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A Review on Regulatory Bodies for Oncology Drug Approval Process – A Global Perspective

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ABSTRACT:

This article explains the role of external advisory bodies in oncology drug development and regulation from a global perspective. It contains the role of external advisors of United States Food & Drug Administration, European Medicines Agency, Health Canada, the Japanese Pharmaceuticals & Medical Devices Agency & the state food & drug administration china in oncology drug development and regulation in each of jurisdiction was explained and mentioned. It gives the clear cut idea about the role of the advisory committee of the countries like USA, Europe, Canada, Japan & China and their regulation system for approval of oncology drug products in global pharmaceutical market.

Keywords: Oncology, Regulatory Bodies, Advisory Committee, Drug Regulation

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INTRODUCTION:

In 2001, Representatives from the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMEA), Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the Australian Therapeutic Goods Administration (TGA) held a annual meeting of oncology drug regulation in conjunction with the American Society of Clinical Oncology and discussed the role of external advisors in oncology drug regulation. This section gives the idea and role of oncology bodies of their respective countries in their regulation and approval of oncology drug products)

United States: USFDA [1-3]

The United States Food and Drug Administration (USFDA) have different external advisors of Oncologists/hematologists who perform various functions for the regulation and approval of oncology products. The Office of Hematology and Oncology Products (OHOP) is responsible for making safe and effective drugs for cancer and hematologic conditions available to the U.S. public. OHOP oversees development, approval, and regulation of (1).Drug treatments for cancer, (2).Therapeutic biologic treatments for cancer, (3).Therapies for prevention of cancer & (4).Products for treatment of nonmalignant hematologic conditions. The staff of OHOP

consists of over 130 highly trained physicians, scientists and regulatory project managers with expertise in oncology, hematology, radiology, internal medicine, pharmacology/toxicology, and regulatory affairs. These professionals work with specialists in other CDER scientific disciplines such as statistics, clinical pharmacology, epidemiology, chemistry, and drug safety to independently review data on new treatments for cancer.

Table 1: OHOP Structure and Division Therapeutic Areas [1]

Division of Oncology Products 1 (DOP1)	Division of Oncology Products 2 (DOP2)	Division of Hematology Products (DHP)	Division of Hematology Oncology Toxicology (DHOT)
Breast, Gynecologic, Genitourinary, Supportive care (non-heme)	Gastrointestinal, Lung/H & N, Neurooncology /Rare cancers /Pediatric Solid Tumors, Melanoma /Sarcoma	Benign hematology, Hematologic malignancy, Hematology support, Pediatric Hematology	Nonclinical Review Division for Hematology /Oncology products

OHOP is committed to facilitating rapid development, review, and action on promising new cancer therapies. Scientists within OHOP are working intensively on incorporating innovations in pharmacogenomics, bioinformatics, and clinical trial design into the drug development process. These efforts will provide the basis for accelerating introduction of new treatments for cancer into practice.

There is another one committee for oncology drug called Oncology Drug Advisory Committee (ODAC) which meets and review of some protocols submitted under the special protocol assessment (SPA) mechanism. The SPA mechanism, described in the Food, Drug & Modernization Act (FDAMA), provides a binding agreement between the sponsor and USFDA regarding the design of a clinical study potentially leading to drug approval.

In 1992, Accelerated Approval Subpart H was added to the new drug application regulations. This addition allows accelerated approval of drugs for serious or life-threatening diseases if the drug appears to provide a benefit over available therapy; the benefit is determined by the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on evidence of an effect on a clinical benefit other than survival.

Advisory committees (ACs) are the primary means by which the USFDA obtains independent scientific advice. Four main assumptions exist with regard to ACs. First, ACs are independent with respect to influence by either the product sponsor or by the USFDA. Secondly, ACs provides 'expert scientific advice', because the committee members are acknowledged to Agency's professional staff.

The purpose of the ODAC is to review and evaluate data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer, and to make appropriate recommendations to the Commissioner of Food and Drugs. The committee consists of a core of 13 voting members, including 1 patient representative and 1 consumer representative and 1 nonvoting industry representative. ODAC meetings occur when decisions about the relative balance of risks and benefits surrounding a cancer drug are not straightforward, and the FDA is seeking advice from a panel of experts regarding the best path forward.

