Proposal for Establishing Compendia Program of Anticancer Agents in Japan

Yasuhiro Fujiwara  MD, PhD

National Cancer Center
Strategic and Planning Bureau
Today’s Topics

1. Problems with off-label use in cancer treatment

2. Solutions to problems with off-label use in clinical practice: taking the US compendia as an example

3. Toward establishing compendia program in Japan

4. Solutions to problems with off-label use in clinical trials; two solutions in the US

5. Important to develop a program in Japan base on the Advanced Medical Care B program
1. Problems with off-label use in cancer treatment
10-20% of daily medical practice involves off label use

NEJM Apr 3, 2008
Arch Intern Med May 8, 2006
10–30% of anticancer drug use is off-label use

Health-care Development

Off-label use of anticancer drugs

Dominique Levêque

<table>
<thead>
<tr>
<th>Types of cancer examined</th>
<th>Country</th>
<th>Study year</th>
<th>Duration of study</th>
<th>Mode of assessment</th>
<th>Setting</th>
<th>Number of prescriptions</th>
<th>Category of off-label use investigated</th>
<th>Frequency (%) of off-label use</th>
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<td>4 weeks</td>
<td>Prescriptions analysis</td>
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<td>Indication, dose, route, age</td>
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<tr>
<td>Children (n=57)</td>
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<td>Prescriptions analysis</td>
<td>Hospital</td>
<td>..</td>
<td>Indication, age</td>
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<td>All except lung and head and neck</td>
<td>Australia</td>
<td>2001</td>
<td>1 day</td>
<td>Prescriptions analysis</td>
<td>Hospital</td>
<td>47</td>
<td>Indication, dose</td>
<td>30</td>
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<tr>
<td>Adult (n=1206)</td>
<td>All except lung and head and neck</td>
<td>France</td>
<td>2002</td>
<td>1 year</td>
<td>Prescriptions analysis</td>
<td>Hospital</td>
<td>6168</td>
<td>Type of cancer, course of disease</td>
<td>6.7</td>
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</tbody>
</table>

Table: Extent of off-label use of anticancer agents
Estimated off-label use of chemotherapies

- Off-label NCCN supported
- Off-label use, NCCN unsupported, FDA-approved cancer site
- Other

Chemotherapy Names

- Docetaxel
- Gemcitabine
- Rituximab
- Trastuzumab
- Bortezomib
- Bevacizumab
- Cetuximab
- Pemetrexed
- Azacitidine
- Paclitaxel albumin bound

J Clin Oncol 31: 1134–1139, 2013 (March 20)
The problem of off-label use has also existed in the US for a long time.

Statement by the US GAO, which is under the direct control of the US Congress.

Objectives—To determine the proportion of Medicare reimbursed drugs used to treat conditions other than those for which the drug has been approved by the Food and Drug Administration; the impact on utilization of the Food and Drug Administration's approved drug uses, and the effect of denials on the treatment of cancer patients. Design,
Pilot survey of off-label use in the US and Japan

- In FY2008, the NCCN compendia was added as a subject of the survey
- Actual differences in the medical insurance system between the US and Japan are investigated.
  - In the US, two-thirds of indications in clinical practice are not actually approved by the FDA.

### Breakdown of 951 indications

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<th>MHLW–FDA</th>
<th>Count</th>
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<tr>
<td>○–×</td>
<td>195</td>
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<tr>
<td>×–○</td>
<td>110</td>
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<tr>
<td>×–×</td>
<td>440</td>
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</table>

- **Japan**
  - MHLW approval
  - Under PAL
  - 401 indications (42%)
  - Covered by medical insurance

- **US**
  - FDA approval
  - 316 indications (33%)
  - Covered by Medicare/Medicaid
  - 107 drugs
  - 951 indications

