Citizen Petition

Date: March 9, 2022

The undersigned submits this petition pursuant to 21 CFR 10.30 of the __ (Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs) to request the Commissioner of Food and Drugs to amend the ***Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics -- Guidance for the Industry***.

A. Action Requested

To amend the *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for the Industry* to require or strongly urge supplementary comparison of *Quality of Life-related patient reported outcome (QoL-PROs*)* for the following surrogate endpoints in randomized controlled clinical trials:

Endpoints Based on Tumor Assessments

Disease-Free Survival (and Event-Free Survival)
Objective Response Rate
Complete Response
Time to Progression and Progression-Free Survival (PFS)
Time to Treatment Failure

The guidance is currently worded as shown for progression free survival:

> *"A large improvement in progression-free survival (PFS) or high, substantiated durable ORR has been used to support traditional approval in select malignancies, but magnitude of effect, relief of tumor-related symptoms, and drug toxicity should also be considered when making the approval decision."*

Presently, important "tumor-related symptoms and drug toxicities" such as fatigue, brain fog, nausea, and pain, which can only be reported by the patient, is typically reported indirectly by the study team.

It is sometimes claimed that an improvement in PFS is in itself evidence of improved quality of life. However, this assumption (to our knowledge) is not supported by evidence or by the following investigation, which found:

> *PFS benefit was not strongly correlated with improvements in patients' quality of life, and, despite the palliative intent of treatments in the*

advanced/metastatic setting, the availability of quality of life data from clinical trials of cancer drugs was poor.[1]

Further, we note that for PFS (a composite endpoint) the word Survival is misleading to patients. It does not always follow that a study showing an improvement in this or other surrogate endpoints reliably predicts that patients will live longer. As reported here the correlation with improved survival is inconsistent and moderate overall:

Thirty-eight trials were included, and they comprised 19,031 patients across 8 tumor types. PFS-2 displayed a moderate correlation with OS (r = 0.67; 95% confidence interval [CI], 0.08-0.69). [2]

Addendum to this guidance urged and requested:

The assessment of *relief of tumor-related symptoms, and drug toxicity* should include a standardized set of **QoL-PROs**[3] on disease symptoms and treatment effects - reported directly by the patients.

Importantly, these outcomes will be secondary to the primary endpoints of tumor response serving to aid regulatory decisions when the magnitude of tumor assessments is questionable but also to inform clinical decisions by patients and physicians should the study protocol gain accelerated or full approval.

B. Statement of Grounds

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry appropriately states that Progression Free Survival gains alone are not sufficient for granting marketing approval:

"A large improvement in progression-free survival (PFS) or high, substantiated durable Overall Response Rate has been used to support traditional approval in select malignancies, but magnitude of effect, relief of tumor-related symptoms, and drug toxicity should also be considered when making the approval decision.'

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[1] Association between progression-free survival and patients' quality of life in cancer clinical trials. Hwang TJ1,2, Gyawali B1,2. | Int J Cancer. 2019 Apr http://bit.ly/2ti7R17

[2] The validity of progression-free survival 2 as a surrogate trial end point for overall survival https://pubmed.ncbi.nlm.nih.gov/34985773/

[3] **QoL-PROs** effects of treatment or symptoms of the disease reported directly by the patients without interpretation from the study investigators or anyone else.

A primary goal of medicine is to provide relief from pain and suffering - and to restore our health by controlling or eliminating disease. Thus, comparing the effect of study drugs on *the patient's quality of life is integral to the assessment of clinical benefit in clinical research.*

Dr. Judith Karp in support of our petition writes:

> *"Quality of life (QoL) is critical to any response (or even without achieving so-called "objective response") -- and even if there is no quantitative improvement in survival, having a life that has quality is paramount to what we are supposed to be trying to accomplish! This has always been one of my major issues with bone marrow transplant -- chronic GVHD is no way to live. Or, in another vein, mere existence really is not fun (the "old man river syndrome:" tired of livin' and scared of dyin')."*

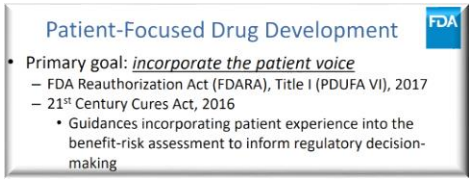
The unfiltered patient experiences compared in well-powered randomized controlled studies provides objective comparisons of the subjective experience of disease and treatment effects.