Oncology drugs are reviewed on the basis of Priority review process. In which priority designation provides the drug sponsor with additional FDA resources and attention for quicker review of the NDA. After a drug sponsor requests priority review, the FDA has 45 days to respond. In USA oncology drugs are approved on the basis of (1).Accelerated Approval Pathways, (2). Fast – track Designation and (3).Breakthrough Therapy Designation.

Accelerated Approval

Accelerated approval may be granted to new drugs used in serious or life-threatening illnesses that do not have acceptable treatments. For those drugs, approval may be granted based upon a surrogate endpoint likely to translate to a clinically meaningful outcome. Approval of the drug is accompanied by an agreement between the FDA and the drug sponsor to complete post marketing studies to confirm the anticipated clinical benefit.

If this occurs, the drug will be granted traditional approval. Conversely, if studies do not confirm the clinical benefit, the FDA may remove the drug or drug indication from the market.

Fast-Track Designation

To gain fast-track designation, a drug must be used to treat a serious or life-threatening condition and fill an unmet medical need. Drugs that achieve fast-track designation are eligible for additional meetings with the FDA to discuss the development plan. Accelerated approval may also be granted. Most drugs eligible for fast-track designation are also eligible for priority review, which speeds up the review and approval process. An application for fast-track designation can be submitted at any time during the drug development process. The FDA must provide a response to the sponsor within 60 days.

Breakthrough Therapy Designation

To gain breakthrough therapy designation, which is the newest designation in the FDA drug approval process, initial clinical data for a new drug must show substantial improvement over available therapy on at least 1 clinically significant endpoint. This is in contrast to fast-track

designation, in which the drug must demonstrate clinical or nonclinical potential to address an unmet medical need. This designation includes even more intense FDA guidance on an efficient drug development program. Application for this designation can be done at any time during the drug development process. The FDA must provide a response to the sponsor within 60 days.

EUROPE: EMEA [4-8]

The European Medicines Agency (EMEA) coordinates a network of 40 national agencies and has undergone significant legislative and institutional changes. The Agency aims to provide a high level of scientific advice, providing a particular emphasis on continuous monitoring of medicines through pharmacovigilance, transparency in communications, and provision of information to patients and Good Manufacturing Practices/Good Clinical Practices.

In 2003, there was introduction of formal scientific advisory groups, including a scientific advisory group (SAG) for oncology (SAG-O) and from 2005 all new oncology drugs must be submitted through the centralized procedure (through the EMEA without the possibility of submission to a selection of individual countries).

Previously, anticancer development in Europe could approach applications for regulatory approval from two perspectives. One option is known as the mutual recognition procedure, whereby a marketing application is submitted to individual countries within Europe. Another option, known as the centralized procedure, consists of a single authorization by the EU based on EMEA review which, if granted, applies to all member states. Starting in November 2005, applications for marketing authorization for certain indications will require submission exclusively through the centralized procedure. These indications include diabetes, AIDS, cancer, neurodegenerative disorders and products with orphan designation.

The Scientific Advisory Group on Oncology (SAG-O) is convened at the request of the Committee for Medicinal Products for Human Use (CHMP) to provide independent recommendations on scientific or technical matters relating to oncology products under evaluation by the CHMP, or on any other scientific issue relevant to the work of the CHMP that relates to this area. The SAG-O is composed of independent European experts selected according to their specific expertise. The SAG-O comprises both a core group and other individual experts who may be called upon to participate in a given meeting and bring additional expertise in specific domains.

The Oncology Working Party was set up by the Committee for Medicinal Products for Human Use (CHMP) in order to carry out specific tasks like preparing, reviewing and updating of guidelines and concept papers related to oncology. The Working Party is composed of European experts selected from or associated with the national agencies with specific expertise in oncology.

Current scientific expertise at the EMEA relies on the EMEA scientific committees, working party members, assessors from national regulatory authorities ('internal assessors') and experts from scientific societies and academic institutions ('external experts'). Internal assessors and external experts are complementary: internal assessors, in addition to their own scientific and clinical expertise have regulatory expertise and are responsible for writing assessment reports and notes for guidance. External experts are mainly clinicians, having recognized expertise in a specialized scientific area.

