

# The Interplay of Laws, Regulations, and Policies: Moving Cancer Therapeutics Development out of the Quagmire

Susan Jerian, MD

ONCORD, Inc.

October 5, 2007

# The Challenge

- Mandate to conduct high quality, impactful cancer clinical trials.
- The current environment undermines this mandate.

The Result: Science is not leading the way.

The Question: How do we get back on track?

# The Situation

- A confluence of regulations and policy decisions have created an environment that has incentivized an approach to cancer therapeutics development which focuses on testing drugs in refractory patients. The promise of personalized medicine is more challenging than anticipated.
- The public wants cancer prevention and cures, but more often gets end stage care.
- The public wants personalized medicine to improve efficacy and reduce toxicity, but there are few developments in this area and the ones that exist are slow to fruition.
- The public wants clinical trials that answer important questions, but often gets what is expedient for business.

# Laws, Regulations and Policies

- Accelerated Approval
- Omnibus Reconciliation Act (OBRA) '90 and '93: Compendial Listings and Reimbursement
- Special Protocol Assessments
- Definition of Combination Product

# Accelerated Approval (AA)

- 21 CFR 312 Subpart H (drugs) and 21 CFR 601 Subpart E (biologics)
  - Not to be confused with 21 CFR 312 Subpart E which addresses additional procedures related to life threatening illnesses (pre-IND, EOP1 meeting, treatment protocol, risk benefit analysis, Phase 4 studies etc.)
- Codified Dec 11, 1992 (57 FR 58959)
  - “...intended to provide expedited marketing of drugs for patients suffering from such [serious or life-threatening] illnesses when the drugs provide meaningful therapeutic advantage **over existing treatment.**”
  - Interpreted by FDA to mean the “ability to treat unresponsive or intolerant patients or improved response compared to available therapy”
- “Full approval for marketing”

# Two mechanisms for AA

1. Approval based on a surrogate endpoint
  - Most commonly applied mechanism in the oncology setting
2. Approval with restrictions
  - Rarely (if ever?) applied in the oncology setting

# Application of AA Regulations

- Surrogate endpoints depend on tumor type and indication
  - Response rate with durable responses
  - PFS or TTP
- Patients who have failed treatment with other available therapies
  - Difficult to define sometimes due to limited benefit of available therapies. Must a patient fail all of these?
  - Ambiguous in regard to other available therapies that are approved through the AA mechanism or are widely used off label.
- The environment can change rapidly
  - Is an AA strategy viable if the standard of care changes during the conduct of the study?

# Example: Renal Cell Cancer

- Dec 2005: full approval of sorafenib based on PFS in a randomized placebo controlled trial of pts who failed one prior txt.
- Jan 2006: accelerated approval of sunitinib based on durable responses in patients who had progressed following available therapy (IL-2 or INF) in two single-arm trials.
- Feb 2007: full approval of sunitinib based on PFS (not OS); randomized trial vs. INF in previously untreated pts.
- May 2007: full approval of temsirolimus based on OS in randomized open label trial vs. INF in high risk patients not previously treated.
- Today accelerated approval might require demonstration of durable responses in patients who had progressed following multiple agents (sunitinib, sorafenib, temsirolimus and possibly cytokines) because these are the “available therapies”.
- If bevacizumab data are favorable (multiple P2 studies), then there will likely be off label use and there is a question as to whether or not this is an “available therapy” for purposes of AA.

# Enforcement of AA: “false teeth”

- Withdrawal of approval following a hearing if...
  - Post-marketing study fails to verify clinical benefit
  - Applicant fails to perform post-marketing study with due diligence
  - Restrictions are not adequate to assure safe use
  - Failure to adhere to restrictions
  - Promotional materials are false or misleading
  - Other evidence that shows drug not to be safe or effective
- No product approval has ever been withdrawn in oncology
  - Would be politically unpopular
  - Iressa probably met the criteria and actions taken by FDA come the closest to a product withdrawal to date

# Accelerated Approval Reality- Pros

- Has improved patient access to safe and effective cancer therapeutics.
- Used by sponsors as a quick path to market.
- Has stimulated commercial sponsors to pursue oncology indications where they may not have previously.