Is relying on the study team to report what only the patient can describe a scientific way to assess how well patients actually live while on treatment and how these effects change from baseline and in follow up?

Bishal Gyawali, and colleagues report (BMJ 2018;363:k4383) that *"studies of cancer drugs often use terms that downplay the seriousness of adverse events:"* [4]

The assessment and comparisons of QoL-PROs may be particularly relevant and to study drugs given continuously until disease progression or until unacceptable toxicity. Here we assert that the patient needs to know, and has a right to be informed about what to expect – if the possible improvements based on tumor assessments are offset, or further supported, by the side effects experienced.

We note that representatives to the F.D.A have called for "incorporating the patient voice," and rightly so. What better and more appropriate way to achieve this goal than to permit the patients participating in clinical research to report symptoms and drug effects directly?[5]



[4] Reporting harms more transparently in trials of cancer drugs | The BMJ 2018 | Bishal Gyawali, http://bit.ly/2BUnArQ

[5] Defining and Assessing Clinical Benefit:
A Regulatory Perspective - Sophia Bous Hufnagel, MD https://www.fda.gov/media/131585/download

Further clarification of the aims of petition:

Benefits

We maintain that the *secondary* assessment of QoL-PROs in registration trials comparing the study protocol with the standard of care would have the following benefits:

1. **Aid in regulatory decision-making.**

   When the primary efficacy outcome is modest in relation to the control and based on a surrogate that may not predict that the intervention is helping patients to live longer.

   An improvement in QoL-PROs in the study group, or no change, together with marginal improvement in PFS could support conditional or full approval; whereas a decline in quality of life would support the decision to require survival data to confirm clinical benefit. Having key secondary QoL-PROs would help the FDA to make and explain its regulatory decisions in close calls. We note that the call for inclusion of the patient experience is widely supported:

   "The American Society of Clinical Oncology, United Kingdom National Institute for Health and Care Excellence, and European Medicines Agency have all outlined the need to improve the quality of PRO trial results to better inform technology appraisals and licensing decisions"[6]

   Here we provide an EXAMPLE in the published literature:
   Quality of Life Effect of the Anti-CCR4 Monoclonal Antibody Mogamulizumab Versus Vorinostat in Patients With Cutaneous T-cell Lymphoma www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(20)30511-5/pdf

   "The symptoms, emotions, function, and overall QoL effects on patients treated with mogamulizumab were generally more improved compared with patients treated with vorinostat across most of the function and symptom areas. Overall, these results suggest that patients receiving mogamulizumab had improved QoL associated with their disease- and cancer-specific conditions and overall QoL, with a statistically significant decreased risk of experiencing a more rapid deterioration in their QoL compared with vorinostat."

- [6] Systematic evaluation of Patient-Reported Outcome protocol content and reporting in cancer trials | JNCI: Journal of the National Cancer Institute | Oxford Academic http://bit.ly/2UmKcYx

Possible scenarios:

Major improvement in time to relapse with modest impairment in QoL.
(Approval could still be justified)

Modest improvement in time to relapse with impairment of QoL
(Longer follow-up justified)

Modest improvement in tumor response with improvement in QoL
(Approval could still be justified)

2. **Foster public trust in clinical research and regulatory decisions** by making what is studied truly patient-centered, and improving its scientific validity. *(If the COVID-19 crisis has taught us anything it is the need to increase public trust in clinical science and in the standards and independence of regulatory review.)*

3. **Guide clinical decisions made by doctors and patients** for the study treatments approved using this methodology. On this Dr. Ethan Basch writes:

"Regulators and industry continue to prioritize survival-based end points rather than patient-experience end points in cancer-drug development. Yet as patients live longer with cancer, they must increasingly choose among agents with varying efficacy–toxicity balances." [7]

We remind that cancer is a disease that disproportionally afflicts the elderly and that comfort care is a common focus of medicine in this population.[8]

Related is the need to raise and create standards for *how QoL-PROs are captured and reported in clinicaltrials.gov*. The results should provide clarity to aid in public and physician understanding.

