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The ODAC Chronicles: Part 3. The FDA's philosophy and process for cancer drug evaluation and approval

'How is the cancer patient best served and protected? Through the approval of new anticancer agents based on reasonable safety and efficacy in Phase II clinical trials.'

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A Lugano story

Some years ago, during the Lugano Lymphoma Meeting, I was having coffee at a lakefront sidewalk café when an old, very large, black and white American automobile slowly drove by. It was a police cruiser like those seen in the movies or on television. All the markings had been painted over and the red and blue revolving lights, as well as all other police equipment, had been removed. The only remaining identifier, still present on the front doors, was the police motto 'To serve and to protect'. This, however, had been skillfully modified. It now read 'No serve, no protect'. I never discovered the owner's intentions in delivering this message publicly in Lugano. I am sure it was more than humor, there must have been some ulterior motive. After all, these are two truly extreme statements just as different as the black and white colors on the police cruiser.

This memory in Lugano reminds me of the *raison d'être* for the US Food and Drug Administration (FDA). The FDA was created in 1938 by an act of congress (FDAC Act) and was originally charged with protecting the consumer by evaluating the safety of new products. The act was revised in 1962, and thereafter, the FDA required that, in addition to safety, efficacy should be established in two adequate and well-controlled clinical trials. In 1997, the FDA's Modernization Act (FDAMA) was approved and it allowed the FDA to accept one clinical trial and other supportive studies as evidence of efficacy [1]. The intent was truly for the FDA, the agency, 'To serve and to protect'. In the case of the oncology division of the FDA, who is to be served and protected? The cancer patient. How is the cancer patient best served and protected? Through the approval, with alacrity, of new anticancer agents based on reasonable safety and efficacy in Phase II clinical trials (BOX 1).

To serve & to protect

Why is it so important to serve and to protect the cancer patient and how should the agency perform this responsibility? We must consider how different cancer is compared with other diseases. Most other diseases already have multiple, efficacious therapeutic options. In many cases, those have optimum efficacy and safety (e.g., diuretics, antihypertensives and antibiotics). Do we need one more quinolone antibiotic? We have an excess of 'me too' and 'new and improved' drugs. In cancer, however, progress has been painfully slow. We still only have a relatively small number of therapeutic agents. Most are toxic and have limited activity. Additionally, cancer is not one but many different diseases. Most other diseases have somewhat better known etiologies and pathophysiologies. Most other diseases can be effectively controlled and will not necessarily lead to death. However, most other diseases cannot be cured (e.g., diabetes, arthritis, atherosclerosis and hypertension). Cancer can be cured. It can be cured even in

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Box 1. Alacrity.

Eager willingness or readiness, manifested by quick, lively action (e.g., the FDA should approve new anticancer agents with alacrity)

New World Dictionary of the American Language

advanced stages (with chemotherapy and/or biologics). Thus, cancer is very different and should be handled differently from a regulatory perspective *vis à vis* other therapeutic areas.

Cancer is also different in that single agents seldom result in cures and we rely on combination and multimodality therapies to achieve cures in patients with leukemia, non-Hodgkin's lymphomas, Hodgkin's disease, testicular cancer, choriocarcinoma and others. We live in an era where the therapeutic options available or under investigation have expanded substantially compared with previous decades. We have made impressive progress in moving on from standard chemotherapeutic agents to targeted therapies such as antibodies, radioimmunotherapy, vaccines and the new small-molecule chemicals. We have improved on the cure rates of what we had considered gold standards. One example is the rituximab plus doxorubicin, cyclophosphamide, vincristine and prednisone (R+CHOP) regimen, where the addition of rituximab to CHOP has resulted in an improved overall survival [2–4]. The R+CHOP regimen is the new gold standard for the treatment of patients with diffuse large B-cell lymphoma. I suspect that today we may already have the ingredients for curative regimens in several other cancers. We will only know when the appropriate combinations have been developed and eventually proven in randomized clinical trials.