# Accelerated Approval Reality- Cons

- We are quickly reaching capacity for studies of “unmet medical need” in multiple tumor types
  - Start to see trials of patients who have failed 3, 4 or 5 “available therapies”.
  - Differences between the clinical standard of care and approved products can lead to challenges in application of the regulations.
- Epidemic of failure to perform post-marketing studies
  - Logistical challenges
  - Competing studies
  - Lack of due diligence

# OBRA 90 and 93: Compendia

- Medicare Benefit Policy Manual Chapter 15 section 50.4.5: Unlabeled Use for Anti-Cancer Drugs (effective Jan 1, 1994)
- “[Medicare] Contractors must not deny coverage based solely on the absence of FDA approved labeling for the use, if the use is supported by one of the following and the use is **not** listed as “not indicated” in any of the three compendia [or FDA approved label].”

# Presently only 2 Compendia

- American Hospital Formulary Service Drug Information
  - Drug monographs including labeled and unlabeled uses
  - Unlabeled uses are supposed to be indicated with daggers
  - Carrier must analyze text to determine if use is supported
  - Promotion of compendium
    - “Official compendium of US Congress”
    - “Extensive off label usages”
    - Expert advice and peer reviewed by over 500 “medical scientists, physicians, pharmacists, pharmacologists, and other professionally qualified individuals.”
- DrugPoints®
  - Published by US Pharmacopoeia
  - Succeeds USPDI which was a merging of the AMA Drug Evaluations and USPDI
  - Can only be purchased in non-paper version and through salesperson

# Compendia (cont.)

- The other “Black Box”
  - Process for assessment of drug products is not transparent even to government agencies.
  - Designation process for off label indications is not delineated.
  - No third party oversight of the process.
  - Third party payers, including CMS, lack the clinical and scientific expertise to evaluate data related to off label use.
- Effort underway for a third oncology specific compendia to be added: National Comprehensive Cancer Center Network (NCCN) Guidelines
- CMS currently considering revisions to specified compendia list
  - MedCAC report: None of the examined compendia met all of their “desirable characteristics” criteria

# Not in Label nor Compendia

- “Use supported by clinical research that appears in peer reviewed medical literature”\*
  - Applies when an unlabeled use does not appear in compendia
  - List of acceptable journals is provided
- “Unlabeled uses may also be considered medically accepted if determined by the [Medicare] carrier to be medically accepted generally as safe and effective for the particular use.”\*
- Effort underway to also include meeting abstracts as part of acceptable medical literature

\* Medicare Benefit Policy Manual, Chapter 15.

# Criteria for judging literature

- “The appropriateness of the study design.”\*
  - Does the design address the investigative question
  - Nonrandomized trials should have a “significant number of patients”
  - Case reports do not provide adequate support
- “The carrier will use peer reviewed medical literature...”\*  
with a specific list of 15 journal titles
- “...the carrier will ask the physician to submit copies of relevant supporting literature.”\*
- Other criteria which are nonsensical in the oncology setting.

\* Medicare Benefit Policy Manual, Chapter 15.

# “Relevant supporting literature”

- Physicians were responsible for finding relevant supporting literature
  - Challenging in a busy practice
  - May be unaware of articles
- Dissemination of literature by Pharmaceutical companies before 1998
  - Highly restricted
  - Specific FDA Guidance
- FDAMA 1998 added more permissive language around dissemination of treatment information (Chapter V, subchapter D)
- 1998 Washington Legal Foundation vs. Henney (FDA)
  - First Amendment rights applied to off label use

# Compendia Reality - Pros

- Has allowed patients to gain access to standard of care treatment for their cancer
  - OBRA '93 is critical legislation that has made a tremendous difference in the lives of patients
  - Improves overall cancer care in the US
  - Is critical to the success of treatment of oncology patients
- Used by sponsors to “expand the market”

# Compendia Reality - Cons

- The new “Black Box”
  - Requires interpretation and application of clinical and scientific data by third party payers who may not have sufficiently sophisticated medical and scientific expertise
  - Sets a different standard for “safe and effective”
  - Lacks adequate oversight thereby making it more susceptible to influence or even corruption
  - Do not meet MedCAC criteria
- Contributes to logistical challenges for conducting impactful cancer clinical trials
  - Patients are being enrolled on studies for compendial listings rather than more rigorous scientific studies intended for registration purposes (esp. full approval)