SAGs are created by the CHMP (Committee for Medicinal Products for Human Use within the EMEA) on a consultative basis to address questions posed by the CHMP. SAG meetings are closed to the industry and the public; the applicant can be invited to give an oral explanation and answer questions from the SAG. The response is a consensus by the deliberation of the members on the question rather than by voting. The CHMP, while taking into account the position expressed by an advisory group, remains ultimately responsible for its final opinion.

Where consensus cannot be reached on an answer to the CHMP list of questions, the conclusion reached by the majority together with any divergent positions within the SAG-O will be noted in the 'SAG Answers and Comments to the CHMP'. The answers and comments of the SAG-O on a specific medicinal product are included in the scientific discussion of European Public Assessment Report of the product.

In Europe oncology drugs are approved on the basis of (1).Accelerated Approval Process, (2).Marketing Authorization under Exceptional Circumstances and (3).Under conditional Accelerated Approval Process

Article 14 (9) of regulation (EC) No 726/2004, states that when an application is submitted for a marketing authorization in marketing authorization. respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. If the committee for Medicinal Products for Human Use (CHMP) accepts the request, the time limit (of 210 days to give an opinion) lay

down in article 6(3), first subparagraph, shall be reduced to 150 days.

Marketing Authorization under Exceptional Circumstances

The EU drug law, as currently codified in the commission directive 2003/63/EC, allows that a marketing authorization may be granted based on a reduced development program. (E.g. based only on phase 2 studies) under so-called "Exceptional Circumstances" These exceptional circumstances include development for use in a rare condition or where in the present state of scientific knowledge, comprehensive information can't be provided or when it would be unethical to collect further data. For anticancer agents to CPMP note for guidance on anti-cancer medicinal products explains how to use these provisions in order to facilitate the development of oncology drugs.

Under conditional marketing authorization

For certain categories of medicinal products like oncology, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally required. In such cases, it is possible for the CHMP to recommend the granting of a marketing authorisation subject to certain specific obligations to be reviewed annually called 'conditional marketing authorisation'. Oncology products are approved on the basis of conditional marketing authorization if it fulfills the criteria like: (1).Benefit/Risk balance is positive, (2).It is likely that comprehensive clinical data will be provided, (3).Unmet medical needs will be fulfilled, (4).Benefit to public health of immediate availability outweighs risks that additional data are still required. The provisions for the granting of such an authorisation are laid down in Regulation (EC) No 507/2006, adopted on 29 March 2006.

CANADA: HEALTH CANADA [9-10]

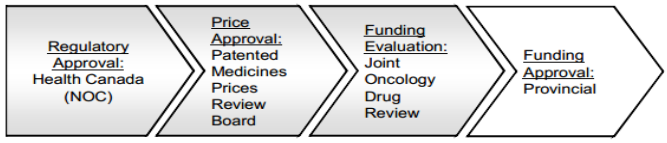
In 2003, Scientific Advisory Committee on oncology therapies was established to provide Health Canada with timely scientific, technical, and medical advice related to the regulation of oncology therapies. Involvement of the scientific, medical and consumer communities in the regulatory review process is expected to enhance transparency and provide opportunity for proactive external guidance, thus facilitating the drug review process.

The SAC-OT provides Health Canada with advice and recommendations, but the decision-making responsibility remains with Health Canada.

The SAC-OT has two types of members, core and ad hoc members. Core members are permanent members who are invited to all meetings for the duration of their terms. The Chair or the Executive Secretary may invite ad hoc members to attend particular meetings or join the SAC-OT for a defined period. Ad hoc members follow the same rules and procedures as core members, and provide advice and recommendations on a particular topic or agenda item. The SAC-OT may also have members from the community to provide user perspective relevant to the work of the committee.

The Canadian system of drug approvals follows a four-step process, outlined in Figure. The federal and interprovincial approval systems are the first gateway to access to cancer drugs in Canada. Factors such as the speed of the review, the rigidity of the process and the relevance of approval criteria to cancer all have an impact on whether and how quickly cancer drugs reach the Canadian market.