Surveyed by Dr Shibata & Dr Fujiwara National Cancer Center
2. Solutions to problems with off-label use in clinical practice: taking the US compendia as an example
In the US, there is a program whereby off-label use in daily clinical practice is reimbursed, and another program whereby results from clinical trials are used to determine whether individual off-label use is reimbursed.
2) (B) In subparagraph (A), the term “medically accepted indication”, with respect to the use of a drug, includes any use which has been approved by the Food and Drug Administration for the drug, and includes another use of the drug if—

(i) the drug has been approved by the Food and Drug Administration: When the safety of a substance has been verified (off-label use is assumed)

and

(ii)(I) such use is supported by one or more citations which are included (or approved for inclusion) in one or more of the following compendia: the American Hospital Formulary Service—Drug Information, the American Medical Association Drug Evaluations, the United States Pharmacopoeia—Drug Information, and other authoritative compendia as identified by the Secretary, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia, or

And listed in an accepted compendia
(reimbursement of off-label use is based on inclusion in the compendia)
Compendia

AHFS Drug Information

With the 2013 edition, the American Hospital Formulary Service (AHFS) accepts the honor of being the leader in keeping you abreast of the latest developments in pharmacy with the American Society of Health-System Pharmacists (ASHP). Each year, an average of over 60% of AHFS content is revised to help you provide the most accurate recommendations for your patients’ drug therapy.

AHFS references are evidence-based and peer-reviewed, compiled without the influence of manufacturers, insurers, regulators, or other interested parties. No other drug information sources can make this claim.

AHFS DI has been designated as an official compendium by the US Congress.

AHFS DI contains information from medical literature and expert advice from over 500 medical professionals. Visit http://www.ahfsdruginformation.com/products_services/di_ahfs.aspx to learn more about this unique compendium.
Three new compendia
Were authorized by the CMS in 2008

<table>
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<th>CMS Manual System</th>
<th>Department of Health &amp; Human Services (DHHS)</th>
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<td>Pub 100-02 Medicare Benefit Policy</td>
<td>Centers for Medicare &amp; Medicaid Services (CMS)</td>
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<td>Transmittal 96</td>
<td>Date: October 24, 2008</td>
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<td>Change Request 6191</td>
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SUBJECT: Compendia as Authoritative Sources for Use in the Determination of a "Medically Accepted Indication" of Drugs and Biologicals Used Off-Label in an Anti-Cancer Chemotherapeutic Regimen

I. SUMMARY OF CHANGES: CMS is recognizing four authoritative compendia and listing them in chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual for use in the determination of a medically accepted indication of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen.

New / Revised Material
Effective Date: June 5, 2008 - NCCN Drugs and Biologics Compendium
June 10, 2008 - Thomson Micromedex DrugDex
July 2, 2008 - Clinical Pharmacology
Implementation Date: November 25, 2008

Programs whereby off-label use can be reimbursed: the US Compendia Program
The US program: Compendia

In the United States, approved medications by the Food and Drug Administration (FDA) for anticancer therapy are offered under Medicare only if the FDA issues the full list of approved medications. However, many medications are not approved for use in certain patient populations, and some medications are not approved for use in any patient population.

Compendia and Anticancer Therapy Under Medicare

Katherine Tillman, RN, MA; Brijet Burton, PA-C, MS; Louis B. Jacques, MD; and Steve E. Phurrough, MD, MPA

Reliability of Compendia Methods for Off-Label Oncology Indications

Amy P. Atkinson, PhD; Jane L. White, PhD; and Kevin M. Stanger, MD

Controlling Off-Label Medication Use

Muriel R. Gillick, MD

Process for controlling use of such drugs, analogous to that used for devices. Once a drug is FDA approved, it would undergo scrutiny using the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination method if its cost exceeds a specified benchmark—for example, $12,000, which is the average cost of a pacemaker. The CMS would pay only for off-label uses for which there is adequate evidence in its National Coverage Determination process. Other insurance companies would probably adopt the recommendations of CMS.
Extensive breadth of listings.

