THERAPY APPROVAL PROCESS SITUATION ANALYSIS 2013

LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

Lymphoma eInformation Project (LeIP)

The cycle – develop therapy, fight to have it approved and then fight to have it funded – cannot continue as it currently stands, it is not working.

ABOUT LYMPHOMA COALITION

The Lymphoma Coalition (LC) is a global patient network of 58 lymphoma patient organisations from 43 countries with a mission to be the global source for lymphoma facts and statistics; to improve awareness and understanding of lymphomas; and to build capacity for new and existing groups.

The Coalition continually disseminates information on all lymphomas including CLL, to ensure that members are kept up to date on advocacy policy, therapy access, lymphoma research and demographics.

Our goal is to encourage the best patient care around the world with the end goal of saving more lives.

SPECIAL THANKS to all the lymphoma patients and the LC member organisations who offered their insight and support as well as to the many other organisations, government agencies, pharmaceutical companies, pharmacists and individuals who generously shared their knowledge, resources and understanding for this report.

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A MESSAGE FROM THE EXECUTIVE DIRECTOR

Karen Van Rassel
Executive Director
Lymphoma Coalition

Lymphoma Coalition's (LC) strength lies in its unique ability to bring the global lymphoma patient organisation network together within an effective platform to share best practice, educational information, as well as to collectively advocate for change.

In last year's report card, standard of care, clinical trials, treatment availability and demographics on both a global scale and at the local level were discussed. This report takes us a step further into a look at regulatory and funding/reimbursement process and procedures. We asked this question, are therapies getting to patients in a timely and cost-effective manner?

A full report summarising our findings comparing different regulatory and funding/reimbursement procedures as well as a summary flow chart for each of the LC member countries support the report card. Please visit the LC website to view this information or scan the code at the back of the report.

LC is privileged to partner with the INTERLYMPH Consortium and their latest findings on risk factors and causes of lymphoma are included. Thank you to the over 100 international members of the consortium for working together to compare research results and expand on the excellent work being done in centres all over the world.

Thank you to Shawn Sajkowski for your hundreds of internet research hours and discussions with many organisations from all over the world and to Leonie Bedford for the compilation and analysis of the research resulting in the following 2013 LeIP Report Card on Lymphomas.

Let's continue to support the patient by being vigilant rather than complacent; never stop raising awareness about lymphoma and the needs of patients with lymphoma. When decisions have to be made, think first, how will this affect the lymphoma patient?

A MESSAGE FROM THE CHAIR OF THE LC MEDICAL ADVISORY BOARD

Dr. Laurie Sehn, MD, MPH
Chair, BC Cancer Agency Lymphoma Tumour Group
Clinical Associate Professor at the University of British Columbia, Vancouver, Canada
Chair, LC Medical Advisory Board

The last decade has brought rapid and significant advances in the management of lymphoma. Advancements in molecular biology have lead to greater biologic insight into the underlying mechanisms of disease, which in turn has translated into the development of a vast array of novel targeted therapies with encouraging potential. While many new drugs are now clinically available, a larger number are being actively investigated in clinical trials and have demonstrated promising efficacy. The rate at which these agents are proceeding through the development process appears to be accelerating, and has been aided by the commitment of organizations such as the US Food and Drug Administration, with the establishment of a "breakthrough therapy" fast track.

While this is an exciting time for lymphoma research and care, it has brought the issue of access to the forefront. The 2013 LeIP Report Card on Lymphomas by the Lymphoma Coalition focuses on the drug approvals and funding process in a large number of countries with affiliated member organizations. The goal was to elucidate the various steps involved in the approvals process and to identify the barriers that result in delays or restrictions in drug availability. The compiled report serves to highlight the universal challenges being faced with respect to regulatory lags and funding constraints. The report also demonstrates notable disparities between countries with respect to timelines and access. This comprehensive review should serve as a valuable resource which can be used to compare and contrast the systems in place and also serve as a tool to guide process change as we strive toward our common goal of achieving better outcomes for lymphoma patients.

A MESSAGE FROM THE ACTING CHAIR OF THE LC BOARD OF DIRECTORS

Pru Etcheverry
CEO, Leukaemia & Blood Cancer New Zealand
Acting Chair, LC Board of Directors

The Lymphoma Coalition (LC) continues to grow in size and to mentor patient organizations around the world through its mission and goals. It is important to understand the systems within which we need to work to ensure that therapies are getting to the patients, and in a timely and cost-effective manner.

The 2013 LeIP Report Card on Lymphomas clearly demonstrates that lymphoma patients and the member organisations that support them face widely differing challenges. Across different regions of the world there is great variance within regulatory frameworks. Regrettably for some patients in some countries access to comprehensive diagnostic services, malignant haematology expertise, good hospital services and drug supply schemes as well as infrastructure to support research-based medicine remains out of reach.

LC aims to track these measurable data further and to evolve this into tracking access to funded therapies. We hope this second annual LeIP report card will provide LC members and patients with the evidence to advocate for improvement in their own organisations and countries. We envisage that in time these reports with support from the LC will help tackle patient needs – for every person in the world living with lymphoma – and lead to better survival and quality of life.

LYMPHOMA COALITION
Worldwide Network of Lymphoma Patient Groups

THERAPY APPROVAL PROCESS SITUATION ANALYSIS 2013

Lymphoma eInformation Project (LeIP)

OVERVIEW

Great advances have been made in the treatment of lymphomas with new developments occurring regularly that should, in theory, provide doctors and patients with many more options when it comes to determining the optimal therapy for patients with lymphoma. With this progress, however, we are confronted with a problem of affordability. Governments and other payers are struggling to find ways to fund or reimburse the cost of therapies and, more importantly, many patients cannot afford them. Given world economic turmoil, governments are reducing their costs by cutting budgets for all sectors including healthcare. And the squeeze on government budgets is likely to worsen as the population ages and the demands on healthcare systems grow.

In addition to the challenge of affordability, a patient diagnosed with lymphoma will likely have to make some difficult decisions in a relatively short space of time about issues that may not only be confusing but also distressing. Among these decisions will be ones relating to treatment: What is the best treatment? Is the treatment available in their country? Is there a clinical trial available and is it a better option than what is being suggested? Is the treatment covered by insurance, funded or reimbursed by government? If not, can the patient afford the treatment? Are there other funding mechanisms in place to help defray the costs associated with treatment? While information about whether a drug is approved as well as funded is available for some countries, it may be incomplete, inaccurate or unclear. In addition, the information can be difficult to navigate making it even more challenging for patients to make decisions.

One of the Lymphoma Coalition's (LC) goals for the Situation Analysis on the Therapy Approval Process was to determine how patients with lymphoma are affected by the changes in healthcare. Specifically, we wanted to determine if patients with lymphoma receive therapy in the most cost-effective and timely manner. **Through its research, the LC discovered that there are a myriad of barriers preventing therapies from reaching patients in a timely and cost-effective way.** Systems (regulatory and funding/reimbursement) are often cumbersome, slow and difficult to access. Within countries, there are multiple layers of approvals with review bodies often appearing to be independent fiefdoms rather than cohesive units that can accept information from one body without having to undertake their own review of the same information. This contributes to enormous time lags between the submission of a drug for regulatory approval and then funding/reimbursement approval. In addition, timelines for both processes can stretch into years.

Therapies being considered by review bodies are for patients who may have a life-threatening illness and who are likely in desperate need for the very therapies under review. Input from patients and patient advocacy groups is critical in both review processes. Patients and patient advocacy groups need to be included and play an active role to ensure that the impact of regulatory as well as funding/reimbursement decisions on the patient is taken into account.

LC's findings are somewhat disheartening, but the hope is that as a community we can work together to find ways to improve patients' lives in spite of governments' best intentions to keep healthcare costs down, the escalating costs of targeted therapies and payers' struggle to meet the demand.

OBJECTIVES

LC undertook a review of the regulatory and funding/reimbursement processes for 42 member countries with particular focus on 12 as well as the European Union (EU). The 12 countries comprised Australia, New Zealand, Switzerland, France, Germany, the United Kingdom (UK), United States of America (USA), Canada, Japan, Spain, Brazil and Argentina. The purpose of the review was to determine what efforts are made to ensure therapies reach patients with lymphoma in a timely and cost-effective manner. These 12 countries and the EU were chosen in order to provide a regional sample. Flow charts showing the regulatory and funding/reimbursement review processes for member countries can be found on the LC website at www.lymphomacoalition.org/global-report.

The objectives of the situation analysis of the 12 countries and the EU were to:

- Provide LC member organisations with, at the very least, a top-line awareness of how other regulatory and funding processes work in order to speak confidently on changes taking place in their own countries;
- Determine if there are roadblocks in the systems that prevent treatment getting to patients in a timely and cost-effective manner;
- Determine best practices, i.e., which countries have relatively straightforward drug approval as well as funding/reimbursement processes and compare them with those that do not.

To address the objectives, this situation analysis focuses on three issues:

1) Timelines, i.e., the length of time for a drug to be approved;
2) Layers of approval, i.e., the number of times the same information is reviewed;
3) Funding/reimbursement, i.e., who pays for the drug.

LC anticipated two other factors that may have been roadblocks in getting therapies to patients in a timely and cost-effective manner: fees (what it costs to get a drug approved) and whether or not a clinical trial had to be conducted in the country as part of the regulatory process. Upon investigating these two factors, it was found that, for the most part, they were not roadblocks. It should be noted, however, that LC would like to see fees reduced as a way of increasing affordability for patients.