Figure 1: Federal and Inter-Provincial Approval Systems for Cancer Drugs in Canada [10]



Health Canada reviews applications from manufacturers against its standards of safety and efficacy. The review process can take from less than one year for priority or "fast-track" reviews to 2-3 years (or more) for non-life-saving drugs. Once approved, the company receives a Notice of Compliance (NOC) and a Drug Identification Number (DIN).

Before making a New Drug Submission to Health Canada for a new chemical entity, companies must do extensive preclinical and clinical testing. For life-saving cancer drugs, however, Health Canada may agree to proceed with a review based on earlier clinical trial results.

Under certain circumstances, a conditional Notice of Compliance (NOC/c) may be granted. The approval to market the drug under a NOC/c requires a commitment by the manufacturer to conduct post-marketing safety studies.

Health Canada is assisted in its regulation of cancer drugs by the Scientific Advisory Committee on Oncology Therapies. This Committee was established to provide the agency with scientific and medical advice related to the lifecycle regulation of oncology therapies and on related policy issues.

Special Access Program

A manufacturer cannot market a drug until it receives a Notice of Compliance or NOC. However, for serious or life-threatening conditions, Health Canada may allow limited release under its Special Access Program while the drug is still under review.

Thus advisory committee on oncology therapies is a new evolving committee and there is need of many implications for regulations of oncology drugs in Canada.

JAPAN: PMDA [11]

In 1996, the Japanese Diet amended the Pharmaceutical Affairs Law (PAL) and its related laws to provide comprehensive drug safety measures at each stage during drug development, from the pre-clinical and clinical phases to the post-marketing surveillance phase, based on the 1996 report of the Committee for Drug Safety Ensuring Measures.

Based on this change in the law, between 1996 and 2001 the Ministry of Health and Welfare (MHW, currently MHLW) revised the regulations implementing the PAL. This resulted in a fundamental reform of the manufacturing (or import) approval application (comparable to the New Drug Application (NDA) in the US) review system. One of the most important changes was the establishment of the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC; 'Shinsa-center') under the National Institute of Health Sciences (NIHS) of the MHLW in 1997.

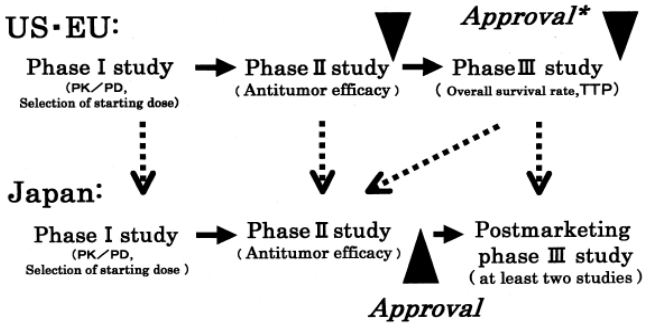
The Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB) in MHLW, PMDEC, and the Organization for Pharmaceutical Safety and Research (OPSR; called 'Kiko' in Japanese) are jointly responsible for drug approval and for review of reexamination and reevaluation applications.

The PMDA is comprised of four offices: Office of Relief Funds, Office of Review, Office of Safety and Office of Research and Development Promotion. The advisory process in Japan has two major elements; clinical trial consultation where the PMDA gives advice to the applicant and the NDA review process including AC where PMDA has discussions with external experts.

During the NDA review process, discussions are held at the PMDA with medical experts appointed from the PMDA. The numbers of clinical external experts are approximately three to five for each application. These discussions are not open to the public or to the applicant. The PMDA always makes the final decision in all applications including those where there may have been a conflict in the recommended regulatory decision between external experts and the PMDA.

After completion of the team review, applications are subject to closed review by the Second Committee as well as the Executive Committee, although the minutes are available to the public. These committees are the advisory board for the MHLW and provide advice on new drug applications.