Factors impeding our progress

We are in the midst of a clinical research crisis in the USA [5]. Very few patients, less than 5% of all available patients, enroll in protocol studies. This situation may not affect other countries to the same degree but it is a major problem in the USA. Regulatory agencies have become more conservative and restrictive [6]. International harmonization, although necessary and critically important, has brought the participating nations down to the most conservative, restrictive and rigid common denominator for cancer drug evaluation and approval. A substantial proportion of new anticancer agents are discovered and developed by small biotechnology companies with limited resources. An unknown number of these go bankrupt before they can obtain approval of their first product. Our process for the development of new combination regimens requires that the new agent be tested initially as monotherapy and then combined with other agents. This is necessary but could be done much faster. As a result of these and numerous other factors, cancer drug development is slow and inefficient. Consequently, the development of new combination regimens is seriously delayed. Let there be no doubt that the development of curative therapies is simply a question of time. The problem is that it is taking too much time [7].

What can be done?

More specifically, how can the FDA best serve and protect the cancer patient?

Importance of approval & marketing

The FDA should recognize that new anticancer agents are not truly available to all who can benefit from them until they are approved and marketed. Many types of expanded access and compassionate-use programs have been tried but these will never substitute for approval and marketing. The fact remains that, prior to marketing, anticancer therapeutics are available only to a select a minority of patients. Thus, the FDA has a very serious responsibility to expedite the approval of anticancer therapeutics. It is simply amazing that cancer patients and their advocates have not been more vocal in demanding that this responsibility be carried out with more alacrity.

A proposal for a small step for mankind

Approve new anticancer agents based on reasonable safety and efficacy in Phase II clinical trials.

Objectives in the development of anticancer therapeutics

Clinical cancer drug development and clinical cancer treatment development are two related but distinct objectives. It is critically important to understand this distinction. The FDA is intended to regulate drug development and not treatment development.

Clinical cancer drug development

Clinical cancer drug development may be defined as the process required for the development of a new anticancer agent. It is usually carried out by a pharmaceutical company, is tightly regulated and influenced by the FDA and has drug approval and marketing as its goal. Clinical cancer drug development consists of a lengthy series of activities that require expert professional staff and complex and costly equipment, systems and procedures (BOX 2).

Box 2. Clinical cancer drug development.

- Clinical development plan
- Investigational New Drug application
- Phase I, II and III clinical trials
- Study implementation and conduct
- Data acquisition, analysis, interpretation, reporting and publication
- Regulatory requirements – good clinical practice and others
- Regulatory dossier – electronic filing
- Oncologic Drug Advisory Committee panel review
- FDA review and approval process
- Marketing

Clinical cancer treatment development

Clinical cancer treatment development may be defined as the process required for the development of a new anticancer treatment (combination or multimodality). It is usually carried out by academic institutions, consortia or cooperative groups, is loosely regulated and not significantly influenced by the FDA, and has the development of new combinations or multimodality treatments as its goal. Clinical cancer treatment development consists of a shorter list of activities (BOX 3).

The FDA's responsibility, as established by law, is the review and approval of new anticancer agents. Pharmaceutical industry is responsible for cancer drug development and this is what the agency is required to regulate. Clinical cancer drug development should consist of the appropriate Phase I and II clinical trials (sponsored by a pharmaceutical company) to determine the safety and clinical activity of a new anticancer agent as monotherapy (Phase III trials have no role in this setting). These trials should be efficient and straightforward, and development should be collapsed to the shortest possible timeframe. This would allow for the early termination of ineffective agents. After all, there is an attrition rate; only one of every six new agents entering clinical trials ever shows the desired efficacy and safety and gets approved. Early termination would also allow for the expeditious development of the truly worthwhile drugs and decrease overall development time and cost. Most importantly, patients would have earlier access to those promising anticancer agents from which they might benefit.