Australia appeared to be the only country studied in this review where, as part of the regulatory approval process for a drug, a clinical trial had to be conducted in its own country in order for the drug to be approved. The reasons cited for undertaking clinical trials in Australia are that they provide clinicians with an opportunity to gain experience using a drug and they have to include a cost-effectiveness component, something not required by either the Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, when the LC searched clinicaltrials.gov to see how many trials were being undertaken in lymphoma, of the 495 trials reviewed, Australia was only participating in 52. This means that patients in Australia are likely missing out on having access to new and better therapies.

METHODOLOGY

The goals of the situation analysis were accomplished through:

- Review and comparison of regulatory and funding/reimbursement processes for cancer drugs in the EU and the 12 countries already mentioned. These countries were chosen as they are viewed as being representative of their geographic region;
- Reviewing information available on the internet and verifying its accuracy through published journal articles, interviews with LC member organisations, representatives of the pharmaceutical industry and review bodies;
- Gathering information on regulatory and funding/reimbursement processes by country and recording it in flow charts. To view the flow charts go to the LC website www.lymphomacoalition.org/global-report. In the development of these charts, more than 500 websites were accessed and approximately 1,200 hours were spent on research.

Definitions

Regulatory process and procedures

Before a therapy can be sold/proposed to a patient, its efficacy, tolerability and safety have to be assessed by the country's respective regulatory body to ensure that it not only provides benefit but that it can be safely used in humans. Each country has its own process for undertaking this review.

Therapy funding/reimbursement process and procedures

Once a drug has been approved, the usual next step is to determine if it will be funded/reimbursed, i.e., who will reimburse or partially reimburse patients who have been prescribed the therapy or what government body will fund a therapy. The types of bodies that may help with funding are government agencies, private payers and, at times, drug manufacturers.

Note: All times shown are in business days. Business days are calculated at 20 per month.

KEY FINDINGS & DISCUSSION

In an effort to combat rising costs, governments not only evaluate a new therapy for its efficacy, safety and tolerability, but also its cost effectiveness in comparison with similar therapies that have already been approved to ensure it provides value for dollars spent. And while such cost-effectiveness assessments may show benefit, the therapy may still not be funded because cost and/or funding decisions made at the national level are not necessarily adopted at the regional or local level. Additionally, the length of time it takes for regulatory and funding/reimbursement reviews to be completed will have a negative impact on patients.

Table 1 provides an economic snapshot of the countries reviewed in this report. Based on the information in the table, healthcare expenditure as a percentage of gross domestic product is highest in the USA at 17.9 per cent and lowest in Argentina at 8.1 per cent.[1] Yet, as the situation analysis will show, a country's wealth does not necessarily correlate with healthcare that is easily accessible as well as affordable. For example, in the USA, approximately 84 million people had either no health insurance or exorbitant out-of-pocket (OOP) health expenses that they were underinsured at some point in 2012.[2] In Argentina, where payers are required by law to cover all cancer therapies at no cost to the patient, payers make every effort to delay providing such coverage and patients often have to resort to legal action.[3]

The following are the key findings from the research along with tables and figures that illustrate some of the seemingly convoluted processes and procedures that take place in the approval as well as funding/reimbursement review processes for new therapies.

1. Timelines

For a drug to be approved for use in patients, a new drug application has to be submitted by the applicant to the respective country's regulatory body. This body reviews the efficacy, safety and tolerability data and based on this review, determines if the drug can be approved for use in patients and how it can be used, i.e., as a first-line treatment, after failure of a first-line treatment, in second line only, etc.

The timeline for approving a drug varies from country to country. None of the review processes (either regulatory or funding/reimbursement), with the exception of the USA's FDA regulatory review process, are particularly timely. For example, someone living in New Zealand could wait up to 1,267 days, maybe longer, before having access to an approved as well as funded therapy.[6,7] Someone living in England/Northern Ireland could wait up to 1,050 days.[8,9] Figure 1 shows how long a standard regulatory review takes comparing the reported time with the actual time. As Figure 1 shows, the actual review times for a standard review are, in general, longer than the reported time. Sections 1 and 2 of this situation analysis will examine some of the factors contributing to the lengthy regulatory review times.

In Figure 2, the reported funding/reimbursement time is compared with the actual time. While actual times are not available for all countries, regardless of which time is looked at, patients generally have to wait a considerable time before being able to access a treatment.

TABLE 1: ECONOMIC OVERVIEW RANKED BY GDP PER CAPITA

Country	GDP per capita, US$[4]	Per capita spending on health based on OECD data, US$[5]	GDP ranking among 56 LC member organisations*	Healthcare expenditure as % of GDP, %[1]	Healthcare expenditure ranking among 56 LC member organisations*	Population[4]
Switzerland	54,600	5,914†	2	10.9	7	7,925,517
USA	49,800	8,507‡	3	17.9	1	313,847,465
Australia	42,400	3,800§	4	9.0	18	22,015,576
Canada	41,500	4,666†	8	11.2	4	34,300,083
Germany	39,100	4,494‡	9	11.1	6	81,305,856
UK	36,700	3,405†	12	9.3	15	63,047,162
Japan	36,200	3,213§	13	9.3	15	127,368,088
France	35,500	4,117‡	14	11.6	3	64,612,939
Spain	30,400	3,072‡	16	9.4	12	47,042,984
New Zealand	28,800	3,182‡	18	10.1	10	4,327,944
Argentina	18,200	___**	26	8.1	22	42,192,494
Brazil	12,000	___**	35	8.9	19	199,321,413

GDP = gross domestic product; LC = Lymphoma Coalition; OECD = Organisation for Economic Co-operation and Development; UK = United Kingdom; USA = United States of America
*As of July 2013; †2012 data; ‡2011 data; §2010 data; **Argentina and Brazil not included in OECD data set

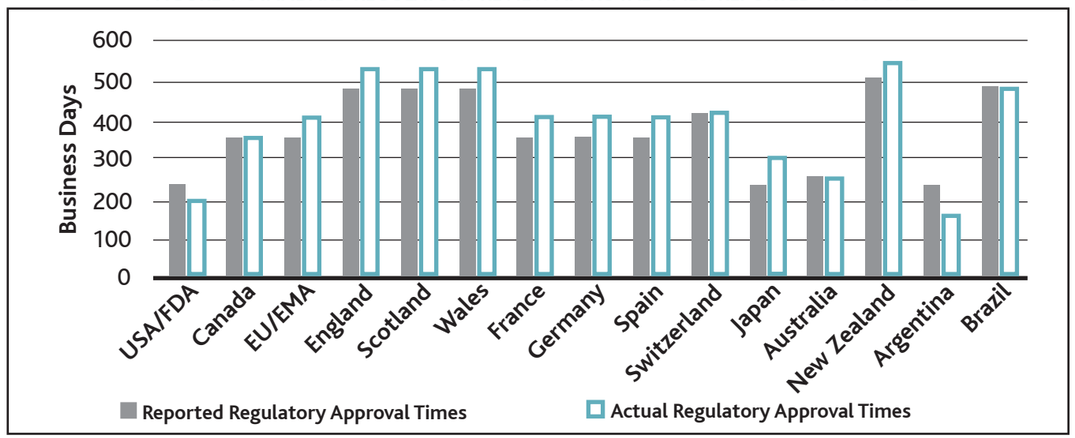
EMA versus FDA

As shown in Figure 1, the regulatory review undertaken by the EMA is considerably slower than that undertaken by the FDA. According to Roberts et al., many times patients have to wait longer for therapies because applications are typically submitted to the FDA first.[10] Cancer therapies intended for use in the EU have to first be reviewed and approved by the EMA before they can be made available in EU member countries. Each EU member country undertakes its own review after the EMA has issued marketing authorisation. Once applications are submitted to the EMA, the reported median review time was 350 versus 120 days in the USA.[10]

A report by Rawson also reported the median review time for the EMA was slower (410 days) than the USA (182 days).[11] Aside from applications being submitted to the FDA first, another reason for the longer approval timeline in the EU is that there are two steps that have to be taken before a drug can be sold: first, the EMA Committee for Medicinal Products for Human Use must issue a positive opinion on marketing authorisation, i.e., the drug is approved for use in humans; second, this opinion has to be adopted by the European Commission.[10]

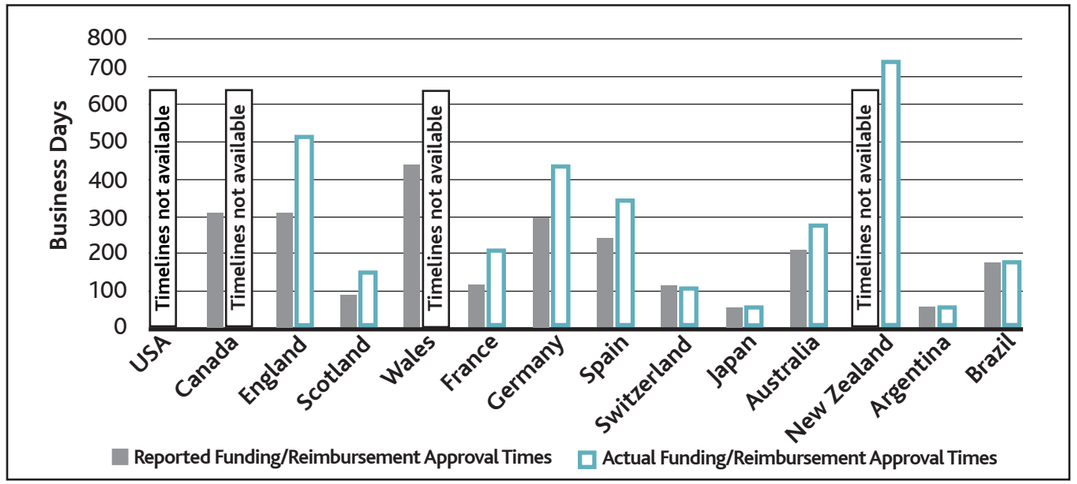
An example of the impact of this difference is shown by the length of time to approve lenalidomide (Revlimid).