Quick processing from application for inclusion to listing.

Detailed description of the evidence reviewed for every individual listing.

Use of pre-specified published criteria for weighing evidence.

Use of prescribed published process for making recommendations.

Publicly transparent process for evaluating therapies.

 Explicit “Not recommended” listing when validated evidence is appropriate.

 Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies.

 Explicit “Equivocal” listing when validated evidence is equivocal.

 “Process for public identification and notification of potential conflicts of interest of the compendia’s parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts.”

In the US, this program serves as an incentive for clinical researchers to conduct good, investigator-initiated clinical trials and publish the results in recognized scientific journals (specified in CMS’ s notice), so that the drugs evaluated can be covered by insurance in clinical use.
- Am J Med
- Ann Intern Med
- JAMA
- J Clin Oncol
- Blood
- J Natl Cancer Inst
- N Engl J Med
- Br J Cancer
- Br J Hematol
- Br Med J
- Cancer
- Drugs
- Eur J Cancer
- Lancet
- Leukemia

Total of 15 journals listed in the CMS manual. In October 2007, 11 journals were added.

- Annals of Oncology
- Biology of Blood and Marrow Transplantation
- Bone Marrow Transplantation
- Gynecologic Oncology
- Clinical Cancer Research
- Lancet Oncology

- International Journal of Radiation Oncology, Biology, and Physics
- Journal of NCCN Radiation Oncology
- Annals of Surgical Oncology
- Journal of Urology

11 Journals, added on October 22, 2007

3. Toward establishing compendia program in Japan
In Japan, there is actually a program whereby the day-to-day clinical use of off-label drugs whose re-examination periods are over can be reimbursed by insurance regardless of their approval status by the Pharmaceutical Affairs Law (PAL).

55年通知を利用 taking advantage of the 1980 MHW’s notification
The Social Insurance Medical fee payment Fund
“Regulatory Review Information Provision Committee”

Please take a look at
http://www.ssk.or.jp/shinsajoho/teikyojirei/index.html
http://www.ssk.or.jp/shinsajoho/teikyojirei/yakuza.html
November 2012: if the usage of a drug with a completed re-examination period is described in clinical practice guidelines (in accordance with MINDS) issued by academic societies affiliated with the Japanese Association of Medical Sciences, the drug will be reimbursed after guideline review by the Social Insurance Medical Fee Payments Fund.
Application of academic investigator-initiated clinical trial results to the approval (based on PAL) process

The Social Insurance Medical Fee Payment Fund

Ethical guideline for clinical research

Approval review based on 2課長通知

PAL approval & covered by insurance

P II (off-label use)
Ethical guideline for clinical research

P III (off-label use)
Ethical guideline for clinical research

Approval review

PAL approval & covered by insurance

P II (off-label)
Advanced Medical Care B

P III (off-label)
Advance Medical Care B

"Chiken"
4. Solutions to problems with off-label use in clinical trials;

two solutions in the US
In addition, a program whereby clinical trials are supported by public insurance was established in the US.

≪In clinical trials, research part is covered by research funding, while practice that is performed as part of usual care is covered by insurance≫
In the US, the cost of usual care performed in government-funded clinical trials is covered by insurance.

The current Clinical Trial Policy can be found by clicking the link below (under Related Links inside CMS) labeled "Current Policy - July 2007 NCD".

Clinical trials are key to understanding the appropriate use of medical interventions of all types and informing

http://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html
On condition of entry into registered studies or clinical trials, promising new medical products and technologies will be reimbursed.
In the US, genetic tests regarding warfarin administration are covered by insurance only for the following two clinical trials:

**Coverage with Evidence Development**

- [Study 1 of 295 for search of: warfarin](http://ClinicalTrials.gov)
- [Genetics Informatics Trial (GIFT) of Warfarin to Prevent DVT](http://ClinicalTrials.gov)
5. Important to develop a program in Japan based on the Advanced Medical Care B program.
In April 2009, the Highly Advanced Medical Technology Assessment program (Section 3. Advanced Medical Care) (called the “Advanced Medical Care B” program since October 2012) was introduced, in which research part of clinical trials that are not registered as “Chiken” (治験; registration trials) is reimbursed.