Figure 2: Extrapolation of foreign clinical data to Japan: oncology drugs. [11]



This figure shows general schematics for drug development in Japan and the US. Solid arrows indicate the flow of development efforts, and the arrows indicate points at which marketing approval may be granted. The dashed lines indicate possible routes for extrapolating data from the US/EU to Japan. Approval in Japan is generally granted based on phase II studies. However, although the general requirement is that at least one study must be conducted in Japan, studies conducted overseas may also be considered. Phase II studies conducted in the US/EU may be submitted in support of a Japanese NDA, to stand in place of one of the required studies. Phase III studies conducted in the US/EU may also be submitted. Phase III studies conducted in the US/EU may also be submitted as a post-marketing phase III study to support an application for Reexamination. This is again subject to the provison that at least one of the post-marketing studies must be conducted in Japan.

CHINA: SFDA [12-13]

There are no specific policies/regulations for oncology drugs. Several Technical guidance for anticancer agents are available or in the development (similar with those of FDA) like Special Review and Approval Procedure (SRAP) applies to Oncology Drugs (2009) in which review time is shortened (~ 80 days). The Special Review and Approval Procedure for Drug Registration of the State Food and Drug Administration, adopted at the executive meeting of the State Food and Drug Administration (SFDA) on November 18, 2005 and established.

This Procedure is formulated for the purpose of effective prevention, timely control and elimination of the hazards of public health emergencies to ensure the health and safety of the public in accordance with the Drug Administration Law of the People's Republic of China.

Figure 3: Some Rules agreed by SFDA for Oncology Clinical Trial Design and Evaluation [13]

General rules for approval of Non-oncology *vs* Oncology products

	Non-Oncology Drugs	Oncology Drugs *
Pivotal studies	At least 2 well-controlled studies	Usually 1 study
Sample size	1,000 ~ 5,000 pts	100 ~ 800 pts
Study design	Placebo control, double blinded needed, e.g., CNS, CVS, Diabetes drugs	Usually active control, Open-label
Statistical Consideration	Higher statistical significance (P value 0.001)	Relatively low statistical significance (P value 0.03~0.05)

Taxotere was approved in US in 2004 but approved in china on 2009. Faslodex was also another example which was approved in US in 2004 but approved in china on 2010. Regional Trial helps Sorafenib got China NDA just 8 months after US approval. In US sorafenib approved in Nov, 2007 & in china it was approved on july, 2008.

Thus, Chinese regulatory system for oncology drugs/ trials is evolving although with challenges. There is a huge need to develop regulations/guidelines for orphan drugs/early development for Oncology drugs in China.

RESULT

Most of all regulatory bodies that described have advisory committee for the regulation of oncology drugs and which comprises of two forms of expertise: advice from individual experts and advice from a group of experts assembled as an advisory group. In some regions, individual experts provide advice based on knowledge and experience during the drug development phase or in the planning phase for the submission of a drug registration package. In other regions, these individuals serve as external evaluators with the primary responsibility for the review of a clinical trials package submitted for drug registration.

DISCUSSION

The Pharmaceutical industry itself is dealing with significant challenges. Oncology drug development and registration involves the use of advisory committee by regulatory authorities globally. The types of experts needed, the expert's role and the transparency of the advisory process reflect the individual needs in different regions. Oncology drug development is a tedious process involving interactions between industry, academia, government regulatory bodies, and patient advocacy groups. The experiences described above from regulatory bodies in the United States, Canada, Europe, Japan and China can be summarized as experiences with two forms of outside expertise: advice from individual experts and advice from a group of experts assembled as an advisory group. Starting with advice from individual experts, regulatory agencies from all regions utilize this form of outside expertise to varying degrees. These individual experts may be involved in both the drug development process (pre submission) or during the evaluation of a registration package. In some regions such as in the United States, external experts are not responsible for the primary review, but provide advice based on knowledge and experience in a certain field. In other regions such as in Europe, external evaluators are given primary responsibility in the review of a clinical trials package for registration. One apparent difference between the USFDA mechanism and the others is the public nature of all aspects of the ODAC's deliberations. In all other regions, deliberations are not open to the public. Finally, none of the advice is binding, and all regulatory bodies reserve the primary right and responsibility for ultimate decision-making. Considering the higher risk associated with the oncology drug products, it is prudent to have conservative approach wherever clear guidance by means of regulations or science is not in place. Ask and do approach with regulatory agencies is advisable for development projects. There is a huge need to develop regulations/guidelines for Oncology drug development worldwide and needs to harmonize the global oncology products market.

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