadrivalent human papillomavirus (HPV), and 7-valent PCV, were introduced in Japan 173, 25, 57, and 104 months later, respectively, than in the UK, whereas the review times for bivalent and quadrivalent HPV, and 7-valent PCV were longer by only 7, 2, and 9 months, respectively, than those in the UK. Although the review time for the Haemophilus b conjugate vaccine was 46 months, this is still much shorter than the launch delay which was 173 months. Of the 16 unapproved vaccines in Japan, 11 were combination vaccines. Indications of the five other unapproved vaccines were for the prevention of infection with meningococcus (3 vaccines) and pneumococcus (2 vaccines).

Table 2 shows the recommendations for and coverage of the vaccines. Hib, PCV, mumps, and HPV vaccines, which are recommended in the UK, are all voluntary in Japan. Meningococcal vaccines are not available in Japan. The coverage of diphtheria, tetanus and pertussis (DTP), and poliomyelitis vaccines was similar between Japan and the UK. That of measles and rubella was higher in Japan. No official coverage data were available for voluntary immunisation in Japan, i.e., for Hib, PCV, and mumps.

4. Discussion

Our study confirmed and characterised the vaccine gap between Japan and the UK. Two of the 4 vaccines that were approved by both countries were approved in Japan 173 and 104 months after their approval in the UK, with a review time of 46 and 25 months, respectively. Although we could not precisely identify the development time, the review time cannot explain the launch delay of these vaccines. Most of the delay is presumably due to delays in

Table 1
Approval data on 20 common vaccines in Japan and the UK.[a]

Generic name	Proprietary name	Approval application (Japan)	Date of approval		Approval delay[b,c]	Review time[b,d]	
			Japan	UK		Japan	UK
Diphtheria, tetanus and poliomyelitis	Revaxis	NA	UA	Jun-03			
Diphtheria, tetanus, pertussis and poliomyelitis	Repevax	NA	UA	Nov-01			
Diphtheria, tetanus, pertussis and poliomyelitis	Infanrix-IPV	NA	UA	Aug-06			
Diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b	Infanrix-IPV + Hib	NA	UA	Jan-05			
Diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b	Pediacel	NA	UA	Oct-02			
Haemophilus influenzae typeb	ActHIB	Mar-03	Jan-07	Aug-92	173	46	
Haemophilus influenzae type b and Meningococcal group C conjugate	Menitorix	NA	UA	Dec-05			
Hepatitis A and Hepatitis B	Ambirix	NA	UA	Aug-02			15
Hepatitis A and Hepatitis B	Twinrix Adult	NA	UA	Sep-96			14
Hepatitis A and Hepatitis B	Twinrix Paediatric	NA	UA	Feb-97			10
Human papillomavirus bivalent	Cervarix	Sep-07	Oct-09	Sep-07	25	25	18
Human papillomavirus quadrivalent	Gardasil	Jul-10	Jul-11	Sep-06	57	11	9
Measles, mumps and rubella (live)	MMRvaxpro	NA	UA	May-06			23
Measles, mumps and rubella (live)	Priorix	NA	UA	Dec-97			
Meningococcal group C conjugate	Meningitec	NA	UA	Sep-07			
Meningococcal group C conjugate	Menjugate	NA	UA	Mar-10			
Meningococcal group A, C, W135 and Y conjugate	Menveo	NA	UA	Mar-10			16
Pneumococcal 7-valent conjugate	Prevenar	Sep-07	Oct-09	Feb-01	104	25	16
Pneumococcal 10-valent conjugate	Synflorix	NA	UA	Mar-09			14
Pneumococcal 13-valent conjugate	Prevenar13	NA	UA	Dec-09			12

NA: not available; UA: unapproved.
[a] As of March 2012.
[b] Represented in months.
[c] Approval delay was defined as the difference between the date of approval in Japan and that of first authorisation in the UK.
[d] Review time was defined as the time between the date of application for approval and the actual date of approval.

application and/or development. The 16 vaccines unapproved in Japan provide stronger evidence for the gap.