FIGURE 1: STANDARD REGULATORY REVIEW APPROVAL TIMES: REPORTED vs. ACTUAL



EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration USA = United States of America

FIGURE 2: FUNDING/REIMBURSEMENT APPROVAL TIMES: REPORTED vs. ACTUAL



USA = United States of America

The FDA took 264 days to approve it; the EMA 387 days. In this instance, applications were made to the FDA and the EMA at the same time (January 2003). Another example is bortezomib (Velcade). The FDA review time was 112 days; EMA 358 days. Applications were submitted to the FDA in April 2005 and to the EMA in February 2006.[10] Once the EMA and the FDA have provided approval, the EU member countries then begin their own regulatory approval process as well as undertake funding and reimbursement reviews. Depending on the EU country, it can be another 111 to 392 days before a patient can access therapy.[12] In the USA, funding and reimbursement reviews are undertaken by public payers (Centers for Medicare & Medicaid Services, Department of Defense and Department of Veterans Affairs), private payers and individual states, respectively.

USA

In the USA, all new therapy applications are reviewed by the FDA who issues marketing authorisation. Most healthcare provided in the USA is privately funded. Section 3. Funding/Reimbursement provides more information on how patients access healthcare in the USA.

In contrast to the drug approval process in most countries, the regulatory approval process in the USA appears to be undertaken in a timely manner. A number of reviews are performed by the FDA; namely, standard, fast track, breakthrough therapy, accelerated appraisal and priority. The two types of reviews examined in this situation analysis are standard and priority.

The reported standard review time has increased from 200 to 240 days; for a priority review the time has increased from 120 to 160 days. The reason for the increase in time is that the FDA requested more time rather than more staff; in exchange, the pharmaceutical company whose drug is under review receives more communication from the FDA.[13]

According to the Prescription Drug User Fee Act Performance Report for 2011, the median approval times improved from 324 days in 2008 to 202 days in 2010. Priority review times improved from 180 days in 2009 to 158 days in 2010.[14] In a report published by the FDA in 2012, the median standard approval time in 2011 was 198 days.[15] These timelines are for all drug submissions not only oncology drugs.

UK

Healthcare in the UK is predominantly funded through national taxation. Within each country (England, Northern Ireland, Scotland and Wales), local health authorities are responsible for purchasing healthcare.

Once the EMA has granted approval that the drug can be accessed in the EU, the UK undertakes its own evaluation. All therapy applications are first reviewed by the Medicines and Healthcare Products Regulatory Agency (MHRA) for safety monitoring, adverse event reporting and drug distribution. The MHRA also reviews the marketing materials the applicant intends to use. Review by the MHRA can take between 60 to 120 days.[13]

The review by MHRA is then followed by a review by the National Institute for Health and Clinical Evaluation (NICE) for England and Northern Ireland, the Scottish Medicines Consortium (SMC) for Scotland and the All Wales Medicines Strategy Group (AWMSG) for Wales. These bodies undertake their own reviews to determine whether or not to fund the treatment; part of the review entails looking at the effectiveness of the treatment. While NICE advises that patients should not be denied access to therapies awaiting review, in reality, local decision makers tend to avoid adding expensive products to formularies, particularly oncology products. As a result, new oncology therapies are not often used prior to a positive appraisal by NICE.[8] Until March 31, 2013, primary care trusts (PCTs) were responsible for administering healthcare at the local level under the direction

of strategic health authorities (SHAs). PCTs and SHAs have now been replaced by clinical commissioning groups (CCGs). CCGs are responsible for requesting the majority of health services. There are 211 CCGs in England.[16]

The reported review time by NICE is between 225 to 315 days depending on the type of review, i.e., a multiple technology appraisal (covers more than one drug, technology and indication) or a single technology appraisal (a single drug or indication). In reality, NICE review time can be up to 520 days.[8,9] The reported review time by SMC is 90 days with the actual time being 154 days.[8] For the AWMSG, the reported review time is approximately 125 days if Wales does its own review. However, Wales only undertakes its own review if NICE takes longer than 240 days to issue guidance; therefore, Wales typically waits 240 days before determining whether it has to undertake its own review.

In essence, if factoring in the time it takes for the EMA to review and approve a drug and the various timelines in the UK, it could be between 990 and 1,050 days in England and Northern Ireland, 624 to 684 days in Scotland and 835 to 895 days in Wales before a therapy receives funding/reimbursement approval. Regardless of whether it is the reported or actual time, patients living in the UK are in for a long haul as none of the processes appear to be geared towards getting life-saving treatments to patients in a timely and cost-effective manner.

France

France's healthcare system is primarily funded by the government with patients required to make small co-payments for some services. More information on how patients access healthcare in France is provided in Section 3. Funding/Reimbursement.

Following receipt of marketing authorisation, all therapies for which funding/reimbursement is sought must be evaluated by the Transparency Commission (TC). This evaluation determines the therapy's medical benefit (SMR) and improvement of medical benefit (ASMR). The SMR determines whether the therapy can be reimbursed and to what extent and the ASMR determines the price of the therapy.[8] More information on the French funding/reimbursement process is provided in Section 3. Funding/Reimbursement.

Patients with cancer can, however, access treatments prior to the EMA issuing marketing authorisation by means of a temporary utilisation authorisation (ATU). ATUs are granted by the Agency for Medical Safety of Health Products if:

- The drug is for the treatment or prevention of a serious or rare disease;
- No suitable therapeutic alternative is available;
- The product has a positive benefit/risk ratio.[8]

Until recently, France has granted a high number of ATUs but there is a sense that the ATU policy may become stricter as a means of controlling the impact on hospital budgets. While ATUs are a way of providing treatment to patients prior to France approving its use, based on discussions with manufacturers, applying for an ATU is a "painful" process.[13] Given that applying for an ATU can be difficult, it may be challenging for doctors to gain access to treatments for their patients.

Reimbursement approval tends to be faster in France. Some of the reasons for this are that unlike the UK and Germany, economic evaluations are not required for the first-time registration of a new drug and French oncologists are not burdened with budget constraints enabling the rapid adoption of new treatments.[8] What does have an impact on the timeline is where the therapy is dispensed. Treatments dispensed in a hospital are usually available earlier than if dispensed on an outpatient basis. For example, the average time to access new treatments in an outpatient setting was 334 days compared with 299 days in the hospital.[8]

Germany

In Germany, more than 90 per cent of the population receives healthcare through the country's statutory healthcare insurance program (GKV). Membership in this program is compulsory for all those earning less than a periodically revised income ceiling. Most of the rest of the population receives their healthcare from private for-profit insurance companies (PKV).[17]

While reimbursement is determined automatically in Germany and all new cancer therapies are immediately available under both the GKV and the PKV following approval by the EMA, in reality, they are not available until the budgeting process is completed. The budgeting process can take up to 440 days.[8] If the EMA has taken 350 days to approve a therapy and Germany takes up to 440 days to complete the budgeting process that makes it 790 days **before** a therapy is available in Germany.

Spain

The 1978 Spanish constitution guarantees that all Spanish citizens have the right to universal access to public health services. However, with the introduction of the Spanish Royal Decree 16/2012 in September 2012, there have been some changes to the way in which healthcare is administered and how patients access care. These changes have also had an impact on the amount of time it takes for new therapies to be assessed for funding/reimbursement.[18] Section 3. Funding/Reimbursement provides additional information on access to care.

Upon receiving marketing authorisation, the Spanish Medicines Agency (AEMPS) issues a licence and no further review is required from a regulatory perspective. However, the funding review time has increased as a result of Spanish Royal Decree 16/2012. It used to take between 120 and 240 days for a therapy to be added to the national reimbursement list. Now, it can take up to 349 days to obtain funding approval.[12] The Interministerial Commission for Pharmaceutical Prices (CIPM), which carries out pharmacoeconomic assessments, delays their decision by often obtaining a second assessment from an independent committee which can result in a delay of up to 240 days. Once, CIPM has made their funding recommendation and the Ministry of Health has approved the decision then the therapy is added to the reimbursement

list. This does not mean, however, that it is readily available within the 17 regional health authorities in Spain as each region makes their own funding decision.[18]

Switzerland

The Swiss system is highly decentralised with the 26 cantons being largely responsible for the provision of healthcare and insurance companies operate primarily on a regional basis. Swiss citizens are obliged, by law, to purchase healthcare insurance. Those with lower incomes are provided with financial assistance.[19]

Patient access to new treatments is often delayed in Switzerland because the applicant may wait to submit a new therapy application to the Swiss Agency of Therapeutic Products (Swissmedic) until **after** the EMA has issued its marketing authorisation as often the same dossier is used in the application. Swissmedic, however, does not always take the EMA's decision into account and as Switzerland is not part of the EU, it undertakes its own regulatory and funding/reimbursement reviews.[13]

Given that it can take the EMA 350 to 410 days[10,11] to approve an oncology therapy, and review and approval by Swissmedic can take up to 420 days, it could be up to 830 days before a therapy is approved. When factoring in the amount of time the funding review body takes (between 100 and 120 days), it could be up to 950 days before a patient could receive a funded treatment.[13]

Other factors that may lead to delays include the increasing amount of administrative time, and a complex application and approval process with applicants not having an opportunity to meet until the formal response period to clarify issues. This often results in further delays. While accelerated reviews are possible, it can be difficult to comply with the requirements.