The responsibility for cancer treatment development should be squarely on the shoulders of the oncology community. It is the oncology community (including academic institutions, cancer centers, cooperative groups and consortia) that, in collaboration with pharmaceutical industry, should take a new anticancer agent through the appropriate Phase II and III clinical trials to find its optimal use in combination with other agents. It is the oncology community that should be responsible for defining the role of a new agent within a treatment regimen and its place in the therapeutic armamentarium. This task is complex and requires multiple clinical trials of different combinations. The Phase III studies require large numbers of patients and take a long time to complete (patient accession followed by observation time). It can take decades before the ultimate use of a new anticancer agent, within combination regimens, can be elucidated. Nevertheless, during this time, patients can benefit from treatment with the new agent even though its optimal use in combination is still in the process of being defined. This process – cancer treatment development – should not be regulated by the FDA.

Box 3. Clinical cancer treatment development.

- Phase II and III clinical trials
- Study implementation and conduct – less intense monitoring, not usually under good clinical practice
- Data acquisition, analysis, interpretation and reporting – more simple, less detailed
- Regulatory requirements – fewer
- Data publication – main goal

Box 4. Agents with significant clinical activity as single agents.

- Clinical activity (response rate) comparable with or better than historic controls
- May or may not synergise with other agents
- Should not need to be studied in combinations for approval
- Should not require Phase III randomized trials
- Should be approved based on single-agent activity seen in Phase II trials
- However, the FDA will not currently approve unless stringent Accelerated Approval criteria are met

Types of clinically useful anticancer agents

It is practical to classify clinically useful anticancer agents into three categories from the developmental as well as the regulatory viewpoint. These are: agents with significant activity as single agents, agents with some activity and/or synergy with other agents, and agents with no significant clinical activity as single agents but with significant synergism with other agents.

Agents with significant activity as single agents

These are agents that have a response rate that compares favorably with that of other available agents (when used as monotherapy) for the proposed indication (BOX 4). They should be approved on the basis of Phase II trials with data from historic controls. The entire application need not include more than 300–350 patients. Some data on response duration, such as time to progression (TTP) or progression-free survival (PFS), would be useful but should not be an absolute requirement. After all, these new anticancer agents are most frequently combined with other agents rather than used as monotherapy. It is the response duration of the combination that is of interest. However, the optimal combination may take years to define. In the meantime, these agents could be approved and made available to patients who may benefit from them. What is the downside of such an approach? At the extreme, the FDA may approve a drug that later shows toxic effects not seen in the original experience included in the application, the response rate may turn out to be lower than originally determined and/or no additive effect is seen when used in combination regimens. It is unlikely that all of these will be observed. If this extreme situation does occur, then approval can be withdrawn or, alternatively, the drug will die on its own as it will not be prescribed (a type of market-induced apoptosis). There are risks but they are small relative to the potential benefit of having an active agent approved earlier rather than much later.

Agents with some activity &/or synergy with other agents

These are agents that have a response rate lower than that of other available agents (when used as monotherapy) for the proposed indication (BOX 5). They may or may not have synergism with other drugs or combinations. Their approval requires a risk–benefit determination. The FDA will not approve such agents unless they show superiority or noninferiority to a standard regimen in a Phase III trial. Thus, in most instances, such an agent will live or die based on its activity within a combination that will probably not be the optimal combination. These agents should be approved based on Phase II trials and the oncology community allowed to conduct the multiple studies that will eventually show how they may best be utilized in combination regimens. As with the agents with significant activity as single agents, there are risks, but I cannot see what is wrong with approving such an agent.

Agents with no significant clinical activity as single agents but with significant synergism with other agents

These are agents that are inactive, as monotherapy, for the proposed indication but exhibit significant synergy with other drugs or combinations (BOX 6). In this case, there is no choice but to carry out controlled, randomized Phase III trials to show the synergistic effect.

Thus, the bottom line is that two of these three types of useful anticancer agents can be approved (with alacrity) based on reasonable safety and efficacy in Phase II clinical trials. They would be available to patients earlier. Development costs and drug prices should decrease. The oncology community could proceed with combination studies earlier. Hopefully, additional curative regimens could be identified within our lifetimes. A criticism might be that pharmaceutical industry will benefit from these earlier approvals. This should be tempered by the additional risk and cost that early approvals entail, including the occasional approval withdrawal or failure in the marketplace. All in all, it seems like a win–win situation for the patient.