(same as the US Clinical Trial Policy)
Research is prohibited under health insurance system

(Ministry of Health and Welfare Ordinance No. 15, April 30, 1957)

- Article 18 (Prohibition of specific treatment) “Health insurance physicians are not allowed to administer specific treatment or new treatment other than that is specified by the Minister of Health and Welfare.”

- Article 19 (Use of pharmaceuticals and dental materials) “Health insurance physicians are not allowed to administer or prescribe pharmaceuticals other than those specified by the Minister of Health and Welfare to patients. Provided, however, that this shall not apply to cases where pharmaceuticals that are being tested in Chiken (registration trials) specified by Article 2 (7) of the Pharmaceutical Affairs Law (Law No. 145 of 1960) are administered in medical care related to such Chiken.”

- Article 20 (Specific policy of clinical practice) “… no tests should be performed for research purposes; provided, however, that this shall not apply to those related to Chiken (registration trials).”
Outline of the Advanced Medical Care B Program
先進医療Bとして実施可能かを審査

・有効性及び安全性を期待できる科学的根拠を有する医療技術であること（国内外の使用実績、有用性を示す文献等）

・緊急時の対応が可能
・医薬品医療機器の入手方法、管理体制が適切
・「臨床研究に関する倫理指針」への対応等

治療技術

技術要件

・有効性及び安全性を期待できる科学的根拠を有する医療技術であること（国内外の使用実績、有用性を示す文献等）

施設要件

・緊急時の対応が可能
・医薬品医療機器の入手方法、管理体制が適切
・「臨床研究に関する倫理指針」への対応等

臨床研究計画

・評価方法
・生物統計学的に適切な症例数
・適切なモニタリング、ロードマップ等

適切な要件の下で保険併用を可能にし科学的評価が可能なデータの収集を迅速化→治験・薬事申請及び保険適用等に繋げ、有用な医療技術の普及を迅速化。

先進医療B(暫定)として認められている技術は38技術（平成24年10月現在）
先進医療Bの実施手続き

保険医療機関（特定機能病院等）

先進医療Bの実施に関する届出

先進医療技術審査部会

技術評価手法としての妥当性の確認

技術の安全性、有効性、倫理性、試験計画等の評価
当該技術を実施する医療機関要件の評価

先進医療技術審査部会での評価結果を踏まえた上で、社会的妥当性、普及性、効率性、将来の保険収載の必要性の評価

今後保険導入の検討を行う対象とする医療技術

先進医療会議

保険との併用の適否の確認

先進医療Bを大臣告示
先進医療B実施医療機関より先進医療としての実施について地方厚生（支）局に届出

評価療養として保険診療との併用が可能
Do we have to obtain clinical research results for unapproved drugs in several patients prior to application for Advanced Medical Care?
Discussion at the Highly Advanced Medical Technology Assessment meeting (September 30, 2009):
First-in-human trials under the Highly Advanced Medical Technology Assessment system

11 未承認若しくは適応外の医薬品又は医療機器を用いる医療技術に係る留意事項関係する法令又は指針の遵守の下で行われた当該施設において数例以上の臨床使用実績があること及びその1症例ごとに十分な検討がなされていることが必要である。

ただし、これを満たさない場合であっても、申請された個々の医療技術の特性に応じて、早期・探索的臨床試験拠点、臨床研究中核病院等の高度で質の高い臨床研究を実施することができる医療機関において、当該医療技術を有効かつ安全に実施できることが明らかである場合には、この限りではない。
Minutes of the first Advanced Medical Care meeting (October 24, 2012)