Given that Switzerland is a wealthy country, LC would hope that better and faster access to new therapies could be achieved for patients.

Japan

Japan has a universal healthcare system. More information on how patients access healthcare is provided in Section 3. Funding/Reimbursement. All new therapy applications are approved by the Ministry of Health, Labour and Welfare in Japan based on the work undertaken by the Pharmaceuticals and Medical Device Agency. Until recently, approval of new drug applications could take as long as 660 days and, in some cases, almost 1,100 days.[20] However, the government has taken steps to shorten the drug approval process.[21] The median standard drug approval time has fallen from 440 days to 300 days and the median priority approval time has gone from 300 days to 180 days.[21]

Canada

Canada has a universal healthcare system, i.e., basic healthcare services are covered. All new therapy applications are reviewed by Health Canada. In addition, if an applicant wants to receive funding from a public payer, an application has to be made to the pan-Canadian Oncology Drug Review (pCODR). Once Health Canada has issued marketing authorisation and pCODR has made its funding recommendation, the provinces or territories then undertake their own reviews to decide whether to fund a therapy. pCODR is funded by all provinces except one.

Like the EMA, Health Canada is very slow in approving therapies compared with the FDA, based on oncology therapy approvals issued between 2003 and 2011 (see Table 2).

TABLE 2: ONCOLOGY THERAPY APPROVAL TIMING: COMPARISON OF FDA, HEALTH CANADA AND EMA[11]

Drug Approval Body	Days (Median) Before Therapy Receives Marketing Authorisation	Number of Oncology Therapies Approved
FDA (USA)	182	30
Health Canada	356	24
EMA	410	26

EMA = European Medicines Agency; FDA = Food and Drug Administration; USA = United States of America

When comparing median times for priority reviews, the USA was much faster than Canada. Timing is not available for priority reviews for the EMA (see Table 3).

TABLE 3: PRIORITY REVIEW TIME: FDA vs. HEALTH CANADA[11]

Drug Approval Body	Days (Median) Before Therapy Receives Marketing Authorisation	Number of Oncology Therapies Approved
FDA (USA)	182	25
Health Canada	326	8
EMA	No time provided as priority review system only introduced in 2007	3

EMA = European Medicines Agency; FDA = Food and Drug Administration; USA = United States of America

Interestingly, Canada's priority drug review system criteria are similar to those used in the USA, yet only a third of the therapies approved in Canada received a priority review compared with 80 per cent in the USA.

Compared with the USA, fewer new oncology products have been approved in Canada in the last decade. In addition, for 40 per cent of the therapies reviewed in Canada, it took 180 days longer to complete the review than it did in the USA for the same therapies.[11] The timelines discussed do not reflect

the time each province or territory takes to review and issue funding/reimbursement guidance.

While the reviews by pCODR and Health Canada are undertaken at the same time, the review time of the provincial bodies is unknown for the most part. Only one province has a reported time for a rapid review process and only one province has reported timelines for both priority and standard reviews.

Australia

Healthcare in Australia is provided by both private and government institutions. All new therapy applications are reviewed by the Therapeutic Goods Administration (TGA). The funding/reimbursement review is undertaken by the Pharmaceutical Benefits Advisory Committee (PBAC). Section 3. Funding/Reimbursement contains more information on how therapies are funded.

The timeline for regulatory approval is between 240 and 260 days. However, where there is often delay is in the time between receiving approval and submitting the file to PBAC for assessment of the therapy's effectiveness and cost effectiveness. In a study examining this issue, there was a delay of 340 days from the time of approval by the TGA to the first review by PBAC.[22] This finding is in keeping with other research that has shown that time between TGA approval and listing on Pharmaceutical Benefits Scheme (PBS) has increased from 272 days in 2000 to 684 days in 2009.[22] The authors state that the possible reasons for companies not applying for listing on the PBS include high submission costs, availability of alternative sources of funding and the need to negotiate a price with the pricing authority.[22] Again, where does the patient fit in these decisions? How is a patient supposed to access a treatment if it's not listed on the PBS? It can't be assumed that a patient has the means or private coverage to obtain the needed treatment.

New Zealand

Healthcare in New Zealand is provided through a mix of private and public institutions. All new therapy applications are reviewed by the Medicines and Medicinal Devices Safety Authority (MEDSAFE); funding/reimbursement reviews are undertaken by the Pharmaceutical Management Agency (PHARMAC).

The New Zealand timelines (regulatory and funding/reimbursement reviews) are very slow when compared with the other countries examined in this analysis. The regulatory approval process undertaken by MEDSAFE can take between 365 and 547 days.[7,23] Additionally, the unknown entity is the length of time it takes for the Minister of Health to approve the application.

Based on information provided by local advocacy bodies, the appeal process is unclear with no agreed timelines and it varies from one application to another. The lengthy review time is also likely a result of the review committees within PHARMAC not meeting on a frequent basis. If PHARMAC needs clinical advice on an application, the application is referred to the Pharmacology and Therapeutic Advisory Committee (PTAC) which meets every 60 days; applications may also be referred to specialist PTAC subcommittees which only meet every 100 days.[6] Reportedly, it can take up to 720 days for a funding/reimbursement review to be completed.[6]

Brazil

The 1998 Brazilian constitution guarantees universal access to healthcare for all citizens. Section 3 of this analysis provides more information on how patients access healthcare. In Brazil, all new therapy applications are reviewed by the National Surveillance Agency (ANVISA) and funding/reimbursement reviews are undertaken by the National Commission for Incorporation of Technologies (CONITEC).

The standard review time in Brazil is between 360 and 480 days.[24] Brazil is taking steps to speed up its priority review time. In March 2013, the CEO of ANVISA announced that the review time for technological innovation and priority medications for hypertension, diabetes and cancer would be reduced to 120 days from the average 180 days.[25] Changes have also been made to the funding/reimbursement review process. Established in 2012, CONITEC set a goal of conducting appraisals within 180 days and, for the most part, has met this goal. Upon a positive decision, the treatment must be available to the public sector within 180 days.[26]

While it's encouraging to learn that Brazil has recognised the importance of speeding up priority regulatory review times, applicants and patients continue to struggle with a lack of transparency in both processes as well as the length of time it takes for marketing authorisation to be granted for therapies that are available in other countries. Lenalidomide (Revlimid) provides an excellent illustration of these issues. Approved in 70 countries including the USA and Europe for multiple myeloma,[27] lenalidomide is still unavailable in Brazil. The dossier was submitted to ANVISA in 2007. It was not approved because there was confusion among advocacy groups as well as other bodies as to whether it was similar to thalidomide and would result in the same negative effects seen in the 1960s. The second time the dossier was submitted for review, it was turned down because no trials had been done comparing it with bortezomib (Velcade), the standard of care at the time. Efforts then had to be made to find studies that compared lenalidomide with other therapies for the treatment of multiple myeloma. This information has been gathered and a decision has to be made whether to submit to ANVISA for a third time.[28]

2. Layers of approvals

Adding to the time it takes for a therapy to receive both regulatory and funding/reimbursement approval, are the number of approval bodies as well as steps involved in each process (see Table 4). **But, what is perhaps more important, is how often the same information is reviewed before a funding/reimbursement decision is made. As a result, it is often an unacceptable length of time before a patient can receive treatment.**

Japan

The regulatory approval process undertaken in Japan appears to be relatively straightforward without too many layers. To review the flow chart, go to www.lymphomacoalition.org/global-report. While there are a few more steps involved in the funding/reimbursement review process, decisions are made within a relatively short period of time (40 to 60 days).[39]

Canada

Canada provides a prime example of where the same information is reviewed by bodies at both the federal and provincial/territorial level. Health Canada examines the therapy's efficacy, safety, drug labelling and marketing information[45]; pCODR examines the clinical evidence and the cost effectiveness (neither of these bodies communicates directly with the other, all communication is done via the applicant).[46] Once Health Canada has issued marketing authorisation and pCODR has made its funding recommendation, each of the provinces then undertakes their own reviews to decide whether to fund a therapy. Keep in mind, pCODR is funded by all provinces and territories except one. While the funding review process undertaken by each of the 10 provinces and the three territories varies, it generally comprises an average of three steps. Again, not a particularly transparent process and one that is not very satisfactory for a patient waiting for treatment.

UK

As already mentioned, the UK undertakes reviews in addition to those completed by the EMA. Upon receipt of marketing authorisation from the EMA, it is up to the applicant to notify the MHRA who reviews the safety monitoring, adverse event reporting, drug distribution and marketing materials. Following review by the MHRA, reviews are then undertaken by NICE (England and Northern Ireland), SMC (Scotland) and AWMSG (Wales). While these reviews are related to determining the level of funding that will be provided, they entail an examination of the efficacy and safety data, information that will have already been reviewed by the EMA.