# Special Protocol Assessment

- Nov 1997 FDA agreed to PDUFA performance goals for special protocol assessments (SPA): 45 day review period
- Three types of protocols
  - Animal carcinogenicity
  - Final product stability
  - Phase 3 clinical trials intended to support an efficacy claim
- Goal: For sponsor to reach binding written agreement with FDA on the protocol design
- Request should include specific questions and role of the study in the overall development program

# Caveats of SPA

- Cannot be requested after a study begins
- Meeting with FDA prior to submission may or may not be necessary
- Submission of revisions to the protocol will reset the 45 day review time clock
- May be rendered non-binding if ...
  - “Public health concerns unrecognized at the time of protocol assessment [arise later]”
  - Sponsor does not follow protocol
  - Relevant data, assumptions are found to change or are false
  - “A substantial scientific issue essential to determining safety or efficacy of the drug has been identified after the testing has begun.”

# Reality of SPA Process - Pros

- Led to improvement of clinical study designs for trials intended to support efficacy claims
  - Improves the likelihood of success for regulatory approval
- Makes it easier for FDA to provide deliberate and organized input to sponsors
- Provides an avenue for clear documentation of agreements

# Reality of SPA Process - Cons

- Delays Product Development
  - It can take 2, 3 or more review cycles to come to an agreement
  - This can lead to significant delays in study start (in some cases up to 6-12 mos)
  - Competitive disadvantage for study in “crowded” field
  - Could cause logistical issues if a competing product is approved in the interim
- The more complex the study design the harder it is to reach an agreement
  - Adaptive study designs definitely fall into this category
  - Biomarker studies (with or without adaptive designs) also fall into this category
- Makes sponsors much less inclined to submit “novel” trial designs

# Definition of Combination Product

- Final Rule “Definition of Primary Mode of Action of a Combination Product” as listed in Federal Register: August 25, 2005 (Vol 70, No. 164)
- First defines a combination product as any...
  - Drug and device
  - Device and biologic
  - Biologic and drug
  - Drug and device and biologic
- A therapeutic (drug or biologic) used with an in vitro diagnostic is now defined as a combination product
  - A drug, device or biological product ... intended for use only with an approved ... drug, device or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose

# Reality of Combo Product Definition as Relates to Biomarkers

- Creates a regulatory link between a therapeutic and biomarker test
  - Leads to an undesirable business outcome between therapeutic sponsor and device sponsor
- Makes it more difficult to introduce scientific advances by not allowing for flexibility as the science advances
  - The understanding of how best to employ biomarkers is rarely present at the onset of clinical trials
  - Complex molecular pathways take time to delineate necessitating a flexible regulatory system.

# The Interplay of AA and Compendia

- The juxtaposition of Compendia and AA regulations has incentivized companies to focus their more rigorous scientific testing on end stage cancer
  - Bring products to market quickly by seeking accelerated approval in refractory cancer patients
  - Expand the market by conducting non-registrational compendial studies
- A vicious cycle has been created that is a disincentive to companies to conduct rigorous registrational studies in less refractory or earlier stage patients
  - Conduct of these studies is hampered by competition for patients many of whom enroll onto “compendial” studies
- This is in contradistinction to what the public wants: more curative therapies at an early point in the disease

# The Interplay of SPA process and Critical Path

- The current regulatory realities are a disincentive to novel trial design implementation in oncology
  - Special protocol assessment process is a necessary step for conduct of studies employing novel trial designs
  - Complexity of the designs coupled with limited FDA resources (e.g. adequate statistical review staffing) leads to multiple review cycles
  - Anticipated delays to initiation of P3 trials are incompatible with business models of commercial sponsors
- The scientifically impactful studies are not conducted due to their complexity

# Interplay of combo definition, SPA and critical path

- Biomarker-therapeutic co-development can be more complex and take longer
  - It would be unusual for a sponsor to delay clinical trials in order to better understand molecular pathways
  - Current path requires first conducting a study to identify a subset of patients more likely to respond, then conducting another study that prospectively looks only at that subset
  - Screening using a biomarker can result in many ineligible patients thereby affecting enrollment timelines
  - Complex studies would be delayed through the SPA process
- The system lacks the agility to address advances in scientific understanding of biomarkers
- Biomarker development is hampered
  - By instituting regulatory links between two different sponsors