Box 5. Agents that have some activity and/or synergy with other agents.

- FDA will not currently approve as a single agent based on Phase II trials
- Efficacy requirements too stringent – superior or noninferior in Phase III trial
- FDA will require either a comparison with a standard drug (X vs. A study) or with a combination (X+A vs. A+B or other study)
- Should be approved based on reasonable efficacy and safety in Phase II trials
- Determination of optimal use in combination should be the responsibility of the oncology community and not the FDA

Box 6. Inactive agents that synergise strongly with other agents.

- Little or no clinical activity as single agents
- Significant synergism with other agents
- Need to be studied in combination with these other agents
- Require randomized clinical trials

Philosophy for cancer drug development & approval

The FDA requires Phase III randomized clinical trials for the approval of new anticancer agents. These trials, in the majority of cases, require comparison of the experimental agent (within a combination) with a standard regimen and are usually designed as X+ABC versus ABC studies. The statistical requirements are stringent and usually involve complex statistical manipulations and the demonstration of superiority with a p-value of less than 0.05 in the case of two or more trials or less than 0.02 if there is only one Phase III trial [6]. As a result, clinical anticancer drug development becomes costly and lengthy, and new agents are not available to patients for many more years. Additionally, the experimental combination is usually chosen from a limited number of Phase II trials and the probability of having chosen the optimal combination is minimal. Furthermore, this approach represents the regulation of cancer treatment development and is not what the FDA was intended to regulate.

An alternative is to pursue an Accelerated Approval. The FDA will approve new anticancer agents on the basis of Phase II data and even single-agent uncontrolled Phase II data, provided certain criteria are met: indication – serious and life-threatening illness, advantage over available therapy (ability to treat patients who are unresponsive or intolerant), single trial plus other supportive evidence, substantial evidence from well-controlled clinical trials regarding a surrogate endpoint reasonably likely to predict clinical benefit, and postmarketing studies to verify clinical benefit [8]. The Accelerated Approval alternative is a reasonable approach and could provide substantial flexibility. However, out of 71 oncology drug applications approved from January 1, 1990, to November 1, 2002, only 14 (<20%) were granted Accelerated Approval [9].

Overall, the FDA's philosophy for cancer drug development and approval appears to lean heavily towards the approval (regular rather than accelerated) of very safe and efficacious anticancer agents, usually within a combination regimen and as a result of Phase III randomized and controlled clinical trials. This needs to continue to evolve towards a greater use of the Accelerated Approval mechanism. Accelerated Approval has been used successfully and needs to be used even more frequently and more efficiently (and with alacrity).

Conclusion

A lot needs to be done but we must start with the approval philosophy and process (BOX 7). The proposal is to approve new anticancer agents based on reasonable safety and efficacy in

Phase II clinical trials. The Accelerated Approval mechanism, if interpreted reasonably (rather than conservatively), actually allows for this. It is the current stringent interpretation that is getting in the way of its application to new anticancer agents. Should the FDA ever accept that its role is really the review and approval of new anticancer agents (rather than cancer treatment review and approval) and should they ever interpret Accelerated Approval more reasonably, we would be witnessing not a small but a giant step forward for mankind. This is the true meaning of 'To serve and to protect'.

Information resources

Additional reference and background material can be found at the FDA's website, www.fda.gov.

Box 7. What can be done in the USA?

- FDA reform – stop being just a buzz word in political campaigns
- We need true and substantial reform to streamline procedures, reduce regulatory requirements, decrease bureaucracy and decrease overall development time for cancer drugs
- Congress – change and simplify the FDA's mandate
- Secretary of US Department of Health and Human Services – more interested (and proactive) in FDA issues
- FDA comissioner – implement the sorely needed changes
- FDA – pursue accelerated approvals even more frequently, more efficiently and with alacrity
- FDA – approve new cancer therapeutics as single agents (cancer drug and not cancer treatment review and approval)
- FDA – approve new anticancer agents based on reasonable efficacy and safety in Phase II clinical trials

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