FIGURE 3: PIXANTRONE REIMBURSEMENT PROCESS[13,47,48*]

May 2012	⇨	EMA approves pixantrone
August 2012	⇨	Application submitted to MHRA
November 2012	⇨	Dossier submitted to NICE
March 2013	⇨	MHRA approves application
April 2013	⇨	NICE issues first negative funding opinion
July 2013	⇨	NICE to consider new evidence in September 2013
October 2013	⇨	NICE issues second negative funding opinion

EMA = European Medicines Agency; MHRA = Medicines and Healthcare Products Regulatory Agency; NICE = National Institute for Health and Clinical Excellence
*Information as of October 2013

England and Northern Ireland

Pixantrone (Pixuvri) is a good illustration of the many layers involved in approving a therapy. A therapy for non-Hodgkin B-cell lymphoma (NHL), pixantrone was approved by the EMA for use in patients whose cancer had relapsed or was refractory to other therapies. NICE, in its initial appraisal, indicated that pixantrone should not be recommended within its marketing authorisation for treating relapsed or refractory aggressive NHL as the benefit of pixantrone had not been established.[13] In October 2013, NICE issued a second negative funding opinion.[47] This process is another example of where the same information is reviewed by more than one body.

So, it begs the question: what was the point of submitting to the EMA only to have NICE say something else? Figure 3 illustrates the layers of review as well as the lengthy time it takes for decisions to be made. Keep in mind that while the number of steps or phases in the MHRA review is unclear, the NICE process comprises 10 phases/steps.

As Figure 3 shows, it's a long drawn out process to have a therapy funded/reimbursed in England and Northern Ireland. Another demonstration of a system whereby a therapy does not get to the patient in a timely and cost-effective manner.

Scotland

In an independent review commissioned by the Scottish Health Secretary, published in May 2013, it was recommended that the SMC should meet in public so both patients and pharmaceutical companies can see how the process works.[49] The review was commissioned in November 2012 after concerns about access to treatments were raised by doctors, charities and patients. It was also recommended that the SMC invite pharmaceutical companies to present evidence when their products are under evaluation so any outstanding questions could be answered.[49] Prior to the review, the Scottish Health Committee had been advised by a number of cancer specialists about problems accessing therapies in Scotland. These specialists had indicated that the current system of prescribing therapies not approved for general use as "an invidious machine" intended for the protection of budgets rather than providing access to treatments needed by patients.[49]

In July 2013, there were further demands that the system for approving new medicines be significantly improved, that it be more transparent and that there should be a national patient treatment request body allowing patients to apply to a single Scottish body for access to a therapy rather than the current system of decisions taken by local health boards.[50]

The Scottish government is in the process of determining what recommendations to adopt. While this sounds commendable, review and approval by the SMC is an additional step as much of the same evidence would have already been reviewed by the EMA as well as the MHRA, similar to what happens in England/Northern Ireland and Wales.

Germany

The funding/reimbursement process in Germany appears to be somewhat labour intensive, as shown in Figure 4, especially in the work undertaken by the Institute for Quality and Efficiency in Health Care (IQWiG). IQWiG undertakes the health technology assessment for new therapies. Note the number of steps in IQWiG's process. While the reported funding/reimbursement timeline is 240 to 300 days, in reality it can be up to 440 days.[8] Treatments granted an orphan designation by EMA do not need to be reviewed by IQWiG.[37]

TABLE 4: OVERVIEW OF REVIEW BODIES

COUNTRY	REGULATORY			FUNDING/REIMBURSEMENT		
	# of review bodies	# of phases/ steps	What review bodies do	# of review bodies	# of phases/steps	What review bodies do
USA	1[29]			Funding provided by public payers (CMS [responsible for Medicare, Medicaid, CHIP], VA, DoD), private payers and individual states[8]		
	FDA	7	Reviews efficacy, safety, quality			
EU	5			Funding decisions by each European Union member country – see below		
	EMA[30]	1	Reviews efficacy, safety, quality			
	CHMP	3	Validates application			
	Rapporteur	1	Undertakes scientific assessment			
	PRAC	1	Conducts risk assessment			
	EU	3	Adopts opinion of EMA			
England/ Northern Ireland	2			1		
	EMA[30]	1	Reviews efficacy, safety, quality	NICE[8, 9]	10	Reviews clinical and cost effectiveness
	MHRA[31]	Information not available	Reviews safety monitoring, AE reporting, drug distribution, marketing materials			
Scotland	2			1		
	EMA[30]	1	Reviews efficacy, safety, quality	SMC[8,32]	8	Reviews clinical effectiveness; undertakes economic assessment
	MHRA[31]	Information not available	Reviews safety monitoring, AE reporting, drug distribution, marketing materials			
Wales	2			1		
	EMA[30]	1	Reviews efficacy, safety, quality	AWMSG[33]	10	Reviews clinical effectiveness; undertakes economic assessment
	MHRA[31]	Information not available	Reviews safety monitoring, AE reporting, drug distribution, marketing materials			
France	1			4[34]		
	EMA[30]	1	Reviews efficacy, safety, quality	TC	4[35]	Determines medical benefit and improvement of medical benefit vs. std. of care
				CEPS	Information not available	Reviews improvement of medical benefit, compares pricing with other countries, negotiates price with applicant
				MoH	Information not available	Approves application
				UNCAM	Information not available	Sets reimbursement rate for national funding
Germany	1			3[8, 36]		
	EMA[30]	1	Reviews efficacy, safety, quality	G-BA	4	Determines drug reimbursement
				IQWiG	8	Assesses benefit. For orphan drugs: no review by IQWiG; only review by G-BA required[37]
				GKV-SV	3	Negotiates reimbursement price with applicant
Spain	2			3[18,34]		
	EMA[30]	1	Reviews efficacy, safety, quality	DGFPS/MoH	2	Approves drug; adds to national reimbursement list
	AEMPS[34]	1	Issues national product code	CIPM	2	Undertakes pharmacoeconomic assessment; negotiates price with applicant
				GCPT	1	Develops advice report for CIPM
Switzerland	1			2		
	Swissmedic[13,34]	5	Reviews efficacy, safety, quality	FOPH[13]	3	Makes reimbursement decision
				FDC	1	Reviews application based on cost effectiveness of existing therapies, compares international prices, gives reimbursement recommendation to FOPH
Japan[38]	3	Information not available		4[39]	Information not available	
	PMDA		Evaluates NDA for efficacy, safety, quality	Medical Economics Div.		Conducts preliminary hearing with applicant; prepares pricing draft
	PAFSC		Nominates outside experts to review NDA	Drug Pricing Org.		Finalizes pricing draft
	MHLW		Reviews PMDA recommendation and makes final decision	Central Social Medical Council		Gives reimbursement recommendation to MHLW
				MHLW		Sets drug price; makes final reimbursement decision
Canada	1			2		
	Health Canada[40]	4	Reviews efficacy, safety, drug labelling, marketing information	pCODR (national body)[41]	9	Reviews cost effectiveness, clinical evidence
				Provincial/territorial approvals	2-6	Assesses budget impact, clinical evidence and effectiveness
Australia	1			3		
	TGA[42]	8	Reviews efficacy, safety, quality	PBAC (see chart at www.lymphomacoalition.org)	9	Assesses clinical and cost effectiveness
				PBPA	3	Assesses clinical and cost effectiveness
				MoH	2	Determines financial and feasibility acceptability
New Zealand	2			2		
	MEDSAFE[23]	4	Reviews efficacy, safety, quality	PHARMAC[43]	8	Undertakes economic assessment, reviews cost effectiveness
	MoH[23]	1	Makes decision based on MEDSAFE recommendation	PTAC	4	Reviews proposal, requests CaTSoP advice, makes recommendation, reviews priority of proposals
Brazil	3			3		
	ANVISA[44]	2	Inspects facility; grants marketing authorisation	CONITEC[26]	2	Reviews efficacy, safety, cost effectiveness
	GEPEC	1	Undertakes pharmacological, safety and efficacy evaluations	MoH	1	Makes funding decision
	CMED	1	Negotiates price with applicant	National, state, municipal		Makes funding decision
Argentina	1			3		
	ANMAT[13]	5	Provides Provision check and signature; gives assignation date and number to Provision	Public payers[13]		Case by case negotiation between applicant and funding body
	• Registration office		Evaluates application, samples, CPP	Semi-private		Each case may need to be negotiated; depends on the payer
	• Drug Evaluation Department		Undertakes medical evaluation	Private		Depends on the payer and how much information payer needs
	• Legal Department		Evaluates evidence of commercialisation, manufacturer, application form, CPP			
	• Technical Secretariat		Provision check, signature			
	• Dispatch Department		Assignation date, number to Provision			