# Proposals and Impact

- Apply the accelerated approval regulations to biomarker-therapeutic co-development
- “Clean-Up” the compendial process
- Revise the special protocol assessment process to reduce delays to study start

# AA: Restricted Distribution

- “...a drug, effective for the treatment of a disease, **can be used safely only if distribution or use is modified or restricted...**to certain facilities or physicians with special training or experience or ...**conditioned on the performance of specified medical procedures...**”

# Apply AA to Biomarkers

- Leverage the restriction on use clause
  - Allows for “a specified medical procedure” as a method of delineating use
- Approval could be based on prospectively agreed upon plan for subset analysis
  - Need to define critical elements of such studies (e.g. survival endpoint)
  - Must discourage “fishing expeditions”
- Confirmatory study would apply use of the biomarker prospectively
  - Show efficacy in those with biomarker designation
  - Show lack of efficacy in those without biomarker designation
  - Substantially enrolled at the time of approval
- Outcomes
  - Greater incentive to commercial sponsors to develop personalized medicines
  - Apply most exciting scientific advances to less ill patients to improve long term outcomes.

# Require Transparency and High Standards for Compendial Process

- Documentation of decisions should be publicly available including identifying responsible individuals.
- Scientific and medical expertise should be required and documented for each product monograph and for reimbursement decisions.
- Depth and quality of data review should be improved.
- Consideration should be given to making MedCAC “desirable characteristics” for compendia a requirement.
- “Safe and Efficacious” standard should be distinguished between compendia and FDA.
- Safeguards to prevent exploitation should be created.
- Overall impact would be ...
  - Higher quality treatment decisions leading to better, science based patient care.
  - Reduction in the number of non-rigorous, “frivolous” clinical studies.
  - Improvement in compliance with AA post-marketing commitments through creation of proper clinical research environment.

# Revise the SPA Process

- Allow sponsors to submit protocol revisions that do not trigger another review cycle especially when requested revisions are “minor”
- Apply “frequent communications” practice to the SPA process
  - It will have a far greater impact on development timelines at this stage than where it is currently applied during the NDA/BLA review
- Hire, train and retain reviewers who are expert in complex trial design issues
- The outcome would be ...
  - Increase in submission of novel trial designs
  - Improved quality of designs for pivotal trials
  - Improvement in product development timelines
  - Better science

# Conclusions

- Existing laws, regs and policies, when taken individually, have had a positive impact on patient access to critical anti-cancer therapies.
- The interplay between the laws, regs and policies, has inadvertently created barriers to conducting scientifically impactful clinical trials.
- Specific actions can be taken within the current framework to promote excellence and efficiency in development of anti-cancer agents.
  - Accelerated Approval
  - Compendial Studies
  - Special Protocol Assessment
- Prioritizing the hiring, training and retention of scientifically and medical experienced review staff at FDA and CMS is critical for the promotion of good science and the best medical care for patients.

# References

- AHFS website: [www.ashp.org](http://www.ashp.org)
- American Hospital Formulary Service Drug Information, 2005 and 2007.
- Code of Federal Regulations, 21 CFR 312 and 21 CFR 601
- FDA Guidance for Industry: “Help-Seeking” and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms,” January 2004.
- Federal Food, Drug and Cosmetic Act, Chapter V, Subchapter D, Dissemination of Treatment Information.
- Federal Register, 57 FR 58942-60, December 11, 1992, Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval.
- Federal Register, 70 FR 49848-62, August 25, 2005, Final Rule: Definition of Primary Mode of Action of a Combination Product.
- Federal Register, 72 FR 38177-8, July 12, 2007, Compendia for Determination of Medically Accepted Indications for Off-Label Uses of Drugs and Biologicals in Anti-Cancer Chemotherapeutic Regimen.
- USP DI website: [www.micromedex.com/products/uspdi](http://www.micromedex.com/products/uspdi)
- Journal of Clinical Oncology, ASCO Special Article: Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications, JCO: 24, 19, July 1, 2006, pp3206-8.
- Journal of Oncology Practice, “ASCO Advocacy for Coverage of Off-Label Oncology Drug Use, September 2006, pp 225-6.
- Journal of Oncology Practice, “Off-Label” Indications for Oncology Drug Use and Drug Compendia: History and Current Status, 2005, pp 103-5.
- Medicare Benefit Policy Manual, rev May 25, 2007.

**END**