The term 'drug lag' [6,7] describes the launch delay of new drugs. Of the 398 new drugs approved either in the US, the EU, or Japan between 1997 and 2007, 220 (55.3%) were approved in Japan [7]; however, the percentage of approval depended on the therapeutic indication. The vaccine gap, with an approval rate only 20% (4/20) in the present study, is outstanding when compared with the much higher anti-infectives approval rate (71.4%) [7].

With the exception of meningococcal meningitis, which has an incidence of only around 10–20 cases per year in Japan [5,23], the vaccine gap results from a complex of regulatory and social problems. We identify three here. First, vaccine regulations in Japan remain to be reformed. There are many stakeholders and governmental organisations for immunisation programmes and policies, including the Ministry of Health, Labour and Welfare (MHLW) Health Service Bureau, the Pharmaceutical and Food Safety Bureau, the PMDA, and the National Institute of Infectious Diseases. Nonetheless, there is no organisation or committee that can gather vaccine data from different areas, assess and evaluate the collected information, and present a recommendation to the government. A body that can lead

Table 2
Comparison of immunisation programme between Japan and the UK.

	Japan		UK	
	Recommendation	Coverage (%)	Recommendation	Coverage (%)
Diphtheria, tetanus, and pertussis[a]	Recommended	98	Recommended	93
Poliomyelitis[a]	Recommended[c]	99	Recommended[d]	93
Haemophilus influenzae type b[a]	Voluntary	ND	Recommended	93
Pneumococcal[a]	Voluntary	ND	Recommended	91
Meningococcal[a]	NA	NA	Recommended	91
Measles[b]	Recommended[e]	94	Recommended[f]	85
Rubella[b]	Recommended[e]	94	Recommended[f]	85
Mumps[b]	Voluntary	ND	Recommended[f]	85
Human papillomavirus	Voluntary	ND	Recommended[g]	87

NA: not available; ND: no official data.
[a] Coverage among 1-year-olds (%) in 2008–2009.
[b] Coverage among 2-year-olds (%) in 2008–2009.
[c] Live attenuated oral vaccine.
[d] Inactivated vaccine given as a combined vaccine with diphtheria, tetanus, and pertussis.
[e] Measles and rubella, but not mumps, given as a combined vaccine.
[f] Measles, rubella, and mumps given as a combined vaccine.
[g] Girls of 12–13 years of age. The number represents the percentage of eligible girls receiving the first dose.

multiple organisations and propose immunisation policies [24] should therefore be established to close the gap. No regulatory guidelines existed for the clinical development and approval of vaccines in Japan before May 2010 [25]. The EU [26] and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [2] have urged the Japanese government to harmonise clinical, regulatory, and technical standards for vaccines with the EU, the US, and the World Health Organization so that foreign vaccines can be imported and Japanese-produced products can be exported. An exemplary case is the polio vaccine. Japan still uses a live vaccine instead of an inactivated one, which has not been approved despite the fact that the live vaccine causes several cases of paralysis per year. On December 15, 2010, an association of polio victims submitted a petition to the MHLW, calling for approval of the importing of an inactivated vaccine. A panel of experts within the ministry also called for such an importation. The ministry's policy, however, is to wait for the four domestic makers to develop an inactivated vaccine. This obvious inaction only deepens the notion that the ministry may try to protect domestic manufacturers' vested interests [11]. Instead, the ministry should delegate vaccine-related decisions to a transparent advisory board [24].

Second, vaccine availability does not provide a single solution for overcoming the gap. The National Health Service in Japan only covers the treatment of diseases, not their prevention. In the case of vaccines covered by the Immunization Law [27], DTP, poliomyelitis, measles, and rubella vaccines are supported by governmental funds and generally provided free throughout Japan, but this does not apply to Hib, HPV, PCV, or mumps vaccines. Some local governments provide subsidies for these vaccines, but the financing policies and recipients' charges differ among these governments [12]. The inevitable consequences are regional disparities [28]. The Immunization Law should be revised to cover Hib, HPV, PCV, and mumps vaccines.