AE = adverse event; AEMPS = Spanish Medicines Agency; ANMAT = National Administration of Drugs, Food and Medical Technology; ANVISA = Brazilian Health Surveillance Agency; AWMSG = All Wales Medicines Strategy Group; CaTSoP = Cancer Treatments Subcommittee of PTAC; CEPS = Economic Committee on Health Care Products; CHIP = Children's Health Insurance Program; CIPM = Interministerial Commission for Pharmaceutical Prices; CHMP = Medicinal Products for Human Use; CMED = Chamber of Drug Market Regulation; CMS = Centers for Medicare & Medicaid Services; CONITEC = National Commission for Incorporation of Technologies; CPP = Certificate of Pharmaceutical Product; DGFPS = Directorate General for Pharmacy and Health Care Products; DoD = Department of Defense; EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; FDC = Federal Drug Commission; FOPH = Federal Office of Public Health; G-BA = Federal Joint Committee; GCPT = Therapeutics Positioning Group; GEPEC = Office of New Drugs Research and Clinical Trials; GKV-SV = National Association of Statutory Health Insurance Funds; IQWiG = Institute for Quality and Efficiency in Health Care; MEDSAFE = Medicines and Medical Devices Safety Authority; MHLW = Ministry of Health, Labour and Welfare; MHRA = Medicines and Healthcare Products Regulatory Agency; MoH = Ministry of Health/Minister of Health; NDA = new drug application; NICE = National Institute for Health and Clinical Excellence; PAFSC = Pharmaceutical Affairs and Food Sanitation; PBAC = Pharmaceutical Benefits Advisory Committee; PBPA = Pharmaceutical Benefits Pricing Authority; pCODR = pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency; PMDA = Pharmaceuticals and Medical Devices Agency; PRAC = Pharmacovigilance Risk Assessment Committee; PTAC = Pharmacology and Therapeutic Advisory Committee; SMC = Scottish Medicines Consortium; std. = standard; Swissmedic = Swiss Agency of Therapeutic Products; TC = Transparency Commission; TGA = Therapeutic Goods Administration; UNCAM = National Union of Health Insurance Funds; USA = United States of America; VA = Department of Veterans Affairs

No question there is room for improvement. This section of the situation analysis – describing layers of approval – will add further evidence that there are likely redundancies in the layers in both the approval and funding/reimbursement processes.

FIGURE 4: FUNDING REVIEW PROCESS FOR GERMANY[36]

	EMA Marketing Authorisation ⇩
Reported timeline: 60 days	G-BA decides whether to investigate drug reimbursement through statutory health insurance ⇩
Reported timeline: 60 days	Applicant submits dossier to G-BA to prove additional benefit against competitive products already available ⇩ IQWiG benefit assessment ⇩ IQWiG forms project group to define outcome criteria ⇩ IQWiG issues preliminary report to G-BA committee ⇩ G-BA committee hearing which includes any statement from applicant and experts ⇩ IQWiG issues report plan; includes research questions, outcome criteria, inclusion and exclusion criteria ⇩ IQWiG reviews evidence and performs assessment ⇩ IQWiG issues preliminary report to G-BA committee ⇩
	External review (quality assurance) | G-BA committee hearing, includes any statement from applicant and experts ⇩
	IQWiG final report with recommendations published on internet ⇩ Applicant and experts have opportunity to submit statements ⇩ G-BA committee makes final decision regarding additional benefit ⇩ Additional benefit decided by G-BA? ⇩
	Yes ⇩ | No ⇩
Reported timeline: 120 days	GKV-SV negotiates reimbursement price with applicant | Drug is priced according to similar drugs in the same therapeutic reference group ⇩ Pricing decision reached? ⇩
	Yes ⇩ | No ⇩
Reported timeline: 60 days	Drug reimbursed through Statutory Health Insurance | Arbitration board makes pricing decision ⇩ Drug reimbursed through Statutory Health Insurance

G-BA = Federal Joint Committee; IQWiG = Institute for Quality and Efficiency in Health Care; GKV-SV = National Association of Statutory Health Insurance Funds

Australia

In Australia, both the regulatory and funding/reimbursement review processes are very time consuming with multiple steps within each phase. The flow chart www.lymphomacoalition.org/global-report. for both regulatory and funding/reimbursement review processes details the multitude of steps required for each process. For example, the regulatory review process comprises eight phases. Within each phase there is an average of three steps. While each phase is not long in itself, once all phases are factored in, it's not a fast process to get a new therapy approved.

Australia's funding/reimbursement review process also seems excessively complex (see flow chart on LC website at www.lymphomacoalition.org/global-report). Two committees review the clinical and cost effectiveness of a new therapy. Within these two review bodies (PBAC and Pharmaceutical Benefits Pricing Authority [PBPA]), there are various subcommittees all seemingly examining the same information. Again, not a patient-centric process.

While review bodies are important, questions need to be asked; namely: are all the review bodies and phases needed? Are there functions that can be done by one review body as opposed to two or three? **Every time a new review body or phase is added, what needs to be considered is whether there is any duplication of effort as well as the impact it will have on the patient outcome.**

3. Funding/Reimbursement

Once a therapy is approved the next part of the puzzle begins which is to see how it will be funded or reimbursed so patients can receive treatment. In many countries, even though the drug is approved at the regulatory level, it is not usually accessible to the patient until the funding/reimbursement process is completed. Funding/reimbursement may be provided by a government body, private insurance, a compassionate access program, an early access program and some pharmaceutical companies may help defray costs through a patient assistance program.

Among the countries studied in this situation analysis, there is great variability in funding/reimbursement. In a study that examined the reimbursement level of licensed indications for 10 cancer therapies including bortezomib (Velcade) and rituximab (Rituxan, MabThera), it was found that Canada, Australia, Scotland, England and New Zealand had the most restricted access to publicly funded therapies with the lowest level of reimbursement compared with France, Germany and the USA, which had the highest levels of reimbursement.[51]

The primary reason for rejecting an application for reimbursement was a lack of cost effectiveness; in New Zealand the primary reason was excessive cost.[51] Although the USA, Germany and France theoretically have the highest levels of reimbursement, their funding/reimbursement systems require providers and payers to pay for part of the therapies. Depending on the level of co-payment, it may mean that patients cannot afford to access all available therapies.

USA

The reimbursement system in the USA can be described as one of fragmentation and decentralisation comprising a mix of public and private payers. Public payers are Medicare, Medicaid, Department of Veterans Affairs, Department of Defense and The Children's Health Insurance Program. There are approximately 50 private payers such as insurance companies, health maintenance organisations and preferred provider organisations.[52]

Medicare provides coverage for those older than 65 years, under 65 years with certain disabilities and all patients with end-stage renal disease. Medicaid coverage is for those with a low income, certain disabilities or those receiving Supplemental Security Income (a government initiative that provides stipends for those with a low income, those aged 65 years or older, those who are blind and those with disabilities). In 2011, 48.7 million Americans were enrolled in some form of Medicare and more than 60 million enrolled in Medicaid.[8]

In spite of all the funding bodies (public and private), results from the Commonwealth Fund 2012 Biennial Health Insurance survey showed that approximately 84 million people (almost half of all working-age adults) had no health insurance at some point or had OOP expenses that were so exorbitant that they could be viewed as being underinsured.[2] The survey also showed that the number of Americans who were uninsured, underinsured or had gaps in their health coverage had increased steadily between 2003 and 2010 with the number of underinsured almost doubling from 16 million in 2003 to 29 million in 2010.

The largest group needing help with healthcare coverage are those who are underinsured. Underinsured patients with Medicare or private insurance often find themselves facing higher drug co-payments or co-insurance burdens, deductibles and OOP maximums. And some, although only a small number, find out that their plans do not cover cancer therapies or branded therapies.[8] Among those who are underinsured, most (78 per cent) are likely to spend 10 per cent of their annual income on medical costs. Patients with cancer often receive combination regimens that may require them to spend far more than 10 per cent of their annual income on healthcare because they need more lab tests, hospitalization and lines of therapy. These patients may also be faced with reduced incomes if they are disabled or the person who is the primary earner has to reduce the amount of hours at work in order to take care of a sick family member.[8]

Several mechanisms exist to try and help patients who either do not have health insurance or who are underinsured. One such initiative is patient assistance programs.[8] Another mechanism to help patients with serious or life-threatening illnesses access treatment is expanded access programs (EAPs), also referred to as compassionate use programs. While the Centers for Medicare and Medicaid and private payers are not obliged to cover the cost of investigational therapies, third-party payers are developing policies that will provide reimbursement for medical care that is related to participation in a clinical trial as well as investigational uses

of products where there is evidence that supports its use. However, cancer therapies provided through EAP programs are usually provided free of charge.[8]

The irony of the system is that the USA spends the most per capita on health compared with any other country at US$8,507 (see Table 1). Yet patients in the USA have the added worry of trying to work out how they will pay for their treatment. Many find themselves deciding if they can even afford the treatment and if they don't have the proper coverage, often find themselves in serious financial hardship.

Efforts are being made to try and improve healthcare coverage in the USA. In 2010, the Affordable Healthcare Act was enacted. The purpose of the act is to lower healthcare premiums, provide coverage for the many Americans who are underinsured and end discrimination against those with a pre-existing condition. A temporary Pre-existing Condition Insurance Plan has been created to provide healthcare coverage to those with a pre-existing medical condition who have not been insured for at least six months. This bridge program will end in 2014 when health plans will have to offer coverage to those who have a pre-existing condition without adjusting premiums.[8] Another change coming in 2014 is that insurance companies will not be allowed to impose lifetime dollar limits on essential benefits, e.g., hospital stays or cap annual OOP maximums for certain plans.[8]

UK

England and Northern Ireland

Obtaining reimbursement approval from NICE is a challenging and long-drawn out process and is referred to as "NICE blight."[8] During this time, which can last up to 520 days, doctors may be reluctant to prescribe a therapy and administrative bodies may refuse to reimburse for any treatments without NICE approval. While NICE says no patients should be denied access to products awaiting appraisal that is not the reality.