Requirements of “accumulating experience of several cases” for Advanced Medical Care B conducted at early-stage or investigative clinical research centers and clinical research core hospitals

http://www.mhlw.go.jp/stf/shingi/2r9852000002lk5j.html
Management of expenses not covered by insurance under the specified medical care coverage program (保険外併用療養費制度)

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<tr>
<th>Basic medical care</th>
<th>Laboratory testing</th>
<th>Imaging</th>
<th>Drugs with the same indication</th>
<th>Other agents</th>
<th>surgery, anesthesia, etc.</th>
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<td>Covered by Research fund</td>
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6 医薬品の治験に係る診療に関する事項

（１） 保険外併用療養費の支給対象となる治療は、薬事法（昭和35年法律第145号）第2条第16項の規定によるもの（人体に直接使用される薬物に係るものに限る。）とすること。

（２） したがって、治験の実施に当たっては、薬事法及び薬事法施行規則（昭和36年厚生省令第1号）の関係規定によるほか、医薬品の臨床試験の実施の基準に関する省令（平成9年厚生省令第28号）によるものとすること。

（３） 保険外併用療養費の支給対象となる期間については、治験の対象となる患者ごとに当該治験を実施した期間とすること。

（４） 保険外併用療養費の支給対象となる診療については、治験依頼者の依頼による治験においては、医療保険制度と治験依頼者との適切な費用分担を図る観点から、治験に係る診療のうち、検査及び画像診断に係る費用については、保険外併用療養費の支給対象とはせず、また、投薬及び注射に係る費用については、当該治験の対象となる薬物の予定される効能又は効果と同様の効能又は効果を有する医薬品に係る診療については、保険外併用療養費の支給対象とはしないものとする。また、自ら治験を実施する者による治験においては、治験に係る診療のうち、当該治験の対象となる薬物の予定される効能又は効果と同様の効能又は効果を有する医薬品に係る投薬及び注射に係る費用については、保険外併用療養費の支給対象と

はしないものとする。なお、いずれの場合においても、これらの項目が包括化された点数を
Optimizing Collection of Adverse Event Data in Cancer Clinical Trials Supporting Supplemental Indications


See accompanying editorial on page 5019

Abstract

Purpose
Although much is known about the safety of an anticancer agent at the time of initial marketing approval, sponsors customarily collect comprehensive safety data for studies that support supplemental indications. This adds significant cost and complexity to the study but may not provide useful new information. The main purpose of this analysis was to assess the amount of safety and concomitant medication data collected to determine a more optimal approach in the collection of these data when used in support of supplemental applications.

Application of academic investigator-initiated clinical trial results to the approval (based on PAL) process

The Social Insurance Medical Fee Payment Fund

Evolution into a Japanese Compendia program is anticipated

P II (off-label use)
Ethical guideline for clinical research

P III (off-label use)
Ethical guideline for clinical research

P II (off-label)
Advanced Medical Care B

P III (off-label)
Advance Medical Care B

Approval review based on 2課長通知

PAL approval & covered by insurance

PAL approval & covered by insurance

"Chiken"

"Chiken"
第7 先進医療による成果の活用

1 治験に先立って実施される未承認医薬品や再生医療、個別化医療に係る先進医療の成果については、薬事戦略相談を活用することにより、薬事承認申請の効率化を可能とする。

2 適応外薬に係る先進医療の成果については、国際的な論文等として公表された場合、効能追加に係る薬事承認申請の効率化を可能とする。

3 未承認又は適応外医療機器に係る先進医療の成果については、国際的な論文等として公表された場合、薬事承認申請の効率化を可能とする。なお、薬事戦略相談を活用することも可能である。

http://www.mhlw.go.jp/seisakunitsuite/bunya/Kenkou_Iryou/Iryouhoken/Sensiniryo/minaoshi/
It is necessary to drastically revise the overall approval process and system of reimbursement by insurance
Thank you for your attention