Third is the issue of public perception [29]. In Japan, as in other developed countries, fear of vaccine-preventable diseases has waned and the awareness of potential vaccine-related risks has increased [30]. The history of the MMR vaccine in Japan provides a case study showing that negative public perception threatens vaccine acceptance.

In Japan, a high incidence of aseptic meningitis [17] followed the introduction of the MMR vaccine in 1989, which was then mandatory. The UK NHS replaced the Urabe mumps strain, which was associated with aseptic meningitis, with the Jeryl Lynn strain and avoided the problem, but the MHLW did not. A huge public outcry ensued, with a number of lawsuits against the Japanese government leading to the withdrawal of the MMR vaccine in 1993. This incident made regulators extremely wary of being sued for vaccine-related adverse events. In 1994, the MHLW revised the Immunization Law, which covered vaccines for measles and rubella but not for mumps. Today, instead of the MMR vaccine, a combined MR (measles and rubella) vaccine is provided, with the mumps vaccine being optional. The withdrawal of the MMR vaccine led to a decrease in coverage, resulting in the exportation of measles [3]. This discrimination has also led to a high incidence of mumps-associated complications in Japan [31]. Despite the availability of the MMR vaccine, the lower coverage rate of measles and rubella in the UK compared with Japan provides further evidence of the negative effect of public perception and widespread concern about the association between the MMR vaccine and autism [14].

Our study has some limitations. First, the cross-sectional observational design limits the establishment of the cause of the gap. Second, the study was based on publicly available data, which do not include subtle issues that were not captured in the deliberation process. Third, there are only a limited number of vaccines approved in Japan or in the UK. This limitation made comparisons between the two countries less conclusive. Fourth, given the heterogeneity in the vaccines considered, formal statistical analysis of the reasons for the gap was not possible.

In Japan, the vaccine programme has been planned and implemented, not on the basis of scientific evidence, but in part as a reaction to lawsuits against the government and media coverage, which has sensationalised the adverse

events and downplayed the benefits of vaccines [11,32]. Because the implementation of immunisation requires not only biological but also social, political, ethical, and economic considerations, multidisciplinary discussions should lead health professionals and the general public to be well informed about vaccines. For example, risk communication is one of the greatest challenges facing any public health authority. In Japan, there is no legal requirement for physicians to communicate the benefits and risks of vaccines to patients. Training programmes to improve physicians' knowledge and communication skills should be provided by the government.

Japan has been a leader in the development of vaccines, such as those for varicella and cellular pertussis, but the aforementioned challenges have stagnated the implementation of newly developed vaccines. We believe our proposals can contribute to a closure of the vaccine gap. The lessons learned so far have helped vaccine policy take a step forward in some respects. The UK experience of the MMR vaccine and its low coverage in urban areas [14] is a good lesson for health care professionals in Japan to improve the public perception of vaccines among Japanese citizens [32]. The Relief System for Injury to Health with Vaccination was introduced in Japan to provide relief in cases of side effects [33]. Routine immunisation is not compulsory but nonetheless high coverage rates have been achieved in Japan [34]. The international community has also contributed to closing the gap. For example, proposals in the EFPIA position paper issued in 2009 [2] had urged the Japanese government to take action to approve bivalent and quadrivalent HPV, and 7-valent PCV vaccines, which were approved in the following years. The notorious exportation [3] and outbreak of measles [35] urged the Japanese government to establish the National Measles Elimination Plan in December 2007. Recent activities among Japanese physicians to establish a strong advisory committee for vaccination policy [24] are encouraging.

5. Conclusions

The present study shows that there is still a large gap between Japan and the UK regarding access to common vaccines and immunisation programmes. The keys to closing this gap include: (1) revision of vaccine regulations, (2) amendment of the vaccine-related laws to secure funding and cooperation between professionals and public health authorities, and (3) improvement in the perception of vaccines among the general public and mass media.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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