4. **Improve safety for study participants** – particularly if QOL-PROs are captured in real time with ePROs – this by alerting the study team to the need for study drug dosing adjustments or discontinuation.[9] Including real-time QOL-PROs could also help to improve accrual in future trials.

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[7] Toward Patient-Centered Drug Development in Oncology
Ethan Basch, M.D. https://www.nejm.org/doi/10.1056/NEJMp1114649

[8] Quality of Life in elderly patients with cancer | Health and Quality of Life Outcomes | Full Text
http://bit.ly/2KEm2sB

[9] Electronic Patient-Reported Symptom Monitoring Associated With Increased Survival Among Patients with Metastatic Cancer - For The Media - JAMA Network | Ethan Basch, M.D http://bit.ly/2XlWB1o

We anticipate that the benefits of including QoL-PROs (particularly making use of electronic instruments for capture and reporting) would add little to the workload of investigators or costs to drug sponsors. In one report on the cost of surveillance using we web-based PROs the study team concluded:

"Surveillance of lung cancer patients using web-based PRO reduced the follow-up costs. Compared to conventional monitoring, this surveillance modality represents a cost-effective strategy and should be considered in cancer care delivery.[10]

For the reasons explained in detail above, we (the undersigned) respectfully request that the F.D.A. take the following actions:

Provide guidance to clinical trialists, drug sponsors, and Institutional Review Boards regarding the need to capture and compare QoL-PROs as secondary (supplemental) endpoints – particularly when the primary endpoint is a surrogate for clinical benefit based on tumor imaging.

Help to set standards for secondary QoL-PRO reporting, beginning with ClinicalTrials.gov. This so that what is reported can be readily utilized to interpret the study results in order to guide clinical practice and better-informed patient choice. Indeed, the failure to include QoL-PROs seems related to how inconsistent and poorly-designed the efforts have been to report QoL-PRO results to date:

"The current standard of reporting of HRQL needs to be improved. Major deficiencies that should be addressed are failure to provide a rationale for HRQL assessment and inadequate description of methodology." [11]

C. Environmental Impact

(A) We claim for categorical exclusion under §§ 25.30, 25.31, 25.32, 25.33, or § 25.34 of this chapter or an environmental assessment under § 25.40 of this chapter.)

D. Economic Impact

The economic impact will be submitted upon the request of the commissioner.

E. Certification

[10] Cost-Effectiveness of Web-Based Patient-Reported Outcome Surveillance in Patients With Lung Cancer https://www.jto.org/action/showPdf?pii=S1556-0864%2819%2930113-3

[11] The standard of reporting of health-related quality of life in clinical cancer trials. - PubMed - NCBI http://bit.ly/2WNqojs J Clin Epidemiol. 2000 May;53(5):451-8. Lee CW1, Chi KN

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Karl Schwartz
Patient advocate, caregiver
Formerly: President of Patients Against Lymphoma, FDA patient representative, CIRB member – adult early phase, NCI Steering committee for lymphoma and co-chair Patient Advocate committee.

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See also below: Endorsing the enclosed Citizen Petition

Related Publications

- **How often and well are QoL-PROs reported in Lymphoma and CLL studies?**

  Presently few phase 3 trials have included quality of life assessment (20%) and fewer have reported results (10%).

  Further the QoL *reporting of results appears lacking in standards* and is difficult to compare or interpret.

  ClinicalTrials.gov
  Search for completed phase 3 Lymphoma OR CLL studies
  including QoL assessments as of 2/4/19:

  Completed Studies | Phase 3
  336 studies http://bit.ly/2GajYG2

  Completed Studies | Phase 3 | QoL OR Quality of Life
  68 studies (20%) http://bit.ly/2UzaSpk

  Completed Studies | Phase 3 | Quality of Life OR QoL | With Results
  34 studies (10%) http://bit.ly/2UEL3E9