Efforts have been made to try and expedite the funding/reimbursement process. As part of the Cancer Reform Strategy published in 2008, NICE was to appraise all new cancer therapies at the same time as licensing was undertaken and by 2010, draft guidance for all new cancer therapies was to be available within 120 days. What has been shown is that it can take up to 520 days before a draft guidance is available. In response to this, the government set up the Cancer Drugs Fund in 2011 as a temporary arrangement to improve access to treatments that have either been rejected by NICE or are awaiting review.[8] However, implementation of this fund varies within the National Health System. In a survey, it was shown that of 84 doctors, approximately half were unable to prescribe the therapies of their choice and one third did not apply to have a therapy prescribed because the procedure was too complicated.[8] The Cancer Drugs Fund, which was supposed to end in 2014, has been extended until 2016. The intention is to move to a system of value-based pricing but there are concerns about how it will work.[53]

It should be noted that once NICE has issued a positive guidance, funding should be in place within 60 days.[8] Again, this may not always be the case as local health authorities may not have the funds available to reimburse patients. This entails some patients having to travel to different parts of the country to receive treatment.[8]

Scotland

The review by the SMC is supposed to be undertaken within 80 to 90 days following submission of the information from the applicant with the aim of publishing its advice as soon after the medicine is available on the market. As noted in Section 1. Timelines, however, the review time can be up to 154 days.[8] Unlike NICE, SMC guidance is non-binding and the Area Drug and Therapeutics Committee can decide how the treatment will be used and whether to include it on the formulary. If the SMC denies funding, a patient cannot appeal the decision unlike patients in England who can.[8] The only appeals allowed in Scotland are for medicines that have been accepted by the SMC but not included in the NHS Greater Glasgow and Clyde Formulary. Unlike NICE, if the SMC rejects an applicant's submission because of a lack of evidence, the therapy is rejected. NICE, on the other hand, will request more evidence from the applicant before making a final decision.[8]

Wales

Unlike the review meetings undertaken by NICE and SMC, AWMSG conducts its appraisals in public. The AWMSG aims to provide its guidance within 120 to 180 days after a therapy has received its licence. AWMSG does not undertake reviews for the same product and indication if NICE publishes its final guidance within 240 days.[8]

France

For a therapy to be reimbursed by public insurance, it has to be evaluated by the TC. The TC determines the therapy's medical benefit (SMR) and its improvement of medical benefit (ASMR). The SMR determines if a therapy can be reimbursed and by how much and the ASMR determines the price of the therapy.[8] Once a therapy is approved, it is placed on the positive list for five years after which time it is re-evaluated and its price reviewed.[54]

Part of the review by the TC is to determine where the therapy fits in relation to existing treatment, the seriousness of the condition for which it's intended, the preventive, curative or symptomatic nature of the therapy, and the therapy's value to public health. These benefits are assessed using a grid that comprises five levels of improvement with Level 1 indicating major therapeutic progress and Level V indicating no improvement.[55]

The TC is supposed to fulfil an advisory role yet the recommendations provided by the TC are usually adopted when determining reimbursement and pricing.[55] While the commission is made up of scientific experts and it is generally assumed their findings are based on scientific facts, it does take economic and financial considerations into account when making a decision. This is evidenced by the increased number of Level V ratings. Between 2003 and 2004, Level V ratings were given in 62% of cases; between 2008 and 2009, they had risen to 89%.[55] The evaluation system for the benefit of new therapies may change as France is considering using a new therapeutic index to replace the complex system of clinical value and added benefit to determine reimbursement rates. In addition, the new system will also compare the benefit of a therapy with an alternative even if it is not yet approved. The proposed index will use ranges from inferior to highly superior.[54] Regardless of the review system used, reviews are likely to become more cost sensitive.

Changes have also been made in terms of what patients have to pay. Until recently, the cost of cancer care was covered almost in its entirety by public insurance. Now, co-payments have been increased per doctor visit, per prescription drug and hospital treatment.[54] While these increases are moderate, they can add up quickly for a patient with a chronic condition requiring years of treatment.

Germany

In theory, new cancer medications are available immediately upon the EMA issuing marketing authorisation. In reality, new treatments are not available until the budgeting process is completed which can take up to 440 days. In addition, the reimbursement process differs depending on where the therapy is administered, i.e., inpatient or outpatient/retail setting.[8] Therapies dispensed in the outpatient/retail setting are automatically reimbursed.

Hospitals have to apply for additional funding via the New Examination and Treatment Methods process (NUB) for newly approved therapies to be paid by the GKV until they are included in the diagnosis-related group (DRG) and/or the DRG supplement list (known as the Zusatzentgelte). It can take up to 220 days for NUB and 440 days for Zusatzentgelte. It can then be another 440 to 720 days for a therapy to be reimbursed under a hospital DRG. This means that until the hospital receives funding, its budget is at risk if it uses the new therapy.[8]

Most standard cancer treatments are available without restrictions for those with GKV, the social health insurance program. The same applies to those with PKV (private health insurance). Those with GKV coverage have to pay both office and drug co-pays. For patients with cancer, the drug co-pay applies to each therapy received during treatment. However, patients with a chronic illness including those with cancer have their total co-pays capped at 1 per cent of their income compared with 2 per cent for other patients.[8]

Spain

As mentioned, under the 1978 Spanish Constitution, all citizens living in Spain have the right to universal access to public healthcare. Until now, patients with a blood cancer (lymphoma, myeloma, leukaemia, myelodysplastic syndrome, myeloproliferative neoplasms) have received their diagnosis and treatment for free through the Spanish Public Health & National Health System. Upon approval by the EMA, the applicant negotiates the price of the therapy with the AEMPS, which is part of the Ministry of Health; the reported time for this process is between 120 to 240 days.[18]

Recently, however, as a result of changes made to the healthcare system in 2012, Spain has undergone major changes to the way therapies are funded/reimbursed. For the first time, a co-payment for therapies delivered by hospital pharmacies will be required. In oncology, this applies to 32 drugs including imatinib (Gleevec, Glivec), nilotinib (Tasinga), dasatinib (Sprycel) and hydroxiurea (Hydrea, Droxia, Mylocel), which are widely used for the treatment of chronic myelogenous leukaemia.[18] What is of even greater concern is that every region in Spain can now re-evaluate or deny, for financial reasons, the use of a therapy that has already been approved by the EMA and the Spanish Ministry of Health. It would appear that Spain is adopting a system similar to Canada's, one that does not work to the benefit of the patient. In July 2013, Spain introduced measures to try and prevent the different regions from making their own funding decisions. It's unclear at this time how successful these measures will be.[56]

While patients can seek treatments in other regions, they often don't have the necessary information about what treatments might be available. Additionally, doctors do not always recommend other, more effective treatments available in other areas and will only use therapies available to them.[18] In essence, the patient is at the mercy of a system that offers disjointed care.

Switzerland

For a therapy to be reimbursed it has to be listed on the drug reimbursement list. This entails an application being made to the Federal Office of Public Health (FOPH). The Federal Drug Commission (FDC) then undertakes a review examining the therapy's cost effectiveness compared with existing therapies. Price comparisons are also made with prices in other countries; this information is weighted heavily in the reimbursement decision and since the FDC conducts pricing reviews every three years, drug prices are exposed to currency fluctuations.[13] Once the review is completed, the FDC gives a reimbursement recommendation to the FOPH.[13] The current review process takes a minimum of 100 days but is often longer. The government is in the process of defining requirements in an effort to have funding decisions made within 60 days.

Japan

Japan has a universal healthcare system that is based on compulsory insurance plans that cover employees, i.e., under 70 years old and their families. Patients pay approximately 30 per cent of their medical costs.[57] Those over 70 years pay only 10 per cent of their medical costs (check-ups, treatment and medication). For those who are students or self-employed, they can access a national health insurance program that is provided by local governments. Those living below the poverty line do not have to pay for their care.[57] Those who have to pay 30 per cent of their medical costs often purchase private supplementary insurance to cover high OOP expenses.[58]

Canada

Once a product is approved by Health Canada patients can, at times, receive it if they pay for it themselves although administering the therapy can be difficult depending on the type of treatment. If it is an infusion, many hospitals will not

administer it because it has not been approved for use by the provincial body and, consequently, the hospital will not be reimbursed. Although some provinces have private clinics, it is unlikely that most patients will be able to pay for their treatment without some sort of funding assistance.

In addition to Health Canada's review and approval of a therapy, an application has to be made to pCODR if the applicant wants reimbursement or funding from a public payer.[46] This process applies to all provinces and territories except for one province. pCODR examines the clinical evidence and cost effectiveness of cancer drugs. The review by pCODR can start prior to Health Canada issuing marketing authorisation but pCODR will not finalise its review and make its funding recommendation until Health Canada has finalised its own review. To ensure no unnecessary delays, often applicants make submissions to pCODR prior to receiving notice of compliance.

Once pCODR makes their funding recommendation for coverage by public payers and provincial cancer agencies, it's then up to each province or territory to decide whether or not to fund the therapy. Interestingly, pCODR is funded by the provinces yet the provinces may still decide not to fund a treatment or to fund it in a different setting, i.e., one not recommended by pCODR or that is reflective of the marketing authorisation.

To illustrate the disparity between the provinces: only three of the 24 oncology therapies approved for use in Canada in 2011 were covered to some degree by government insurance in all 10 provinces by March 2012. Seven other therapies were funded in some provinces. And, more importantly, 14 of the oncology therapies had no provincial coverage.[11] What the Canadian system demonstrates is that where the patient lives determines the type of care they will receive.

It should be noted that only five provinces have their oncology drug formularies on the internet and while there is a website that provides information on government coverage, this information is provided by the drug manufacturer. As the author states: "...but since manufacturers pay to have the information on the web site, the comprehensiveness, accuracy, and timeliness of the information are unknown."[11] Canada is not unique in requiring manufacturers to pay to have therapy information included on a government website.

Australia

Australia's funding/reimbursement review process seems to be excessively complex (see flow chart on LC website at www.lymphomacoalition.org/global-report). Two committees review the clinical and cost effectiveness of a new therapy. Within these two review bodies (PBAC and PBPA), there are various subcommittees all seemingly examining the same information. And even when PBAC does provide a positive response, the government may not be in agreement. While it is rare for the government to reject a recommendation by PBAC, in February 2011, the government suspended eight medications and vaccines. "Although none of these medicines was for the treatment of cancer, the significant deviation from the routine process signalled a policy shift towards fiscal control rather than patient access."[59] The newly elected government in Australia has pledged that patients with blood cancer should have timely and affordable access to life-saving medications.[60] Time will tell if the new government is true to its word.

Brazil

Over the last few years, the Brazilian government has made efforts to improve access to treatment through expanded federal financing. For a therapy to be funded in Brazil it requires a positive recommendation from CONITEC. Established in 2012, CONITEC set a goal of conducting appraisals within 180 days and, for the most part, has met this goal.[26] Upon a positive decision, the treatment needs to be available to the public sector within 180 days. Since the establishment of CONITEC, it has issued 32 appraisals that have assessed 48 health technologies (85 per cent for therapies) for 26 therapeutic indications. This is almost twice the number the former health technology assessment commission CITEC (Commission for Incorporation of Technologies) evaluated in an average year. In addition, of the evaluated technologies, 71 per cent received a positive funding recommendation from CONITEC versus 55 per cent with CITEC.[26]

While this sounds impressive, a number of factors should be noted:

- CONITEC will not evaluate any technologies for which NICE has issued a negative appraisal;
    - However, a positive appraisal by NICE does not necessarily mean a positive appraisal by CONITEC as 35 per cent of technology submissions were denied funding. The reasons for negative funding recommendations were:
        - Insufficient evidence to support efficacy and safety claims (73 per cent);
        - Studies not undertaken for a long enough period (36 per cent);
        - Insufficient sample size, no phase III/IV studies included (20 per cent).
- All innovative treatments receiving a positive appraisal were for relatively small patient populations;
- All appraisals requested by the Ministry of Health received positive recommendations; nearly all appraisals submitted by pharmaceutical companies were rejected.[26]

As a result of this situation, patients resort to legal action in order to force the government to provide the medication. While the 1998 Brazilian constitution guarantees universal access to healthcare for all citizens, not all medicines available in Brazil are included in the formulary.[61] If the court decides in favour of the patient, then the treatment must be available within 72 hours or health authorities will be fined. Often, it is cheaper for the government to be sued rather than include a therapy in the formulary. This changes when there are too many legal actions and it is therefore more cost effective to include the therapy. Table 5 shows the number of lawsuits that occurred in 2005 and 2010 and the costs associated.

TABLE 5: LEGAL ACTION TO OBTAIN TREATMENT[61]

	2005	2010
Federal costs (in US$)	1,031,901	5,949,138
	2009	**2011**
Number of lawsuits	3,200	19,500
Lawsuits most frequently occurring in oncology and rare diseases		

Funding/reimbursement is also tied to the type of cancer a patient has. With the new treatments available, funding/reimbursement is often inadequate as the treatments are too expensive. Rituximab is a good illustration of this issue. In 2009, the Minister of Mines and Energy Resources, Dima Rouseff who is now the current president of Brazil, was diagnosed with NHL. She was surprised to learn that her treatment was not part of the formulary. In August 2010, rituximab was finally included.[61]

Another hurdle is that even if a treatment is included in the formulary, as public healthcare funding is collected and distributed at the state and municipal levels, treatment may not be widely available in every state or municipality for a number of reasons; namely, only a few patients have been diagnosed with the illness, a lack of awareness of the therapy being on the formulary, and a lack of commitment on the part of doctors to ensure patients have access to treatment.[62]

Argentina

Argentina has probably one of the more complicated funding/reimbursement systems in that most cases have to be negotiated to determine whether coverage will be provided. Coverage is provided by a mixture of public, semi-private and private funding bodies.[13] The process entails a patient receiving a diagnosis and being provided with a prescription. This may then require the doctor to contact the pharmaceutical representative who, in turn, contacts the payer to provide the payer with the information that the prescription fits the diagnosis. In breast cancer, coverage for 70 to 80 per cent of new cases had to be individually negotiated! While Argentinean law requires payers to cover all therapies, it's a common perception among pharmaceutical companies that payers make every effort to delay providing such coverage.[13] By law, patients with cancer including those with lymphomas are supposed to receive an approved therapy for their treatment at no cost to them.[3] As well, patients can also receive a therapy that has been approved in another country, e.g., the USA, even if it is not approved in Argentina. The reality seems to be somewhat different and patients often resort to taking legal action to receive the required therapy.[3]

MOVING FORWARD

This situation analysis has shown there is not much to be satisfied about when it comes to getting therapies to patients with lymphomas in a timely and cost-effective manner. Bringing all players to the table to come up with solutions as to how to make therapies more affordable must be considered. Biologics or targeted therapies, which are becoming the mainstay of therapy in the treatment of lymphomas, are expensive. Consequently, there is a high risk that fewer of these therapies will be covered by government funding agencies or third-party payers resulting in fewer patients receiving appropriate therapy due to affordability. **The cycle – develop therapy, fight to have it approved and then fight to have it funded – cannot continue as it currently stands, it is not working.**

Based on the research undertaken for this situation analysis, the only country that appears to issue marketing authorisations at the regulatory level in a timely manner is the USA. While the USA may have more resources than some of the countries studied in this situation analysis, it might be of benefit to study how their system works.

With a view to harmonising requirements, collaboration among countries could reduce the amount of time taken to issue marketing authorisations. Such collaboration would mean that data would not have to be scientifically re-assessed by each country's review body. The FDA and the EMA have recognised the importance of collaboration to speed up development and availability of new therapies and have undertaken a number of combined initiatives. For example, they created a program to provide joint scientific advice to pharmaceutical companies that has often enabled makers of oncology products to use the same clinical trials to support approvals in both the USA and the EU.[10]

In 2011, Health Canada also began a pilot project using reviews from other countries in an effort to speed up review times following a recent recommendation from the Auditor General that Health Canada "should ensure that it meets service standards for the review of all drug submission types." Evaluation of the pilot project will be completed by March 31, 2014.[62]

As a Coalition, we call for:

- A round-table discussion with all parties (government, drug developers, patients, patient advocacy groups, physicians) to come up with solutions to make therapies more affordable for patients;
- Increasing the level of transparency at all levels of the process with all parties involved. It should be clear what is going on at every stage of the regulatory as well as funding/reimbursement review processes;
- Patients, patient advocacy groups as well as applicants to be included on committees throughout the decision-making process;
- Expectations of clinical trials to be communicated clearly at the start and then adhered to during the process. If changes are made to regulatory requirements part way through the trial, these changes should not affect reviews already underway.

As a lymphoma community, we can support patients and ensure they receive therapy in the most timely and cost-effective manner possible. To assist with this, consideration can be given to:

- Governments harmonising their processes and procedures;
- Governments reducing the cost of evaluating therapies;
- Challenging drug developers that state their goal or mission is to provide better therapies to patients to do so affordably;
- Drug developers collaborating on the development of biomarker testing that can be shared so patients receive the right drug at the right time.

Let's support the patient by being vigilant rather than complacent; never stop talking about lymphoma and the needs of patients with lymphoma. Keep the big picture in the background, don't let it become overwhelming; instead look at what your local area needs and what you can do to help patients with lymphoma. If you see a need bring it to the attention of the LC or the local lymphoma organisation.

In Phase III of LeIP, LC will make efforts to host a round table that includes all parties involved in getting new therapies to the patient to come up with solutions as to how to make therapies more affordable and accessible.

In addition, LC will continue to:

- Monitor and report on the funding/reimbursement and regulatory policy changes as they occur around the world and work with local communities to be a voice for patients;
- Develop as the global resource for lymphoma facts and statistics; include information on therapies that are funded/reimbursed;
- Develop ways in which healthcare professionals can be conduits between newly diagnosed patients and patient groups for support and lymphoma education;
- Ensure that clinical trial information is made more readily available to the patient community. This will be accomplished by updating the therapy access by country chart and adding information on clinical trials as it becomes available. It is also the intent of the Coalition to determine how this information can be made available in languages other than English;
- Work closely with drug developers to ensure that as the development and use of oral therapies become more prevalent for the treatment of lymphomas, patient needs are taken into account, e.g., provide patient education to deal with compliance issues, use of blister packs, etc.

If nothing else after reading this situation analysis, think of one thing you can do to make a difference to patients with lymphomas in your country so they can receive therapies in a timely and cost-effective manner.

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